RESEARCH ARTICLE
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Impact of Hyberbaric Oxygen Therapy on Olfactory Function and Bulb Volume in Diabetic Patients with Olfactory Dysfunction

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ABSTRACT

Objective: Investigating the efficiency of Hyperbaric Oxygen Therapy (HBOT), recommended adjuvant therapy for diabetic neuropathy patients, in changing olfactory bulb volume and function in diabetic patients with olfactory dysfunction.
Materials and methods: 12 individuals, from a pool of type-2 diabetes mellitus (DM) patients with diabetic foot, had olfactory dysfunction based on olfaction test results. Olfactory tests and Magnetic Resonance Imaging (MRI) were used to measure and evaluate olfactory bulb volume and function changes in response to HBOT in these 12 patients (comparing Group 1 to Group 2). Similar analysis was carried out to compare the findings to those of 13 healthy patients (Group 3).
Results: Patients in Group 1, 2, and 3 were categorized as moderately hyposmic, mildly hyposmic, and normosmic, respectively based on olfaction test results. HBO treatment seems to be efficient as the OBV values and olfaction test results of Group 1 were significantly lower than those of Group 2. Comparison of olfactory tests shows statistically significant improvement in post-treatment odor perception.
Conclusion: It has been shown that both olfactory function and OB volumes based on MRI have increased significantly after HBO therapy in diabetic patients with olfactory dysfunction.

Keywords: Diabetes, anosmia, hyposmia, hyperbaric oxygen therapy, olfactory bulb volume

INTRODUCTION

The incidence of type-2 diabetes mellitus (DM) is gradually increasing, related to increased DM-associated morbidity and complication incidence. Decreased sense of smell is a major global health problem leading to reduced quality of life in affected individuals. The sense of smell presents crucial data about the surrounding and also takes part in the maintenance of protection and survival, feeding, social life, and sexuality (1).

Diabetic neuropathy, nephropathy and retinopathy are well-established complications of DM, but few studies have been conducted on the outcome of dysglycemia on the olfactory system. DM, in particular, can cause serious micro- and macrovascular complications that are related with significant morbidity, low life quality, shortened expectancy of life, and high cost of health services. The inititation and advance of DM complications are highly associated with injury to the renal glomeruli, peripheral nerves and retina, caused by dysglycemia and oxidative stress (2). Visual system is well-known to be affected by DM presence; however, there is inadequate data on the effect of DM on other sensory systems, such as olfaction. Patients with DM showed olfactory dysfunction, but its etiology is unclear (3).

It has also been suggested that olfactory function screening can be used as an early indicator of the existance of diabetic microvascular complications, like diabetic neuropathy (4).

While cranial neuropathies are often too rare, their association with diabetic neuropathy has been established very clearly. The frequency of cranial nerve involvement in patients with DM is

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reported to be 1% (5). Depending on the effect on the olfactory nerve, olfactory dysfunction may develop in DM. This can be considered as a sign of central neuropathy. It has been proven that olfactory dysfunction is related with diabetic neuropathy and peripheral retinopathy (6).

Hyperbaric Oxygen (HBO) rises, collagen production, angiogenesis and fibroblast proliferation improve tissue hypoxia and tissue perfusion, while reducing edema and inflammation. Systemic HBO therapy is proposed for the treatment of diabetic neuropathies (7).

The aim of study is to examine whether there is a change in olfactory function and olfactory bulb volume (OBV) after HBO therapy in patients with diabetic olfactopathy.

MATERIAL AND METHODS

Ethics approval was acquired from the local Research Ethics Committee before the study (Date: 07.10.2020, No: 2/2020.K-067). All individuals in this study were given a written informed consent for participation. This work was done in accordance with the rules of the Declaration of Helsinki.

Patients

Participants of the study were informed about the study, and they voluntarily signed the written consent forms. Demographic information of patients and healthy participants were recorded. 94 type-2 DM patients with diabetic foot who were followed up by the Internal Medicine Clinic took olfaction test. Only 12 patients were diagnosed diabetic olfactopathy and were included in our first group (Group 1). The second group in our study (Group 2) consists of the same 12 patients, who returned for control after receiving 30 sessions of HBO therapy. Finally, healthy volunteers were included in Group 3.

Evaluation of olfaction

To evaluate the olfactory function in the participants, the Connecticut Chemosensory Clinical Research Center (CCCRC) orthonasal olfaction test, for which validity and reliability in Turkish language were proven, was used. The CCCRC test consists of the n-butanol odor threshold test and the odor identification test. Detailed data on these tests has been provided in former studies (8). Olfactory tests were performed individually, and the maximum score was 7 (0: worst, 7: best olfaction), and the average score was calculated as the total CCCRC test score. According to the CCCRC orthonasal test, the scores were grouped as shown in Table 1.

Other causes of olfactory dysfunction in all participants of these three groups were examined in detail. Patients with other pathologies like inflammatory diseases were excluded from the study.

The standard treatment was designed with HBO therapy applied at a maximum atmospheres of absolute pressure (ATA) of 20 atm using a 10 m^3 volume single pressure chamber (Patterson Companies, Inc., St. Paul, MN, USA). The treatment consisted of two or three ATA for 90 minutes. The treatment was applied as two sessions per day, then one session the next day, and alternated during the therapy period which typically extended for 20 to 30 days. HBO treatment was evaluated clinically considering the duration of the therapy, expenses, contraindications, and complications. Contraindications include ocular aneurysm, lung disorders associated with risk of pneumothorax, high blood pressure, claustrophobia, convulsion due to oxygen toxicity, and rupture of the eardrum (9).

Magnetic Resonance Imaging (MRI) of Olfactory Bulb Volume (OBV)

OBV measurements were performed with a General Electric Signa MRI device using an 8-channel head coil. For OBV measurements, coronal T2-weighted three-dimensional turbo spin-echo (TSE) images were taken with a 2 mm section thickness and without section gap (gap=0). OBV values were evaluated by an experienced radiologist, and a double-blind technique was used on both sides via manual segmentation. OBV values were calculated in cubic millimeters (mm^3) (10) (Figure 1).

Statistical analyses

The data was analyzed using the MedCalc® v11.4.4 software. Mann Whitney U test was used to evaluate the effect of treatment,

Table 1: Classification of olfactory function according to CCCRC test

	Score Ranges
Anosmia	0-1.75
Severe hyposmia	2-3.75
Moderate hyposmia	4-4.75
Mild hyposmia	5-5.75
Normosmia	6-7

CCCRC: Connecticut Chemosensory Clinical Research Center test score

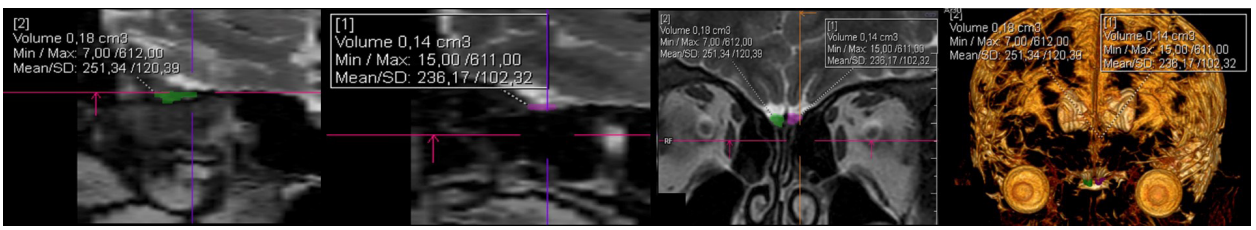

Figure 1: 44-year-old male diabetic patient with olfactory dysfunction before HBO treatment. Three-dimensional volume measurements of the bilateral olfactory bulbs: 140 mm^3 on the left side, 180 mm^3 on the right side. Right olfactory bulb, sagittal T2W MRI; Left olfactory bulb, sagittal T2W MRI; Bilateral olfactory bulbs, coronal T2W MRI; Bilateral olfactory bulbs, three-dimensional (3D) Volume rendering (VR) T2W MRI, respectively.

comparing the two dependent groups (Group 1 to Group 2), while we used the Kruskal Wallis to compare all three groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean ± standard deviation of the patients' ages were 54.16±3.21 years and 55.23±4.22 years in Groups 1 and 2, respectively. Treatment groups (Groups 1 and 2) contained 10 male and two female participants, while Group 3 contained 11 male and two female participants. No statistically significant difference was found between the groups in terms of age and gender. Total mean ± standard deviation of CCCRC scores was 4±0.71 in Group 1, 5.08±0.70 in Group 2, and 6.42±0.31 in Group 3; the scores differed significantly among the groups. The mean CCCRC scores in Group 1, Group 2, and Group 3 were adequately hyposmic, mildly hyposmic, and normosmic. Figure 2 and Figure 3 show boxplots of the CCCRC scores and OBV of pre-treatment patients, post-treatment patients, and healthy individuals, respectively. Average ± standard deviation of OBV values was 60.08±5.35 mm^3 in Group 1, 71.29±6.55 mm^3 in Group 2, and 76.46±11.36 mm^3 in Group 3. OBV values and CCCRC test scores of Group 1 were significantly lower than those of Group 3 (both p-values<0.01). When Group 1 and Group 2 were compared, a statistically significant increase was observed in OB volumes following HBO treatment.

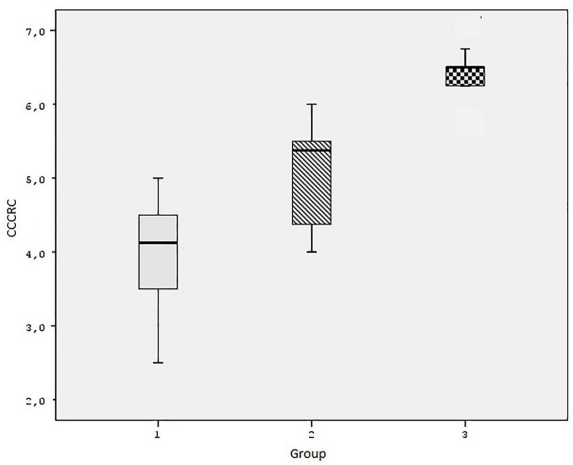

Figure 2: Boxplots for CCCRC scores of the groups of pre-treatment patients, post-treatment patients, and healthy individuals.

In Group 1, three patients were severely hyposmic, eight were adequately hyposmic, and one was mildly hyposmic. In Group 2, five patients were moderately hyposmic, five were mildly hyposmic, and two cases were normosmic. In Group 3, two individuals were mildly hyposmic, and the remaining 11 were normosmic. Average ± standard deviation of OBV values was 60.08±5.35 mm^3 and 71.29±6.55 mm^3 in Group 1 and Group 2, respectively. These values differed significantly between the two groups (p<0.005).

Total CCCRC score was 4±0.7 in Group 1 (moderately hyposmic), 5.08±0.70 in Group 2 (mildly hyposmic), and 6.42±0.31 in Group 3 (normosmic). The differences in CCCRC scores among the groups were statistically significant (p=0.001) (Table 2).

When healthy individuals (Group 3) were compared with other groups, the OB volumes of them were significantly higher than those of the pre-treatment group (p<0.005), but comparable with the values in the post-treatment group (p=0.24). However, CCCRC scores of healthy individuals were significantly higher than those in both pre-treatment and post-treatment groups.

DISCUSSION

HBO therapy is a medical technique in which high pressure pure oxygen is provided to the patient in a special cabin or a custom-made system consisting of several chambers. Undersea and Hyperbaric Medical Society states that 100% pure oxygen should be applied at a pressure of at least 1.4 atm (11).

For physiological effects to occur, HBO therapy should elevate plasma oxygen level to 0.3-6 ml/L under 3 ATA pressure. HBO

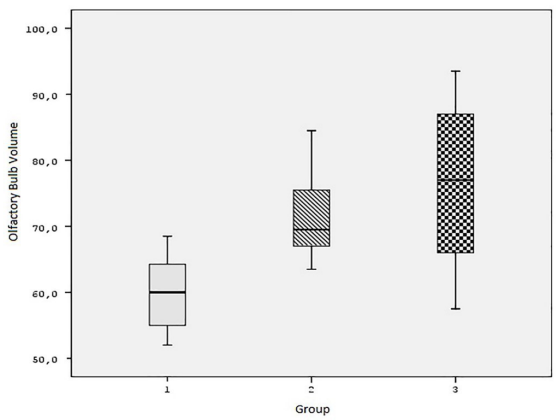

Figure 3: Boxplots for OBV of the groups of pre-treatment patients, post-treatment patients, and healthy individuals.

Table 2: Descriptive statistics of all groups

	Group 1-Pre-treatment n=12			Group 2- Post-treatment n=12			Group 3-Healthy n=13		
Variables	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (yr)	54.2	3.2	50-60	54.2	3.2	50-60	55.2	4.2	50-63
CCCRC	4	0.7	2.5-4.5	5.1	0.7	4-6	6.4	0.3	5.75-7
OBV	60.1	5.4	54.5-68.5	71.3	6.6	63.5-84.5	76.5	11.4	57.5-93.5

CCCRC: Connecticut Chemosensory Clinical Research Center test score, OBV: Olfactory Bulb Volume

therapy provides many physiological, medical, and physical effects into action. It maximizes tissue oxygenation by increasing the oxygenated hemoglobin in solution and oxygen content (12). The American Diabetes Association approves HBO therapy as an adjuvant option in diabetic neuropathies that are unresponsive to any other treatment, are inoperable, and are life-threatening, especially when associated with ischemia (13).

A different study has proven that the hypobaric environment causes lower scores in the olfactory thresholds compared to the hyperbaric environment (14).

A group of 40 healthy volunteers were evaluated olfactory functions under hyperbaric 2.4 (atm abs) and 1 absolute atmosphere (atm abs) environment. Olfactory functions were shown to increase significantly with hyperbaric conditions (15).

Olfaction tests have been utilised as preclinical indicators to prognosticate the development and onset of various diseases with inflammatory processes (16).

Sequalae related to macrovascular diseases such as ischemia are assumed to be adversely affected. Additionally with the coexistence of DM and olfactory dysfunction, it has been reported that olfactory function scores are less in terms of DM-related complications (17).

Olfactory dysfunction in diabetic patients may be due to olfactory nerve damage, which is a sign of central neuropathy. It has been shown that the ability of patients to identify odors correctly decreases with increasing intensity of peripheral neuropathy. Olfactory dysfunction may occur in DM patients due to conduction or sensorineural problems (18,19).

The mechanisms causing the possible development and progression of olfactory dysfunction in patients with DM are unknown. Many hypotheses have been tried to explain the underlying mechanisms, including direct effects on the olfactory nerve or the central nervous system due to micro- and macrovascular changes or other abnormalities (20).

Olfactory dysfunction may happen in DM patients due to a weakened olfactory nerve. Therefore, it is an indicator of central neuropathy. Compatible with the former articles, all diagnostic scores were significantly lower in the diabetic olfactopathy group in this study, suggesting that the olfactory nerve is affected by DM similarly to that of the other cranial nerves. Further studies on these existing findings are needed to define whether olfactory testing and OBV measurement can be regarded as a test for diagnosis of central diabetic neuropathy.

In our study, it has been shown that OBV was remarkebly smaller in patients with type-2 diabetic olfactopathy compared to the healthy individuals with the same age group. An improvement in olfactory tests and an increase in OBV after HBO treatment was observed in patients with DM, which could be an indicator of a potential improvement in neuropathic progression.

This is a preliminary study. This type of research is very costly, and the number of cases has been tried to be limited and kept to a minimum. For this reason, studies have been conducted with cases close to the number of cases taken in previous MRI studies on olfactory bulb.

The reason for taking hyperbaric oxygen therapy was not diabetic olfactopathy, the patients were randomly selected from patients who underwent HBO treatment protocol for diabetic foot. Therefore, the HBO treatment duration, dose and treatment scheme is the standard diabetic foot protocol and has not been changed.

Smell function disorders in diabetes are a highly controversial issue. While planning this study, it was designed according to the study of Veyseller et al. In the literature and in their study, they reported an improvement in odor functions with HBO treatment in diabetic patients. In our study, we obtained results that support their study findings in relation to patients with diabetic olfactopathy in olfactory functions. However, in our study, we conducted a preliminary study to see whether HBO therapy has an effect on olfactory bulb. This study aims to shed light on future treatments and studies.

OB has a plastic structure. In people who have been away from olfactory stimuli for years, Veyseller et al. reported an increase in OB volumes after treatment in laryngectomy patients and showed that even after years, OB increased in volume with its plastic structure. Therefore, we have shown in this study that there is an increase in OB volumes in diabetic patients, even if the mechanism is not fully known.

CONCLUSION

In this study, a significant olfactory dysfunction was observed in patients with T2-DM compared to healthy individuals. This is a preliminary study to report that OBV is decreased in patients with diabetic olfactopathy and that OBV can improve with HBO therapy.

Ethics approval was obtained from the Istinye University, Research Ethics Committee before the study (Date: 07.10.2020, no: 2/2020.K-067). All patients in this study signed a written informed consent form for participation. This work was done in accordance with the principles of the Declaration of Helsinki.

Ethics Committee Approval: This study was approved by Istinye University Clinical Research Ethics Committee (Date: 07.10.2020, No: 2/2020.K-067).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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