Effects of hyperbaric oxygen on blood glucose levels in patients with diabetes mellitus, stroke or traumatic brain injury and healthy volunteers: a prospective, crossover, controlled trial

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Abstract

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Introduction: A decrease in blood glucose levels (BGL) during hyperbaric oxygen treatment (HBOT) is a well-recognised phenomenon, but studies of this are limited and inconclusive. This study evaluated the effect of HBOT on BGL in patients with diabetes mellitus (DM), traumatic brain injury (TBI) or stroke and healthy volunteers in a prospective, open, controlled trial.

Methods: Thirty-nine participants were enrolled and evaluated twice: once during HBOT (90 minutes at 203 kPa), and once during a control session on normobaric air. Sessions were held up to two weeks apart and participants were instructed to eat the same diet. BGl was measured before, during and at the completion of each session.

Results: For the whole study group, there was a small but statistically significant decrease in BGL in both the HBOT (7.27 ± 3.66 mmol L^{-1} before to 6.71 ± 3.88 mmol L^{-1} after, $P = 0.037$) and control (air) sessions (7.43 ± 3.49 mmol L^{-1} before to 6.71 ± 3.77 mmol L^{-1} after, $P = 0.004$). This fall did not differ between the two conditions ($P = 0.59$). Examining the three groups separately, BGL fell in all three subgroups, but this fall was only statistically significant for the air session in the diabetic group. There were no statistically significant differences in the BGL reduction when HBOT was compared to normobaric air in any of the three subgroups.

Conclusions: BGL may decrease during HBOT and accordingly it should be monitored before entering the chamber. However, this decrease in BGL should probably not be attributed to the hyperbaric environment per se.

Key words

Hyperbaric oxygen, blood glucose, prospective controlled trial, blood pressure, heart rate

Introduction

Hyperbaric oxygen treatment (HBOT) is an established treatment for a variety of acute and elective medical conditions and usually involves exposure to 100% oxygen at a pressure of 152–284 kiloPascal (kPa).[1–3] The main purpose of HBOT is to facilitate the repair of damaged hypoxic tissues. Accordingly, there is an increasing use of HBOT for relatively high-risk groups of patients, such as those with diabetes mellitus (DM) and its related complications or patients with neurological deficits resulting from brain injury (post radiation, stroke or traumatic brain injury, TBI). These populations are relatively vulnerable and more prone to be affected by changes in their blood glucose level (BGL) as well as in haemodynamic parameters.

In a study comparing BGL in five diabetic patients with five healthy volunteers treated with HBOT at 203 kPa for 90 minutes, a decrease in BGL was seen in the diabetic group but not among volunteers.[4] Another study investigated the influence of HBOT on patients with and without DM and hypertension (HTN).[5] Patients were exposed to 100% O_2 at 203–254 kPa in a monoplace chamber for 60–90 minutes. BGL decreased after treatment in the DM group. In a controlled study of 27 patients with DM, 13 insulin-dependent, eight on oral hypoglycaemics and six controlled on diet alone, a decrease in BGL was found after HBOT.[6] This was most evident in the insulin-dependent patients. A comparison was also made with normobaric air for five of the patients, with no similar decrease of BGL.[6] The major limitation for these clinical studies was the lack of a control group or a relatively small study group.

Therefore, the effect of HBOT on BGL in patients with DM and volunteers is inconclusive and the effect in patients with neurological deficits, who are more prone to convulsions, is unknown. The primary objective of the current study was to evaluate the effect of HBOT on BGL in patients with DM, brain injury due to stroke or TBI and healthy volunteers in a prospective, crossover, controlled trial.

Methods

STUDY POPULATION

Subjects were recruited from patients treated in the Hyperbaric Institute of Assaf Harofeh Medical Center, Israel. Participants were patients with Type 2 DM, insulin- (IDDM) and non-insulin-dependent (NIDDM), treated for non-healing wounds, or patients with TBI or stroke treated for neurological deficit. Healthy volunteers were recruited as well. Exclusion criteria were: patients who refused or could not sign an informed consent; recent ear surgery or ear problems; claustrophobia; chest X-ray pathology;

Table 1
Patient characteristics; mean (standard deviation); BMI – body mass index

	All subjects	Healthy volunteers	Diabetic patients	Neurological patients
	(*n* = 39)	(*n* = 13)	(*n* = 13)	(*n* = 13)
Age (years)	51 (17)	32 (7)	74 (7)	57 (14)
Sex (M/F)	16/23	5/8	3/10	8/5
Smokers	8	1	5	2
BMI (kg m^{-2})	26 (6)	22 (3)	31 (7)	25 (4)
Hypertension	12	0	8	4

chronic lung disease, sinusitis or respiratory tract infection and pregnancy. The protocol was approved by the Assaf Harofeh Medical Center Helsinki Committee for Human Experiments, approval number 218/10.

STUDY DESIGN

Patients were recruited after at least 10 HBOT sessions in order to reduce confounders such as anxiety, and to allow adjustment to the chamber environment. At baseline, all patients underwent a physical examination and a chest X-ray. Patients were evaluated in two separate sessions. In the first session, participants underwent full HBOT for 90 minutes at 203 kPa. On a different day, with a time interval of between one and 14 days, the control session, with room air at sea level pressure, took place in the hyperbaric unit and lasted for the same duration as the HBOT exposure. The two sessions were held at the same time of day. In order to disrupt patient care as little as possible and to enhance compliance with the study, all patients had HBOT prior to undertaking the control session. Participants were instructed to eat the same meal of 300 calories (including 50 grams of carbohydrates) two hours prior to each of the two sessions and to continue all medications including oral hypoglycaemics and insulin as usual. Whole blood was drawn for the measurements of BGL before, in the middle of and at the end of each session. Glucose was measured by an enzymatic colorimetric assay with a Roche/Hitachi 912 analyzer. Arterial blood pressure, heart rate and oral temperature were monitored during the study.

STATISTICAL ANALYSIS

BGL is expressed as mean ± standard deviation (mmol L^{-1}) and within-subject changes were compared using Student's paired *t*-tests. The two sessions (HBOT and air control) were compared by repeated measures ANOVA test. Non-parametric data are expressed as absolute numbers. The before and after data are presented.

Results

Forty-two participants signed informed consent; three withdrew consent prior to the initiation of the study. Thirty-nine participants were included in the final analysis, 13 patients with DM, 13 patients with stroke or TBI and 13 healthy volunteers. Demographic and clinical characteristics are presented in Table 1. In the diabetic group eight were controlled with oral hypoglycaemics and five with insulin. The mean interval between the HBOT and the control sessions was 6 days (range: 1–14 days). There were no differences in the baseline physiologic parameters measured at the beginning of the control and HBOT sessions.

BLOOD GLUCOSE LEVELS

For the whole study cohort, there was a small but statistically significant decrease in BGL in both the HBOT (7.27 ± 3.66 mmol L^{-1} before to 6.71 ± 3.88 mmol L^{-1} after, $P = 0.037$) and control (room air) sessions (7.43 ± 3.49 mmol L^{-1} before to 6.71 ± 3.77 mmol L^{-1} after, $P = 0.004$), but this fall did not differ between the two sessions ($P = 0.59$). Examining the three groups separately, BGL fell from baseline in all three groups, but this fall was only statistically significant during the control (room air) session in patients with DM (Table 2). There were no statistically significant differences in the BGL reduction when HBOT was compared to the control air session in each of the three study subgroups.

The insulin-dependent patients had no change in BGL either during HBOT (13.0 ± 4.0 mmol L^{-1} before to 13.2 ± 5.7 mmol L^{-1}after, $P = 0.88$) or during the control session (13.15 ± 2.7 before to 13.2 ± 4.7 mmol L^{-1} after, $P = 0.96$). The NIDDM patients had a significant decrease in their BGL during both sessions; from 9.2 ± 3.0 mmol L^{-1} to 7.3 ± 3.0 mmol L^{-1} ($P = 0.047$) during HBOT and from 9.9 ± 2.9 to 7.8 ± 3.4 mmol L^{-1} ($P = 0.004$) during the control session.

Since there were clearly no significant differences between the groups, the study was terminated after a total of 39 patients had completed the protocol. Post-hoc power analysis gave 83.8% power, alpha = 0.2, for detection of a 30% difference in BGL between the groups for $n = 13$ in each group.

Discussion

Many patients treated electively with HBOT suffer from DM or neurological deficits due to stroke or TBI. These populations are relatively susceptible to fluctuations in BGL. It is well known that diabetic patients are at increased risk for hypoglycaemic events during HBOT. However, there might be other factors unrelated to the hyperbaric environment responsible for the fluctuation in BGL, such

Table 2
Effect of HBOT on blood glucose levels and comparison to control session on room air; mean (standard deviation); HBOT – hyperbaric oxygen treatment

Group	Session	Baseline		End of session		*P* value
All subjects	Room air	7.43	(3.49)	6.71	(3.77)	0.004
	HBOT	7.27	(3.66)	6.71	(3.88)	0.037
Diabetes group	Room air	11.15	(3.38)	9.82	(5.0)	0.036
	HBOT	10.71	(4.05)	9.6	(5.32)	0.15
Neurologic group	Room air	6.38	(1.83)	5.7	(1.6)	0.08
	HBOT	6.38	(2.21)	6.0	(2.1)	0.1
Healthy group	Room air	4.71	(0.5)	4.5	(0.4)	0.37
	HBOT	4.71	(0.38)	4.55	(0.27)	0.25

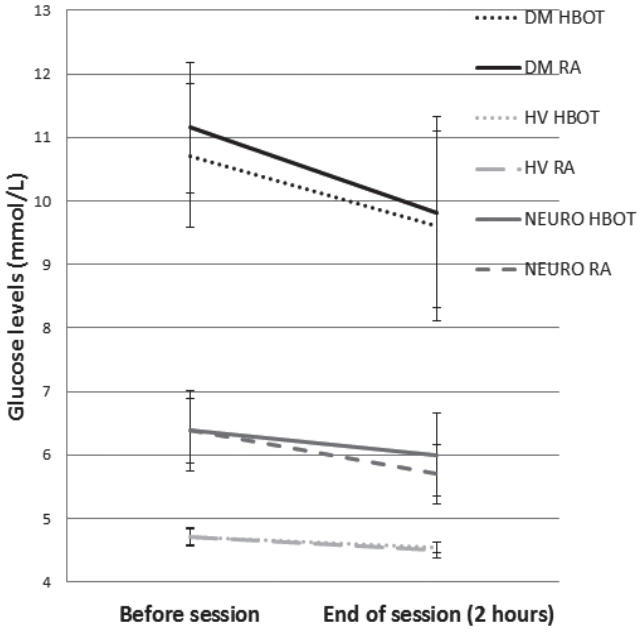
as diet (for example, fasting during transportation and waiting time), maladjustment of glucose lowering drugs, decrease in catecholamine levels and changes in BGL and insulin requirements during infectious or other intercurrent diseases.[7]

Previous studies in humans, summarised earlier, were relatively small, uncontrolled or included mainly insulin-dependent diabetics.[4–6] For example, the study by Ekanayake et al did show a decrease in BGL compared with a control session but it included a relatively small cohort of patients, mostly insulin-dependent diabetics.[4] In the study by Trytko et al, although 27 patients were studied during a total of 237 sessions, a control session using room air was held in only five of them.[6] They found that a decrease in BGL of more than 2 mmol L^{-1} was associated with HBOT. Since there was a wide variability in BGL measurements, it is not possible to know which patient on which session had a significant decrease in BGL. Trytko's study included 14 non-insulin-dependent diabetics (six of them controlled with diet alone) and 13 were insulin-dependent; the more prominent decrease in BGL occurred in the insulin-dependent patients. In our study, in the patients with DM, there was a decrease in BGL only in NIDDM patients but this decrease was not related to the hyperbaric environment.

This study aimed to evaluate whether the change in BGL is related to the hyperbaric oxygen environment per se. The question was investigated in a prospective, crossover, controlled manner. The study cohort was chosen to be representative of the typical population of patients treated electively with HBOT. Type II DM patients suffering from non-healing ulcers represent one of the largest populations treated by HBOT, whilst TBI and post-stroke patients are a relatively new group of patients being studied and treated with HBOT. Recently, HBOT has been shown to induce neuroplasticity and improve brain metabolism in post-stroke patients.[8] Stroke patients are more prone to seizures, a tendency that rises with stroke severity.[9] Brain metabolism is highly glucose-dependent and, under normal conditions, the brain utilizes 25–30% of the overall body glucose consumption. As demonstrated in rat models, HBOT increases brain glucose utilization and accordingly increases its susceptibility to any reduction of blood glucose concentration.[10,11] HBOT may also increase insulin secretion in diabetic patients, in addition to improving insulin resistance.[12,13] Currently there is no literature concerning the effect of HBOT on blood glucose in TBI or post-stroke patients. However, since brain injury, in addition to change in glucose utilization, can lead to autonomic and/or endocrine changes, it is important to explore whether this group would have a different response to HBOT. Another important reason for including this group of patients is their relatively high risk for seizures. Since hypoglycaemia by itself can cause seizures and patients with brain injury are more prone to seizures, it is important to investigate this issue.

The results indicate that the decrease in BGL was similar during HBOT and during a normobaric air session in all three subgroups. This suggests that food deprivation during the treatment and the control sessions, and not the hyperbaric environment, is probably the primary cause for the decrease in BGL. In the diabetic subgroup, there was no significant decrease in BGL during HBOT, which is also true for the subgroup of insulin-dependent patients. Unlike previous studies, the BGL at the beginning of each session was two hours postprandial. This can serve as a possible explanation for the absence of hypoglycaemic episodes. Since each patient had the same meal with the same drug regimen, and since the evaluation sessions were held at the same time of the day, it can be assumed that the hyperbaric effect on BGL was isolated. Furthermore, the same effect on BGL was apparent among healthy volunteers and post-stroke and TBI patients. Another possible explanation for the lack of difference may be a study effect: anxiety could have increased the counter-regulatory hormones and possibly diminished the expected decrease of glucose levels. Additional large-scale studies are needed regarding specific subgroups of patients treated with HBOT, including patients with IDDM, children, those with myocardial infarction, etc. Since hyperbaric medicine is still a developing field in terms of indications for treatment, and co-morbidities and poly-pharmacy are integral aspects of our daily practice, it is important to study the groups of patients most vulnerable

Figure 1
Blood glucose before and after hyperbaric oxygen treatment (HBOT) or normobaric air (RA); mean (SEM) shown in three groups of patients: diabetics (DM), neurological injury (neuro) and healthy volunteers (HV)



to the physiological and biological effects of HBOT.

Conclusions

BGL may decrease during HBOT and accordingly it should be monitored before entering the chamber. However, this decrease in BGL should not necessarily be attributed to the hyperbaric environment per se.

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