

Hyperbaric oxygen therapy of olfactory dysfunction in diabetic neuropathy with type 2 diabetes mellitus and a new definition “Diabetic Olfactopathy”*

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Abstract

Background: Hyperbaric Oxygen therapy is recommended as an adjuvant therapy for diabetic neuropathy. To investigate olfactory dysfunction and show the effectiveness of hyperbaric oxygen treatment in patients with type 2 diabetic neuropathy.

Material and Methods: Patients diagnosed with Type 2 DM and diabetic neuropathy were included in the group 1. Patients of Group 1 were administered with a hyperbaric oxygen therapy for 30 sessions and patients who returned for a check up following 30 sessions were incorporated into the Group 2. Healthy volunteers with no medical problems were included in the study as a control group (Group 3). Connecticut Chemosensory Clinical Research (CCCRC) test and the subjective visual analog scale (VAS; 0-100) were utilized to evaluate the olfactory function.

Results: There was a statistically significant difference both between the control group and the patient group as well as before and after the HBO therapy in terms of total CCCRC scoring averages and VAS Scoring averages.

Conclusion: When compared to normal individuals, type 2 diabetic neuropathy can cause an olfactory dysfunction, and a statistically significant improvement in olfaction can be obtained with HBO therapy. This is the first study demonstrating that the HBO therapy can play a role in treating olfactory dysfunctions suffered by the patients with diabetic olfactory neuropathies.

Key words: Type 2 diabetes mellitus, olfactory dysfunction, diabetic neuropathy, hyperbaric oxygen therapy

Introduction

The importance of olfaction seems to be ignored when compared to other senses. However, the loss of olfaction impairs life quality and potentially risks one's safety. After the effects of insulin, ghrelin and leptin on olfaction were proven, the olfactory system turned out to be related with the endocrine system⁽¹⁾. Accounting for olfactory dysfunctions in diabetes mellitus (DM), some macrovascular^(2,3) and microvascular⁽⁴⁾ mechanisms are set forth. In addition to the association of DM with olfactory dysfunctions, studies report that olfactory scores are even lower when it comes to diabetic complications⁽²⁻⁵⁾. While cranial neuropathies are rare enough to ignore most of the time, their relation with diabetic neuropathy is clearly proven. The incidence of

cranial nerve involvement for diabetic patients is reportedly 1%⁽⁶⁾. An olfactory dysfunction in DM can develop due to an effect on an olfactory nerve. This can be regarded as an indicator of a central neuropathy. An olfactory dysfunction has been proven to be related to diabetic retinopathy and peripheral neuropathy⁽⁶⁾. In proportion to the severity of peripheral neuropathy, the olfactory recognition capability was found out to be diminished⁽⁷⁾. Therefore, making use of olfactory tests is considered an option for the early diagnosis of diabetic complications^(2,3). Hyperbaric Oxygen (HBO) increases perfusion in tissues and mitigates edemas and inflammation while boosting fibroblast proliferation, collagen production and angiogenesis, and improving tissue hypoxia⁽⁸⁾. Systemic HBO therapy is recommended

for the medical treatment of diabetic neuropathies⁽⁹⁾. This study was carried out in an effort to show the role of olfactory dysfunctions in patients with type 2 diabetic neuropathies, and prove the effectiveness of HBO therapy on olfactory functions.

Materials and methods

Patient characteristics

Upon obtaining an approval from the Ethics Committee of Clinical Trials, healthy volunteers and patients diagnosed by the Internal Medicine Clinic with type 2 DM and diabetic neuropathy caused by diabetic foot were included into the study.

Participants of the study were informed of the study subject and granted a voluntary written consent.

Patients diagnosed with Type 2 DM and diabetic neuropathy were included in the group 1 of the study. These patients were administered with a HBO therapy for 30 sessions and patients who returned for a check up following 30 sessions were assigned into the Group 2. Lastly, healthy volunteers were included in Group 3. After recording demographic information of the patients and the healthy volunteers, Connecticut Chemosensory Clinical Research (CCCRC) test was utilized to evaluate olfactory functions.

Other causes to lead to olfactory dysfunctions in all volunteers of the three groups were thoroughly examined. Those with neurological disorders, septal deviation, nasal polyposis, previous nasal surgery, head trauma, chronic rhinosinusitis, allergic rhinitis, Parkinson's disease and Alzheimer disease, as well as major depression and schizophrenia were excluded from the study.

Evaluation of olfactory function

The Connecticut Chemosensory Clinical Research Center (CCCRC) test was conducted as described previously elsewhere (10,11). The CCCRC test is composed of n-butanol odor threshold test and odor identification test. Olfactory tests were conducted individually and were scored out of 7 (0: worst, 7: best olfaction) and mean score was calculated as the total CCCRC test score. As in the CCCRC orthonasal test, scores were grouped as follows: 0 to 1.75, anosmia; 2.00 to 3.75, severe hyposmia; 4.00 to 4.75, moderate hyposmia; 5.00 to 5.75, mild hyposmia; and 6.00 to 7.00 normal.

Subjective olfactory measurement

Olfactory function was measured using the subjective visual analog scale (VAS; 0-100) where 0 was evaluated as the worst and 100 as the best.

HBO therapy

Standard therapy was supplemented with HBO treatments administered at a maximum working pressure of 20 atmospheres absolute (ATA), using a unichamber pressure room (Patterson

Companies, Inc., St. Paul, MN, USA) employing a volume of 10 m³ at 2 to 3 ATA for 90 minutes. Treatment was administered as 2 sessions per day, followed by 1 session on the following day, alternating throughout the course of therapy, which was typically extended for a period of 20 to 30 days. The HBO therapy was clinically evaluated considering time, cost, complications, and contraindications. The HBO therapy was clinically evaluated considering time, cost, complications, and contraindications. The contraindications include ocular aneurysm, pulmonary diseases due to risk of pneumothorax tension, claustrophobia, convulsion associated to toxicity of oxygen, and rupture of ear drum^(12,13).

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences version 13.0 software for Windows (SPSS Inc, Chicago, Illinois, USA). All quantitative variables were estimated using measures of central location (i.e. mean and median) and measures of dispersion (i.e. standard deviation (SD)). Data normality was checked using the Kolmogorov-Smirnov tests of normality. Chi Square test was used for comparisons of the groups' gender distribution. For the comparison of groups among each other, the Repeated ANOVA test was applied (The difference among groups was considered to be $p < 0.05$). To determine the days among which there were differences, the Tukey HSD test was administered as a post-hoc test. Since this was a multiple comparison, the Bonferroni correction was applied and $p < 0.016$ was accepted as the value of significance.

Results

There was no statistically significant difference in terms of gender and age average between the patients of Group 1 (average age of 14 males and 18 females: 55.9 ± 7.4), Group 2 (average age of 13 males and 14 females: 56.1 ± 6.1) and Group 3 (average age of 16 males and 14 females: 54.7 ± 5.8) ($p > 0.05$).

Butanol threshold averages of the groups were analyzed. Average butanol threshold test score of Group 1 was 4.56 ± 1.29 , while it was 5.62 ± 0.74 for Group 2 were found and 6.43 ± 0.66 for Group 3. Statistically significant difference's between the groups ($p = 0.014$) (Table 1-2) (Figure 1).

The olfactory discrimination averages were analyzed. Average olfactory discrimination test score of Group 1 was 4.40 ± 1.89 while it was 5.37 ± 0.92 for Group 2 and 6.55 ± 0.71 for Group 3 with statistically significant difference between the groups ($p = 0.001$) (Table 1-2) (Figure 1).

The total CCCRC scoring averages of the groups were analyzed. Total scoring average of Group 1 was 4.45 ± 1.48 (moderate hyposmic) while it was 5.50 ± 0.66 (mild hyposmic) for Group 2 and 6.49 ± 0.54 (normosmic) for Group 3 with statistically significant difference's between the groups ($p = 0.001$) (Table 1-2) (Figure 1).

VAS Score averages of the groups were analyzed. It was $54.23 \pm$

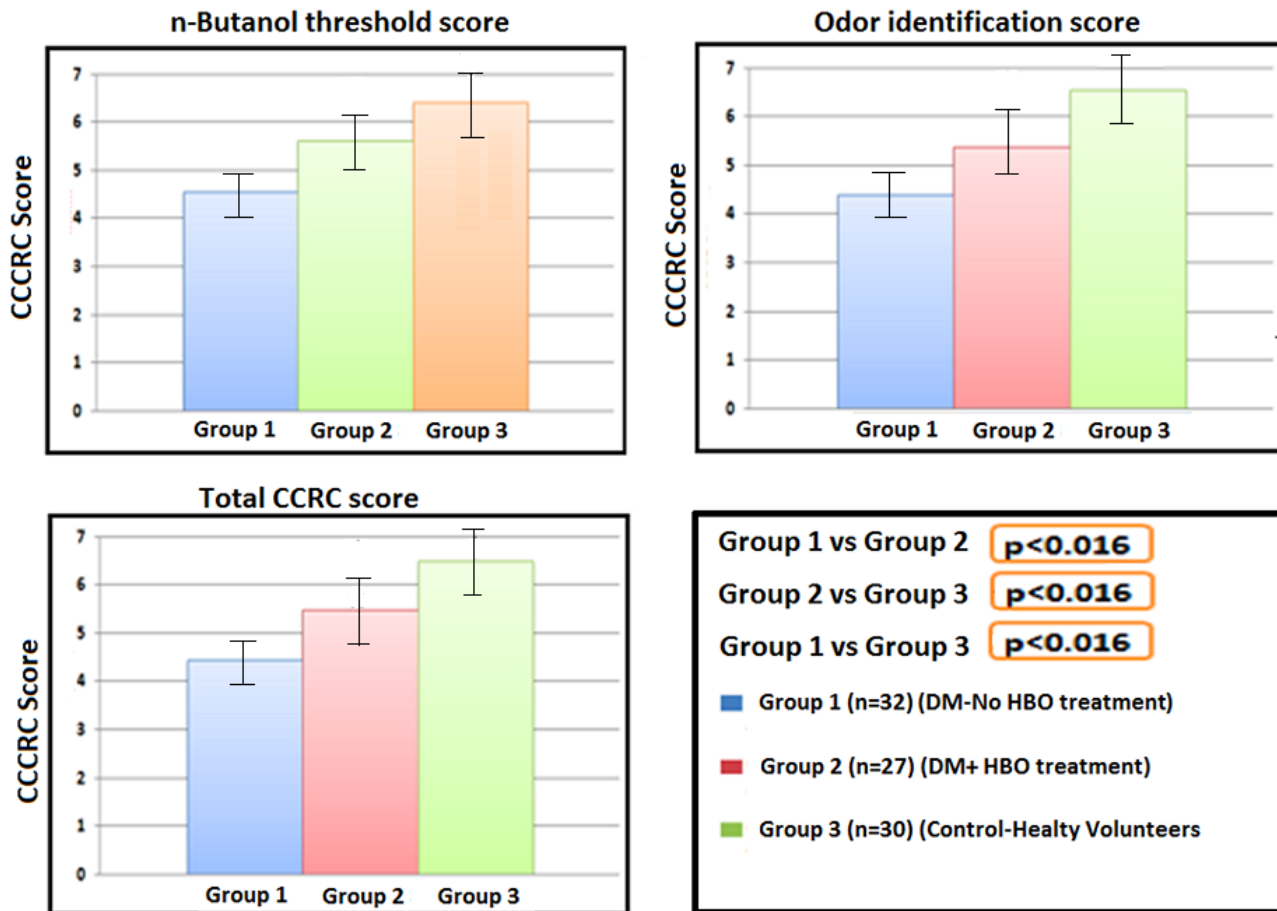


Figure 1. Comparison of Groups for CCCRC scoring averages.

7.09 for Group 1, 75.04 ± 5.18 for Group 2 and 98.25 ± 3.26 for Group 3. There were statistically significant differences between the groups ($p=0.001$) (Table 1-2) (Figure 1).

Before HBO treatment, according to the CCCRC scores, three patients were classified as normal, five as mildly hyposmic, nineteen as moderately hyposmic, and four as severe hyposmic. After HBO treatment, 11 patients were normosmic, 12 as mildly hyposmic, three as moderately hyposmic and one severely hyposmic (Table 1).

Discussion

Olfactory dysfunctions are mainly common following sinonasal infections and head trauma. In addition, they may also manifest themselves as a result of alcoholism, exposure to toxic chemicals, endocrine disorders, neurodegenerative diseases (Parkinson, MS and Alzheimer), psychiatric disorders (schizophrenia and depression), intracranial tumors and surgical interventions (nasal and paranasal surgeries). Olfactory dysfunctions are referred to as idiopathic olfactory dysfunctions in cases where the reason behind them can not be explained⁽¹⁴⁻¹⁶⁾.

Increasing prevalence of type 2 DM enhances the importance of the effects of diabetic complications on morbidity and life qua-

lity. The term diabetic neuropathy refers to peripheral nervous system disorders caused by neuropathy. However, it is known to point to central nervous system dysfunctions and effect cognitive function similar to depression^(17,18). Mononeuropathy is defined as the weakness of cranial nerves. Cranial neuropathies are commonly seen in elderly patients with long-term DM. The majority of these patients previously experienced various comorbidities and poor glycemic checks⁽¹⁹⁾. The isolated paralysis of the third, fourth or sixth cranial nerves are characteristically followed up for diabetic neuropathy⁽²⁰⁾. Diabetes manifests itself in the majority of patients with the isolated third nerve involvement and 11% of inpatients with the third nerve involvement⁽²¹⁾. The third cranial nerve paralysis is not often complete as the pupillary reflex is usually intact. Diplopia is the main symptom for almost all cases. Unilateral deviation in eyes, ptosis and limited medial and upward sight are obvious. Patients with diabetic oculomotor nerve paralysis can improve by themselves in 2 to 3 months regardless of any glycemic check⁽²²⁾. A deficiency manifests itself in rotation, depression and abduction of the eye balls when it comes to trochlear and abducens nerve disorders which are rare. The incidence of cranial nerve involvement for diabetic patients is reportedly 1%⁽⁶⁾. The fact that the incidence of cranial

Table 1. CCCRC olfactory test results for Groups.

CCCRC orthonasal test	Range	Group 1 (n=32)	CRSwNP	AFRS
Normosmia	6.0-7.0	3 (9.37 %)	11 (40.7 %)	22 (73.3 %)
Mild hyposmia	5-5.75	5 (15.6 %)	12 (44.4 %)	5 (16.6 %)
Moderate hyposmia	4-4.75	19 (59,3 %)	3 (11 %)	2 (6.6 %)
Severe hyposmia	2-3.75	4 (12,5 %)	1 (3.7 %)	1 (3.3 %)
Anosmia	0-1.75	-	-	-

nerve involvement is high for diabetic patients shows that the olfactory nerve is involved. An olfactory dysfunction in DM can surface due to a disorder and weakness of an olfactory nerve. Therefore, this can be regarded as an indicator of a central neuropathy⁽⁶⁾. In this study, the diabetic neuropathy group proved significantly low results for the butanol threshold test, olfactory discrimination test and the CCCRC total scoring averages, these results are in accordance with the literature when compared to the healthy control group (p<0.001). Therefore, it is safe to say that the olfactory nerve, which is the first cranial nerve, is affected by diabetes as much as other cranial nerves. Thus, the term “diabetic olfactopathy” could be a more acceptable phrase to define an olfactory dysfunction for DM.

HBO therapy is breathing pure oxygen while under increased atmospheric pressure. There are numerous articles released in the last two decades with regard to the fact that breathing 100% pure oxygen under high pressure is potentially beneficial for the treatment of many diseases. HBO therapy is a medical method of treatment where high-pressured pure oxygen is provided in a custom-made system composed of a special cabin or a few rooms. The Undersea Hyperbaric Medicine Society reports that

100% pure oxygen should be provided under at least 1.4 atm of pressure^(23,24). HBO therapy should be increased to 0.3 - 6 ml/L in plasma oxygen level under 3ATA pressure in order to manifest physiological effects. HBO therapy brings about many physiological, medical and physical effects. It makes the tissue oxygenation reach the maximum level by increasing the quantity of oxygenized hemoglobin and oxygen in solution. In addition, HBO therapy increases the flexibility of erythrocytes and the local microcirculation⁽⁸⁾. Diabetic foot ulcer is a common and serious neuropathy for diabetes⁽²⁵⁾. HBO therapy is recommended as an adjuvant therapy for diabetic neuropathy⁽²⁶⁾. The American Diabetes Society recommends HBO therapy as an adjuvant choice for severe diabetic neuropathies that are not responsive to any other therapy, impossible to have surgery on, and are ischemia-related life threatening in particular⁽²⁷⁾. Another study on olfactory functions shows that atmospheric pressure and humidity play a role in evaluating the olfactory discrimination and threshold. When compared with a hyperbaric environment, the hypobaric environment proved low scores in olfactory thresholds⁽²⁸⁾. A group of healthy volunteers consisting of 40 people were examined in terms of olfactory functions under 1 absolute atmosphere (atm abs) and in a hyperbaric (2.4 atm abs) environment. Olfactory functions increased to a significant extent under hyperbaric conditions⁽²⁹⁾. For this study, we administered HBO therapy for olfactory dysfunctions in patients with Type 2 DM in an effort to both improve the olfactory functions and treat the diabetic olfactopathy, a neuropathy induced by DM. We compared pre- and post- olfactory functions of the patients. When Butanol threshold test, olfactory discrimination test and CCCRC total score averages were analyzed, the patients significantly improved in olfactory functions when compared to pre-treatment (p<0.001). This study is the first in literature in terms of showing that the HBO therapy can play a role in treatment of olfactory dysfunctions in patients with diabetic olfactopathy. However, further studies covering more patients are required.

Table 2. CCRC olfactory averages for Groups*

Parametres	Butanol Mean ± SD	Identification Mean ± SD	Mean ± SD	VAS Score Mean ± SD
Group 1 (n=32) (DM-No HBO)	4.56 ± 1.29	4.40 ± 1.89	4.45 ± 1.48	54.23 ± 7.09
Group 2 (n=27) (DM+HBO)	5.62 ± 0.74	5.37 ± 0.92	5.50 ± 0.66	75.04 ± 5.18
Group 3 (n=30) (Control)	6.43 ± 0.66	6.55± 0.71	6.49 ± 0.54	98.25 ± 3.26
Oneway ANOVA	p=0.001	p=0.001	p=0.001	p=0.001
TukeyHSD Grp 1 vs 2	p=0.014	p=0.001	p=0.001	p=0.001
Grp 1 vs 3	p=0.001	p=0.001	p=0.001	p=0.001
Grp 2 vs 3	p=0.001	p=0.001	p=0.001	p=0.001

*For the comparison between groups, the one-way analysis of variance (ANOVA) test was used (p<0.05 was accepted as statistically significant). Tukey’s HSD was administered as a post-hoc test to identify within-group differences (p<0.016 was accepted as statistically significant).

Our study is a preliminary study considered as a proposal. The main limitation of our study is lack of separate groups containing patients being diabetic without neuropathies and healthy controls undergoing HBO therapy.

Conclusion

When compared to healthy patients, the olfactory functions of the patients with type 2 DM were significantly low. We believe that diabetic neuropathy, which is a common complication for DM, affects the olfactory system for such patients, and leads to diabetic olfactory dysfunction. The HBO therapy administered to treat

diabetic neuropathy has been proven to be effective in diabetic olfactory dysfunction which is a neuropathy as well. In this respect, the study offers a new perspective in the literature.

Authorship contribution

BV: Manuscript design and drafting the article; RD, ST, EED: Drafting the article; AY: Drafting and submission the article; FA: Manuscript design; OO: Manuscript design and drafting the article.

Conflict of interest

The authors have no conflict of interest.

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