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Potential benefits of hyperbaric oxygen therapy on atherosclerosis and glycaemic control in patients with diabetic foot

Korzystny wpływ leczenia tlenem w komorze hiperbarycznej na czynniki ryzyka miażdżycy i kontrolę glikemii u chorych z zespołem stopy cukrzycowej

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Abstract

Introduction: The aim of this study was to investigate the effects of hyperbaric oxygen therapy (HBOT) on glycaemic control, atherosclerosis, inflammatory markers, and other clinical and laboratory parameters in patients undergoing systemic HBOT for diabetic foot ulcerations.

Material and methods: Twenty-eight patients with Wagner grade 2–4 diabetic foot ulcerations were included. All patients were given 100% oxygen at 2.4 absolute atmosphere (ATA) for about 105 minutes, five times a week for a total of 30 sessions. Fasting blood glucose (FBG), haemoglobin A_{1c} (HbA_{1c}), homeostasis model measurement-insulin resistance (HOMA-IR), high sensitivity C-reactive protein (hs-CRP), uric acid, mean platelet volume (MPV), complete blood count, and lipid profile were tested.

Results: Upon completion of treatment, a statistically significant improvement was observed in the mean values of all assessed parameters.

Conclusions: HBOT was shown to have beneficial effects on atherosclerosis and glycaemic control in diabetic patients. Further large-scale randomized studies are needed to study the systemic effects of HBOT. **(Pol J Endocrinol 2010; 61 (3): 275–279)**

Key words: *hyperbaric oxygen therapy, diabetes, diabetic foot, atherosclerosis, glycaemic control*

Streszczenie

Wstęp: Celem badania była ocena wpływu leczenia tlenem w komorze hiperbarycznej (HBOT, *hyperbaric oxygen therapy*) na kontrolę glikemii, czynniki ryzyka miażdżycy, wskaźniki zapalenia oraz inne kliniczne i laboratoryjne parametry u chorych z owrzodzeniem w przebiegu zespołu stopy cukrzycowej poddanych systemowej HBOT.

Materiał i metody: Do badania włączono 28 chorych z owrzodzeniem stopy 2–4 stopnia według skali Wagnera. Wszyscy chorzy odbyli 30 sesji terapii 100-procentowym tlenem przy ciśnieniu 2,4 ATA przez około 105 minut, 5 razy w tygodniu. Zmierzono następujące parametry: glikemię na czczo, odsetek HbA_{1c}, wskaźnik insulinooporności HOMA-IR, stężenie wysokoczułego białka C-reaktywnego (hs-CRP, *high sensitivity C-reactive protein*), stężenie kwasu moczowego, średnią objętość płytek krwi, a ponadto zbadano morfologię krwi i profil lipidowy.

Wyniki: Po zakończeniu terapii stwierdzono istotną poprawę średnich wartości wszystkich badanych parametrów.

Wnioski: Wykazano, że HBOT wpływa korzystnie na czynniki ryzyka miażdżycy i kontrolę glikemii u chorych na cukrzycę. Potrzebne są dalsze, prowadzone na szeroką skalę badania z randomizacją, aby ocenić ogólnoustrojowe efekty HBOT.

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Słowa kluczowe: *leczenie tlenem hiperbarycznym, cukrzyca, stopa cukrzycowa, miażdżyca, kontrola glikemii*

Introduction

Atherosclerotic complications represent the most significant cause of morbidity and mortality in diabetic patients. According to a multinational study by the World Health Organization (WHO), cardiovascular disease is the leading cause of death among diabetic patients, accounting for 44% and 52% of deaths in patients with types 1 and 2 diabetes mellitus, respectively [1]. In long-term epidemiologic studies, the risk of coronary

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heart disease, stroke, or peripheral arterial disease was 2–3-times higher in diabetic patients than in patients without diabetes [2–5].

Poor glycaemic control not only predicts an increased risk of microvascular events, but is also an important risk factor for macrovascular complications, such as cardiac or cerebrovascular events, in diabetic patients [6, 7]. Large and functionally active platelets are also known to contribute to thrombosis and atherosclerosis. The mean platelet volume (MPV) has been shown to increase after myocardial infarction [8] and in patients with diabetes [9]. In addition, the inflammation marker, C-reactive protein, and insulin resistance are emerging as independent risk factors of cardiovascular disease in several studies [10, 11].

Hyperbaric oxygen therapy (HBOT) is a well-known treatment for diabetic foot ulcerations [12, 13]. The beneficial effects of HBOT have been proposed for a variety of conditions. Recently, HBOT was observed to reduce the progression and accelerate the regression of atherosclerosis in animal models [14, 15].

The aim of this study was to investigate the effect of HBOT on glycaemic control, atherosclerosis, inflammatory markers, and other clinical and laboratory parameters in patients undergoing systemic HBOT for diabetic foot ulcerations.

Material and methods

Twenty-eight diabetic patients (11 women and 17 men) scheduled to undergo HBOT due to diabetic foot ulcerations were included in this study. The inclusion criteria were as follows: 1) diagnosis of type 2 diabetes for at least 5 years, 2) Wagner scale 2–4 diabetic foot ulceration, 3) no contraindication against receiving HBOT, and 4) prior written consent. HBOT was applied as 1 session per day, 5 times a week, over a 6 week period, totalling 30 sessions. All patients were treated only with insulin. None of the patients had received antihypertensive or antilipidaemic therapy during the study period. Each session consisted of 105 minutes of 100% oxygen at 2.4x absolute atmosphere (ATA) pressure. Standard wound care was applied in addition to HBOT. The study plan was reviewed and approved by our institutional review committee, and informed consent was obtained from all patients

The demographic properties and medical history of all patients were recorded on the first visit, including gender, weight, height, body mass index (BMI), duration of diabetes, and current diabetes treatment regimen. Fasting blood glucose (FBG), MPV, and high sensitivity C-reactive protein (hs-CRP) levels were measured after session numbers 10, 20, and 30 of HBOT. Haemoglobin A_{1c} (HbA_{1c}), homeostasis model measurement-insulin resistance (HOMA-IR), uric acid, complete blood count, (white blood cells [WBC], platelets, haemoglobin, and hematocrit), and lipid profile (high density lipoprotein [HDL], low density lipoprotein [LDL], and triglycerides) were measured.

Statistical methods

SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numerical variables were reported using descriptive statistics (mean ± standard deviation); categorical variables were reported as percentages. Normal distribution was verified. Fasting blood glucose, MPV, and hs-CRP variables were analyzed using variance analysis for multiple measurements, and the LSD test was used for comparisons. The paired samples test was used for comparisons of dependent groups. The Student-t test was used for gender comparisons. The Pearson correlation test was used for correlation analysis. The statistical significance level was set at $p < 0.05$.

Results

Twenty-eight patients between the ages of 40 and 54 years with diabetic foot (11 women and 17 men) were included in this study. All patients were receiving insulin treatment for type 2 diabetes. The mean duration of diabetes history was 9.9 ± 2.2 years. The mean BMI was 26.8 ± 2.0 kg/m^2. There was no significant difference between the genders regarding the duration of diabetes or BMI. According to the Wagner classification, 53.6% and 46.4% of the foot ulceration cases were grade 3 and 4, respectively.

Glycaemic control was assessed by FBG and HbA_{1c}. HOMA-IR was calculated to determine the degree of insulin resistance. Inflammation process was assessed by hs-CRP and WBC counts. The lipid profile, uric acid levels, platelet count, and MPV were measured as atherosclerotic risk markers.

At baseline, the mean FBG was 152 ± 37 mg/dL and the HbA_{1c} was 9.1 ± 1.3%. The mean insulin resistance was 7.9 ± 1.2. The complete blood count revealed mean values of 13.8 ± 1.3 g/dL for haemoglobin, 35.3 ± 1.1 % for hematocrit, 11.2 ± 3.0 x $10^3/\mu$L for WBC, and 371 ± ± 91 × $10^3/\mu$L for platelets. The mean MPV value was 13 ± 1.6 fL. The lipid profile was as follows: HDL, 35 ± ± 2 mg/dL; LDL, 122 ± 17 mg/dL; and triglycerides, 146 ± 33 mg/dL. The mean hs-CRP was 4.4 ± 1.3 mg/dL.

Between baseline and the completion of 30 sessions of HBOT, a statistically significant improvement was observed for the mean values of all assessed parameters (Table I). For a more detailed follow-up of the beneficial effects of HBOT, FBG, hs-CRP, and MPV, data were collected at baseline and after sessions 10, 20, and

Table I. *Baseline and post-hyperbaric oxygen treatment comparisons of glycaemic control, inflammation markers and atherosclerosis risk factors*

Tabela I. *Porównanie kontroli glikemii, wskaźników zapalenia i czynników ryzyka miażdżycy przed i po leczeniu tlenem w komorze hiperbarycznej*

	Baseline (mean ± SD)	After HBO (mean ± SD)	P value
Glycaemic control and insulin resistance			
FBG [mg/dL]	152 ± 37	113 ± 14	< 0.001
HbA_{1c} (%)	9.1 ± 1.3	8.0 ± 1.1	< 0.001
HOMA-IR	7.9 ± 1.2	6.3 ± 1.0	< 0.001
Inflammation and atherosclerosis			
hs-CRP [mg/dL]	4.4 ± 1.3	1.6 ± 0.7	< 0.001
WBC [× $10^3/\mu$L]	11.2 ± 3.0	7.7 ± 2.1	< 0.001
MPV [fL]	13.0 ± 1.6	8.3 ± 1.2	< 0.001
Platelets [× $10^3/\mu$L]	371 ± 91	275 ± 71	< 0.001
HDL [mg/dL]	35 ± 2	38 ± 8	< 0.001
LDL [mg/dL]	122 ± 17	104 ± 20	< 0.001
Uric acid [mg/dL]	9.6 ± 1.3	7.2 ± 1.1	< 0.001

HBO — hyperbaric oxygen; FBG — fasting blood glucose; HbA_{1c} — haemoglobin A_{1c}; HOMA-IR — homeostasis model measurement- insulin resistance; hs-CRP — high sensitivity C-reactive protein; WBC — white blood cells; MPV — mean platelet volume; HDL — high density lipoprotein; LDL — low density lipoprotein

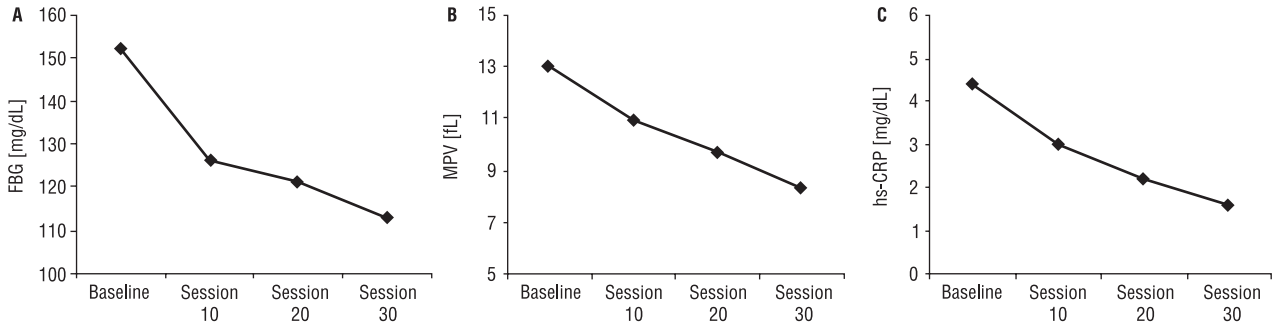

Figure 1. *Gradual decrease in mean values of glycaemic control (**A**), atherosclerosis (**B**), and inflammation (**C**) markers after sessions 10, 20, and 30 of hyperbaric oxygen treatment. P < 0.001 between all data points. FBG — fasting blood glucose; MPV — mean platelet volume; hs-CRP — high sensitivity C-reactive protein*

Rycian 1. *Stopniowe zmniejszenie wartości wskaźników kontroli glikemii (**A**), miażdżycy (**B**) i zapalenia (**C**) po 10, 20 i 30 sesji tlenoterapii w komorze hiperbarycznej. Wartość p < 0,001 dla wszystkich porównań. FBG — glikemia na czczo; MPV — średnia objętość płytek krwi; hs-CRP — wysokoczułe białko C-reaktywne*

30 of HBOT as representative markers of glycaemic control, inflammation, and atherosclerosis, respectively (Fig. 1). Between baseline and the completion of HBOT, the FBG decreased by 24.7% (± 13.7%) in 27 out of 28 patients. The observed decrease was significant between each pair of measurements (baseline-to-session 10, $p < 0.001$; sessions 10-to-20, $p = 0.026$; and sessions 20-to-30, $p = 0.005$). Similarly, the hs-CRP and MPV values decreased significantly at each measurement ($p < 0.001$ for both [pairwise comparisons]). At baseline, the MPV was above the normal range (7.3–10.1) for all patients, while upon completion of treatment, the MPV dropped to the normal range in 26 out of 28 patients.

Discussion

In this study we have shown that glycaemic control, atherosclerosis, and inflammation markers were significantly improved in patients undergoing HBOT for diabetic foot ulcerations.

This is the first report in the English literature regarding the effects of HBOT on atherosclerosis in humans. A few reports in other languages involving diabetic patients with ischaemic extremities due to atherosclerosis were cited in a review by Al-Waili et al. [16]. The findings reported in these studies appear to be in correlation with the findings reported in this study [17––19]. In terms of the effects of HBOT on glycaemic control, the decrease in blood glucose levels that we observed in this study (24.7%) was consistent with the reduction in blood glucose levels (23%) reported in a study investigating the effect of HBOT on blood pressure, heart rate, and blood glucose [20].

Hyperbaric oxygen therapy involves the administration of 100% oxygen under high pressure conditions. HBOT is used as an adjuvant therapy for a variety of conditions, including chronic wounds, infections, oedema, stroke, tissue transplantation, anaemia, and cancer management [16, 21]. HBOT is known to improve antibacterial defences, increase blood flow, reduce oedema, maintain tissue oxygenation, stimulate fibroblast and collagen production, and prevent lipid peroxidation [22]. The exact mechanism by which HBOT leads to regression of atherosclerosis and improves glycaemic control is unclear.

In animal models HBOT has been shown to attenuate atherosclerosis in cholesterol-fed New Zealand white rabbits and apoE knockout mice and to have a powerful effect on the redox state of relevant tissues [14, 15]. In addition, HBOT was found to attenuate proinflammatory and immune responses to oxidized LDL in apoE knockout mice [23].

A recent hypothesis postulated that HBO might exert its beneficial effects in diabetic patients by restoration of vascular reactivity through modulating production of vasoconstrictors and vasodilators and increasing vessel sensitivity to these factors [24]. In support of this hypothesis, HBO was found to alter the expression of cyclooxygenase 2 (COX-2) and endothelial nitric oxide synthase (eNOS) in experimental systems [25, 26], and local nitric oxide (NO) levels were shown to increase in diabetic foot patients responsive to HBO treatment [27]. Since all the risk factors for atherosclerosis in diabetics are highly interrelated, the potential effect of HBO on endothelial function per se could be sufficient to explain the significant decrease that we have observed in atherosclerotic, glycaemic, and inflammation markers. Indeed, endothelial dysfunction is closely associated with the development of diabetic retinopathy, nephropathy, and atherosclerosis in both insulin-dependent and non-insulin dependent diabetes [28]. In addition, MPV, which recently emerged as a risk factor for atherosclerosis, is associated with glycaemic control in diabetic patients [29]. Moreover, endothelial dysfunction is intimately related to insulin resistance so that improved tissue sensitivity to insulin improves vascular endothelial function and vice versa [30].

Conclusions

The major limitation of this study was the absence of a randomized control group with diabetic foot whose ailments could be treated using standard wound care instead of HBO treatment. Also, we did not follow up the patients for extended periods to determine the durability of the beneficial effects of HBO treatment. However, based on this preliminary data, we believe that a larger randomized controlled clinical trial is required to study the effects of HBO treatment on glycaemic control and atherosclerosis.

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