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EFFECT OF HYPERBARIC OXYGEN THERAPY ON FASTING BLOOD GLUCOSE AND INSULIN RESISTANCE

HİPERBARİK OKSİJEN TEDAVİSİNİN AÇLIK KAN ŞEKERİ VE İNSÜLİN DİRENCİ ÜZERİNDEKİ ETKİSİ

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ABSTRACT

Objective: The subject of this study was to investigate the effect of hyperbaric oxygen (HBO2) therapy on fasting blood glucose levels and insulin resistance. The study investigated whether HBO2 therapy is effective in reducing peripheral insulin resistance in patients with and without Diabetes Mellitus (DM).

Material and Methods: The study included 27 patients with and without DM who received hyperbaric oxygen therapy at a pressure of 2.4 ATA for 120 min per session with 5 min breaks in between three 25-minute O2 periods, one session per day, five days a week, for 20 sessions. Patients were divided into two groups: those without DM and those with DM. Fifteen patients did not have DM while 12 patients had DM Type 2. Glucose, C-Reactive protein (CRP), HbA1c, C-peptide, and Homeostasis Model Assessment Insulin Resistance (HOMA-IR) values were compared at the beginning and end of treatment.

Results: In repeated measurements, there was a statistically significant decrease in the mean fasting blood glucose levels in patients with DM. Patients without DM also showed a reduction in the mean fasting blood glucose levels in repeated measurements, but this decrease was not statistically significant. There was a statistically significant decrease in the mean C-pep level in repeated measurements in patients with DM and the mean insulin level in repeated measurements in patients without DM. There was a statistically significant decrease in the HOMA-IR values calculated in repeated measurements in patients with and without DM.

ÖZET

Amaç: Bu çalışmanın konusu hiperbarik oksijen (HBO2) tedavisinin açlık kan şekeri düzeyleri ve insülin direnci üzerindeki etkisidir. Çalışmanın amacı, HBO2 tedavisinin hem Diabetes Mellitus-lu (DM) hem de DM olmayan hastalarda periferik insülin direncini azaltmada etkili olup olmadığını araştırmaktır.

Gereç ve Yöntem: Diyabeti olan ve olmayan 27 hastaya haftada beş gün, günde bir seans, 2,4 ATA basınçta, her biri aralarda 5 dakikalık hava molası verilen üç 25 dakikalık oksijen periyodu içeren 120 dakikalık 20 seans hiperbarik oksijen tedavisi uygulanmıştır. Hastalar DM olmayanlar ve DM olanlar olmak üzere iki gruba ayrılmıştır. Hastaların 15'i diyabeti olmayan, 12'si ise tip 2 DM'liydi. Tedavinin başında ve sonunda glukoz, C-Reaktif protein (CRP), HbA1c, C-peptid (C-pep) ve Model Assessment Insulin Resistance (HOMA-IR) değerleri karşılaştırıldı.

Bulgular: Tekrarlanan ölçümlerde, diyabetli hastalarda ortalama açlık kan şekeri seviyelerinde istatistiksel olarak anlamlı bir düşüş görülmüştür. DM olmayan hastalarda da tekrarlanan ölçümlerde ortalama açlık kan şekeri seviyelerinde azalma görüldü, ancak bu azalma istatistiksel olarak anlamlı değildi. DM'li hastalarda tekrarlanan ölçümlerde ortalama C-pep seviyesinde ve DM olmayan hastalarda tekrarlanan ölçümlerde ortalama insülin seviyesinde istatistiksel olarak anlamlı bir düşüş olmuştur. DM olan ve olmayan hastalarda tekrarlanan ölçümlerde hesaplanan HOMA-IR değerlerinde istatistiksel olarak anlamlı bir düşüş vardı.

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Conclusion: In our study, insulin resistance decreased in patients receiving HBO2 therapy. The fact that this decrease was also shown in patients without DM strengthens the idea that this decrease is related to HBO2 therapy. Further research is needed to gain a more comprehensive understanding of the therapeutic potential of HBO2 therapy in managing insulin resistance.

Keywords: Blood sugar level, diabetes mellitus, hyperbaric oxygen therapy, insulin resistance

Sonuç: Çalışmamızda HBO2 tedavisi alan hastalarda insülin direnci azalmıştır. Bu azalmanın DM olmayan hastalarda da gösterilmiş olması, bu azalmanın HBO2 tedavisi ile ilişkili olduğu fikrini güçlendirmektedir. HBO2 tedavisinin insülin direncini yönetmedeki terapötik potansiyelinin daha kapsamlı bir şekilde anlaşılması için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Kan şekeri, diyabet, hiperbarik oksijen tedavisi, insülin direnci

INTRODUCTION

Hyperbaric Oxygen (HBO2) therapy is a medical treatment that involves the intermittent inhalation of 100% O2 at a pressure higher than that of the atmosphere in a closed system (1). HBO2 therapy has been a preferred treatment for decompression sickness and management of air embolism. In addition, studies have shown the benefit of HBO2 therapy in several medical conditions, including non-healing wounds, radiotherapy-induced tissue damage, and necrotising tissue infections (2-4).

Many studies have shown that HBO2 therapy causes hypoglycaemia in patients with Diabetes Mellitus (DM), and a systematic review supported this view (5). Therefore, all HBO2 therapy facilities have protocols to monitor the plasma glucose levels of patients with DM and to provide an oral replacement for those with low levels. HBO2 therapy may increase insulin sensitivity and lead to hypoglycaemia in patients with DM. Although research in this area is ongoing, there is insufficient evidence to suggest that HBO2 therapy may affect insulin sensitivity in individuals without DM.

Hypoxia has been associated with insulin resistance in white adipose tissue and skeletal muscle (6, 7). In two other studies of individuals with obesity, insulin resistance seems to be associated with hypoxia, inflammation, and oxidative stress in white adipose tissue, which are also observed in the pathogenesis of type 2 DM (8 ,9). Considering HBO2 therapy's potential to reduce inflammation and enhance antioxidant defence systems, it may be beneficial in treating insulin resistance through these mechanisms (10).

This study investigated whether peripheral insulin resistance, proposed as a mechanism explaining the hypoglycaemic effect of HBO2 treatment, is reduced in patients with and without DM.

MATERIAL AND METHODS

This study was approved by the İstanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 24.08.2012, No: 346). Patients with and without DM who received 20 sessions of HBO2 therapy at a pressure of 2.4 ATA, each session lasting 120 minutes with 5-minute air breaks in between three 25-minute O2 periods, one session per day, and five days a week were included in the study. Patients under 18 years of age, over 80 years of age, receiving systemic steroid therapy, having a known diagnosis of hyperthyroidism, acromegaly, Cushing's syndrome, pheochromocytoma, or having undergone HBO2 therapy in the six months prior were excluded from the study. HBO2 therapy was administered in a multiplace chamber (Hypertech® Zyron12, Turkey). This chamber can accommodate up to 12 patients and one inside attendant in the main chamber. The study was conducted on patients undergoing HBO2 therapy for various conditions. The patients were divided into two groups, with and without DM, to evaluate the metabolic effects of HBO2 therapy separately within each group rather than to compare the two groups. All patients with DM had type 2 diabetes and were on insulin treatment. During the study, the insulin dose was adjusted for patients when necessary. Patients who interrupted the treatment for two days or more were excluded from the study. Informed consent was obtained from all patients and their relatives before participation in the study.

A standardised data recording form was created before the study. In this form, demographic information about the age, gender, height, and body weight of all patients was recorded, and height and weight indices were calculated. The results obtained from the laboratory measurements of the study were also recorded on this form. In our study, the C-Reactive protein (CRP) level was set as an indicator of infection stress since it's an acute phase reactant and was analysed (11).

Blood was collected from the antecubital vein of all patients who participated in the study after fasting for at least 8 h before starting HBO2 therapy (e.g., Fasting blood glucose (FBG) 1, Insulin 1, etc.), after the tenth session (e.g., FBG 2, Insulin 2, etc.) and after the 20th session (e.g., FBG 3, Insulin 3, etc.). The Biochemistry Laboratory analysed the following blood values within 1 h of collection;

- Fasting blood glucose, insulin, HbA1c, and CRP levels in patients without DM,
- Plasma glucose, C-peptide (C-pep), HbA1c, and CRP levels in patients with DM.

The Homeostatic Model assessment (HOMA) has become a widely used and reliable clinical and epidemiological tool (12, 13). Although the hyperinsulinaemic-euglycaemic glucose clamp test is considered the gold standard for measuring insulin resistance (IR), its clinical applicability is limited because it is labour-intensive and costly (14, 15). HOMA-IR is calculated using plasma glucose and insulin concentrations and is easy to perform, safe, less invasive, and less expensive (16). Its results correlate well with the euglycemic clamp test (17, 18). Because of these strengths, we calculated and applied HOMA-IR to estimate IR in our participants. HOMA version 2 software developed by the Diabetes Research Unit of Oxford University was used to calculate HOMA (19).

Statistical analysis

The measurements taken at baseline and after sessions 10 and 20, were analysed by comparing the repeated measurements and their differences. The data obtained from the study were transferred to the SPSS 22.0 (IBM SPSS Corp., Armonk, NY, USA) statistical programme. Values were obtained as mean and standard deviation. In comparing the groups within each other, Friedman's test, which allows non-parametric examination in matched groups in repeated measurements, was used because of the limited number of patients, regardless of the parametric values. "Wilcoxon Test," a non-parametric test method in paired groups, was used to determine the differences between the groups. The difference was considered statistically significant if the p-value was less than 0.05.

RESULTS

The study initially involved 37 patients. However, five patients had to be excluded from the study because they could not continue HBO2 therapy. In addition, two patients could not comply with the treatment, one patient developed claustrophobia, one patient passed away during the study, and one patient expressed a desire to leave the study. Eventually, the study included 27 patients, out of which 15 were without DM and 12 were with DM. The diagnoses for 10 patients with DM were diabetic foot, while one patient had chronic osteomyelitis and another had peripheral vascular disease. Among the patients without DM, 5 had avascular necrosis, 5 had chronic osteomyelitis, 3 had venous ulcers, 1 had Buerger's disease, and 1 had radiation cystitis. Of the patients without DM, 8 were inpatients and 7 were outpatients; of the patients with DM, 10 were inpatients and 2 were outpatients. None of the patients participating in the study had severe renal failure or cirrhosis.

Among the patients with DM, three were female and nine were male. The mean age of patients without DM was 38.67±18.3 years, and the mean BMI was 26.8±4.84 kg/m^2; the mean age of people with DM was 61.42±13 years, and the mean BMI was 25.87±3.95 kg/m^2. The demographic data of the patients included in the study are shown in Table 1.

Table 1: Demographic data of the participants

	n	%	Mean	SD	Min-max
Patients with DM	12				
Age (year)			61.42	13.1	44-79
Gender					
Male	9	75.0			
Female	3	25.0			
Height (cm)			166	8.17	157-177
Weight (kg)			71.2	10.4	53-88
BMI (kg/m^2)			25.87	3.95	22.0-33.7
Normal	7	58			
Overweight-obese	5	42			
Patients without DM	15				
Age (year)			38.67	18.3	
Gender					
Male	10	66.6			
Female	5	33.3			
Height (cm)			174	8.7	155-187
Weight (kg)			80.3	11.9	64-100
BMI (kg/m^2)			26.8	4.8	20.7-36.9
Normal	5	33.3			
Overweight-obese	10	66.6			

DM: Diabetes Mellitus, BMI: Body mass index, Normal: BMI=18.5-24.9, Overweight-obese: BMI: ≥25

The data obtained from multiple measurements are presented in Table 2. The table shows the results measured before the HBO2 therapy session, after the 10th HBO2 therapy session, and after the 20th HBO2 therapy session. The statistical significance levels of the data obtained from the study groups' repeated measurements are presented in Table 3. The statistical significance levels of the data obtained in each measurement step for the study groups are presented in Table 4.

In the patients without DM, a decrease was found in mean fasting blood glucose levels in repeated measurements. However, this decrease was not statistically significant (p=0.458). A statistically significant reduction was found in mean fasting blood glucose repeated measurements in patients with DM (p=0.002) (Table 3).

In patients without DM, a statistically significant decrease was found in HOMA-IR values calculated in repeated measurements (p=0.015) (Table 3). When the measure-

Table 2: Means and standard deviations of patients' measurements

	Patients without DM (n=15)		Patients with DM (n=12)	
Parameters	**Mean**	**SD**	**Mean**	**SD**
FBG 1 (mg/dL)	89.87	6.85	167.5	50.69
FBG 2 (mg/dL)	89.27	8.67	110.25	25.61
FBG 3 (mg/dL)	87.47	8.35	109.91	40.67
Insulin 1 (mIU/L)	11.65	7.17		
Insulin 2 (mIU/L)	10.18	4.39		
Insulin 3 (mIU/L)	8.94	3.91		
C-pep 1 (ng/ml)			2.32	1.63
C-pep 2 (ng/ml)			1.71	1.34
C-pep 3 (ng/ml)			1.57	0.88
HOMA 1	1.5	0.88	2.02	1.37
HOMA 2	1.3	0.54	1.38	1.12
HOMA 3	1.14	0.53	1.21	0.61
CRP 1 (mg/dL)	19.46	26.94	64.44	77.39
CRP 2 (mg/dL)	15.04	25.98	8.59	6.59
CRP 3 (mg/dL)	20.43	39.07	10.04	11.46
HbA1c 1 (%)	5.44	0.31	8.67	1.52
HbA1c 3 (%)	5.3	0.32	7.31	1.03

FBG: Fasting blood glucose, (FBG1: first measurement, FBG2: second measurement, etc.) C-pep: C-peptide, HOMA: The Homeostasis Model assessment, CRP: C-reactive protein, DM: Diabetes Mellitus. Note: Because the insulin level was measured in only one patient in the diabetic group and the C-pep was not measured in the non-diabetic group, neither data was compared. 1. 2 and 3 refers to pre-treatment, 10th session and 20th session measurements respectively

ments were evaluated among themselves, no statistically significant difference was found between the first and second measurement (p=0.145) and between the second and third measurement (p=0.080), while the difference between the first and third measurements was statistically significant (p=0.047) (Table 4).

A statistically significant decrease was found in HOMA-IR values calculated in repeated measurements in patients with DM (p=0.034) (Table 3). When the measurements were evaluated among themselves, the decrease between the first and second measurement (p=0.041) and between the first and third measurement (p=0.041) was statistically significant, while the decrease between the second and third measurement was not statistically sig-

Table 3: Statistical significance levels of comparision of mean levels in repeated measurement

	Patients without DM (p)	Patients with DM (p)
FBG	0.458	**0.002**
Insulin	**0.007**	
C-pep		**0.045**
HOMA	**0.015**	**0.034**
CRP	0.282	**0.002**

FBG: Fasting blood glucose, C-pep: C-peptide, HOMA: The Homeostasis Model assessment, CRP: C-reactive protein, DM: Diabetes Mellitus.

Table 4: Statistical significance levels of comparision of mean levels obtained in each measurement step

Measurement	Patients without DM (p)	Patients with DM (p)
FBG 1-2	0.700	**0.004**
FBG 2-3	0.216	0.722
FBG 1-3	0.248	**0.003**
INS 1-2	0.280	-
INS 2-3	**0.047**	-
INS 1-3	**0.041**	-
C-pep 1-2	-	**0.033**
C-pep 2-3	-	0.878
C-pep 1-3	-	0.063
HOMA 1-2	0.145	**0.041**
HOMA 2-3	0.080	0.593
HOMA 1-3	**0.041**	**0.041**
CRP 1-2	0.334	0.004
CRP 2-3	0.865	0.929
CRP 1-3	0.057	**0.004**
HbA1c 1-3	0.160	**0.002**

FBG: Fasting blood glucose, FBG1: first measurement, FBG2: second measurement, etc. INS: insulin, C-pep: c-peptide, HOMA: The Homeostasis Model assessment, CRP: C-reactive protein, DM: diabetes mellitus. Note: Repeated measurements for each data were compared in pairs: 1. 2 and 3 refers to pre-treatment, 10th session and 20th session measurements respectively

nificant (p=0.593) (Table 4).

When HOMA-IR changes were evaluated according to the BMI of the participants, no significant difference was found in the patients with DM (p=0.432) and those without DM (p=0.254).

In patients without DM, a very slight decrease was found in the mean HbA1c values before and after treatment. However, this decrease was not statistically significant (p=0.160). On contrary, a statistically significant decrease was observed in the mean HbA1c values before and after treatment in patients with DM (p=0.002) (Table 4).

During the study, one patient experienced sinus barotrauma, and two patients experienced middle ear barotrauma as a side effect of HBO2 therapy, which did not suspended treatment.

DISCUSSION

In this study, we determined the effects of HBO2 therapy on insulin resistance and plasma glucose levels in patients with and without DM. Our findings revealed that HBO2 therapy did not significantly affect the plasma glucose levels of patients without DM. Patients without DM have better glucose homeostasis to prevent drops in blood glucose, so it is unclear whether HBO2 therapy has a blood glucose-lowering effect. Further studies are needed to understand this. However, in patients with DM, we observed a rapid decline in plasma glucose levels within the first 10 sessions of HBO2 therapy, which remained low until the final session. Several other studies have also demonstrated a similar effect of HBO2 therapy in lowering plasma glucose levels (20-23).

Wilkinson et al. showed that insulin resistance decreased significantly with HBO2 therapy, but this decrease was insignificant in people without DM (24). In studies conducted on subjects with obesity, both with and without DM, it was shown that HBO2 therapy resulted in decreased insulin resistance (25, 26). In two studies comparing HBO2 therapy with normobaric O2 and hyperbaric air (27, 28), the HBO2 therapy groups showed a significant decrease in insulin resistance, whereas no decrease was found in the control groups. In our study, insulin levels measured in patients without DM and C-pep levels measured in patients with DM decreased significantly during the study period. HOMA-IR values calculated using these results showed a significant decrease in both groups. In addition to the decrease in patients without DM, no correlation was found between being overweight and the decrease in insulin resistance in both groups. This result shows that HBO2 therapy may decrease insulin resistance in non-overweight individuals. In patients without DM, HOMA-IR did not significantly decrease until after the 20th HBO2 therapy session, indicating that longer sessions may be necessary to observe the effect.

Our study found that patients with DM experienced a more remarkable improvement in their metabolic parameters during the early phase of treatment. This is because both metabolic disorders and infections were treated in addition to the HBO2 therapy at this stage. Although these patients had already recovered from their metabolic disorders and infections, their insulin resistance tended to decrease during the last 10 sessions. This continuous decline indicates that HBO2 therapy may also contribute to improving the condition in patients with DM.

Considering that insulin resistance is associated with hypoxia, oxidative stress, and inflammation, it can be hypothesised that HBO2 therapy decreases insulin resistance by increasing the anti-hypoxic, anti-inflammatory, and antioxidant defence systems (29-31). Research has revealed that in patients with Polycystic Ovary Syndrome, the activation of NF-κB and increased transcription of the TNF-α gene is due to higher production of reactive oxygen species. This, in turn, may lead to insulin resistance (32). On the other hand, HBO2 therapy has been found to inhibit the inflammatory response initiated by TNF-α and NF-κB signalling in patients suffering from hearing loss (33). Many similar connections can be found in the existing literature. In addition, in a recently published study, it was emphasised that the decrease in insulin resistance with HBO2 therapy is probably due to decreased endoplasmic reticulum stress and increased mitochondrial capacity and that HBO2 therapy probably leads to low-dose reactive oxygen radical-mediated mitohormesis in humans with type 2 DM (34).

During the first 10 sessions, it was observed that there was a significant decrease in CRP levels in patients with DM. This could be attributed to the fact that patients with DM were diagnosed with an infection-related disease, such as diabetic foot, and subsequently received antibiotic treatment. It is possible that controlling the infection made it easier to regulate blood levels in patients with DM. At this point, a decrease in CRP levels is expected to affect glucose insulin resistance. In contrast, the patients without DM did not always suffer from an underlying disease that would increase CRP. Although we cannot definitively conclude that HBO2 therapy directly caused the decrease in insulin resistance in patients with DM, this study's strength lies in demonstrating the reduction in patients without DM.

In a study in which HbA1c levels decreased significantly in patients without DM with HBO2 therapy, no significant decrease was found in both groups' fasting blood glucose and insulin levels (24). Our study found no significant reduction in HbA1c levels in patients without DM with HBO2 therapy. This may be because our study had fewer HBO2 sessions compared with the study above.

Our analysis showed that patients with and without DM experienced a metabolic response after 10 sessions, which was more pronounced in people with DM.

Our study included women, unlike other studies on this subject (25, 26, 28, 32). The study suggests further research on female-only populations and individuals without DM with high insulin resistance to understand the gender-specific effects of HBO2 therapy on insulin resistance. Future research could focus on evaluating the long-term effects of HBO2 therapy and comparing its benefits with other treatment modalities, such as exercise or pharmacological approaches. Investigating the impact of HBO2 therapy on metabolic pathways related to insulin sensitivity could provide valuable information on its underlying mechanisms. Additionally, exploring the clinical applicability of HBO2 therapy in managing insulin resistance, including its potential as an adjunctive therapy, could be beneficial.

However, our study had limitations, such as a shorter follow-up period and fewer patients than desired; the study was conducted within budget constraints, limiting our ability to perform extensive laboratory analysis. This limitation may have affected the scope and depth of the data collected. The initial study design considered only the minimum required laboratory tests and prioritised the collection of these types of data. As a result, valuable insights that could have been provided by additional laboratory tests such as haemograms, serum creatinine/eGFR, and liver function tests might have been missed. Although our study had a very short follow-up period and a very small sample size to observe significant changes in BMI, the reduction in BMI may have improved insulin resistance in both groups. The limitations of our study include the lack of follow-up on BMI. In the patients with DM, both HOMA-IR and HbA1c levels improved after HBO2. Besides the reduced inflammation/infection during HBO2, it could be related to intensive blood glucose monitoring, proper diabetic diet, additional oral antidiabetic or insulin treatments, antibiotics, or other additional treatments (e.g., quinolones and beta-blockers could cause hypoglycaemia) and reduced appetite related to infective state during the hospitalisation/HBO2 therapy. In addition, decreased haemoglobin levels during hospitalisation/HBO2 therapy due to repetitive blood samplings or surgical interventions could cause false low levels of HbA1c. In patients without DM, improved HOMA-IR may be linked to the treatment of pre-existing conditions, hospitalisation, reduced appetite, and weight loss due to critical conditions.

CONCLUSION

In conclusion, our study found that insulin resistance decreased significantly in patients with and without DM during HBO2 therapy. This suggests that HBO2 therapy may have an effect on managing insulin resistance in various patient groups, but further research is needed to gain a comprehensive understanding of its potential.

Ethics Committee Approval: The study has ethical approval from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 24.08.2012, No: 346).

Informed Consent: Informed consent was obtained from all patients and their relatives before participation in the study.

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