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Evaluation of olfactory bulb volume in patients with diabetic olfactopathy and comparison with healthy individuals

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ABSTRACT

Objective: Diabetic olfactopathy is defined as olfactory dysfunction in patients with diabetic neuropathy. In this study, we evaluated the olfactory bulb volume (OBV) using magnetic resonance imaging in patients with diabetic olfactopathy and compared the results with those of healthy individuals.

Methods: This study included 12 patients who were diagnosed with type 2 diabetes mellitus (T2DM) and were found to have diabetic olfactopathy using the Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test (Group 1); their OBV was evaluated using MRI. For comparison, 13 healthy individuals of a similar age, without any medical problems, were included as a control group (Group 2); their OBV and olfactory functions were also evaluated.

Results: Total CCCRC scores were 4.27 ± 0.67 in Group 1 and 6.42 ± 0.31 in Group 2; these scores significantly differed between the groups. The mean CCCRC scores in Groups 1 and 2 were moderately hyposmic and normosmic, respectively. The mean OBV values were 65.04 ± 6.97 mm^3 and 76.46 ± 11.36 mm^3 in Groups 1 and 2, respectively. Group 1 had significantly lower OBV values and CCCRC scores, compared with Group 2 ($p < 0.01$ for both groups).

Conclusion: The OBV was lower in patients with T2DM who developed diabetic olfactopathy than that in healthy individuals; the olfactory bulb was adversely affected by diabetes mellitus. This is the first study to demonstrate that the olfactory bulb is adversely affected by the presence of diabetic olfactopathy.

Keywords: Anosmia, diabetes mellitus, diabethic olfactopathy, hyposmia, olfactory bulb volume, smell disorder

Introduction

The sensation of smell (or olfaction) is one of the basic senses of human beings. It provides crucial information regarding the environment and also plays an important role in maintaining survival and safety, feeding, social relations, sexual reproduction, and quality of life (1, 2). Diabetes mellitus (DM), which affects millions of people worldwide, is a worldwide health problem (3). Although diabetic retinopathy, nephropathy, and neuropathy are known complications of DM, there have been few studies regarding the effect of dysglycemia on the olfactory system. The importance of olfaction is often overlooked compared with the importance of other senses, and olfactory dysfunction is often underrecognized. Notably, DM can lead to many vascular complications associated with prominent morbidity, low quality of life, early mortality, and increased health costs. The beginning and progression of DM complications are associated with dysglycemia and oxidative stress-induced injury to the retina, kidney glomeruli, and peripheral nerves (4). Vision is known to be affected by the presence of DM; however, there is limited information regarding the effects of DM on other senses, such as olfaction. Furthermore, olfaction is frequently overlooked and not evaluated in routine clinical practice. Individuals with DM have been reported to exhibit olfactory dysfunction; however, its etiology remains unclear (5). Some authors have recommended that screening for olfactory

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dysfunction can be used as a primary indicator for the existence of diabetic microvascular complications, such as diabetic neuropathy (6, 7). Problems related to olfactory dysfunction can expand beyond poor quality of life in patients with DM. Because olfaction is presumed to change nutritional status, alterations in nutritional habits or desires for some foods that follow altered olfactory processes may affect metabolic control and cause poor long-term consequences (8). In this study, we aimed to investigate the presence of olfactory dysfunction in patients with type 2 DM (T2DM) and diabetic neuropathy, and to determine whether a change occurred in olfactory bulb volume (OBV).

Methods

Ethics approval was obtained from the local research ethics committee of İstinye University prior to the study (protocol number of ethics committee approval 2017-KAEK-120/2/2020.G-068). All the individuals in this study provided written informed consent to participate. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Patient characteristics

Our study included two groups of similar age and sex distributions—12 patients diagnosed with T2DM who had diabetic olfactopathy and foot complications, whose clinical examination had not revealed any pathologies that could impair olfactory function (Group 1), and the control group with 13 healthy individuals without any medical problems (Group 2). The OBV and olfactory functions of the individuals in both groups were evaluated using MRI and the Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test, respectively. Parenchymal and nonparenchymal aspects of the disease were evaluated during neurological examinations of the patients; relationships with olfactory tests were investigated.

The presence of other pathologies that could lead to olfactory dysfunction was investigated in all the participants in both groups. Patients with such pathologies were excluded from the study. Patients with neurological diseases, septal deviation, nasal polyposis, a history of nasal surgery, chronic rhinosinusitis, allergic rhinitis, Parkinson's disease, Alzheimer's disease, major depression, or schizophrenia were excluded from the study.

Main Points:

- This study investigates the presence of olfactory dysfunction in patients with type 2 DM (T2DM) and diabetic neuropathy, and to determine whether a change occurred in olfactory bulb volume.
- Within the scope of Olfactory Bulbus Volume measurements, consecutive coronal T2-weighted three-dimensional (3D) turbo spin-echo (TSE) images were obtained with a slice-thickness of 2 mm and interslice gap of zero.
- The CCCRC orthonasal olfaction test, which has undergone a Turkish validity and reliability study, was used to evaluate olfactory function in the participants.
- Olfactory Bulbus Volume was significantly lower in patients with diabetic olfactopathy than in healthy individuals. This is the first study to show that the olfactory bulb is affected in patients with diabetic olfactopathy.

Table 1. CCCRC Score Ranges

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

Olfactory evaluation

The CCCRC orthonasal olfaction test, which has undergone a Turkish validity and reliability study, was used to evaluate olfactory function in the participants. The CCCRC test includes the butanol threshold test and odor identification test. Detailed information regarding these tests has been provided in previous studies (9, 10). In the CCCRC orthonasal test, the scores are classified as shown in Table 1.

MRI measurement of OBV

OBV measurements were carried out using the General Electric Signa Excite 1.5 T MRI device with an 8-channel head coil. We also acquired conventional cranial MR sequences covering the whole brain to exclude organic brain disorders. Within the scope of OBV measurements, consecutive coronal T2-weighted three-dimensional (3D) turbo spin-echo (TSE) images were obtained with a slice-thickness of 2 mm and interslice gap of zero. The images were evaluated by a radiologist with 11 years of experience in head and neck radiology and blinded to the clinical data of the patients. Volumetric analysis was performed on sequential slices using multiplanar reconstruction, which allows to use the data from coronal T2W images to create axial and sagittal images. The olfactory bulb was manually contoured on all these sequential slices in these three planes. Once the manual contouring is completed, the volume is automatically generated. This process is repeated to measure both left and right OB volumes separately (Figure 1) (11, 12). The OB volumes we present (Table 2) and analyze in this study are the means of the OBV measurements on both sides (i.e., left and right).

Statistical analysis

We present the results of our statistical analysis to answer the following question: Are the CCCRC and OB volumes of the group of diabetic patients with olfactopathy significantly (statistically) lower than those of the control group?

To answer this question, we first present the descriptive statistics in Table 2. The mean ages were 55.23 ± 4.23 years and 54.25 ± 3.96 years in Groups 1 and 2, respectively. There were 10 men and two women in Group 1 and 10 men and three women in Group 2. According to the Wilcoxon-Mann-Whitney test, we did not find sufficient evidence for a meaningful difference in age between the two groups ($p = 0.5382$). As for sex, the Fisher's exact test was used, and the two groups seemed to have a similar profile (p of almost 1). This indicates that the two groups were "similar" in terms of age and sex, and thus, the comparison between the two groups allowed us to discern the impact of DM on CCCRC and OBV (Table 2).

The box plots in Figure 1 clearly show that the CCCRC scores and OB volumes are noticeably lower for patients with DM. The

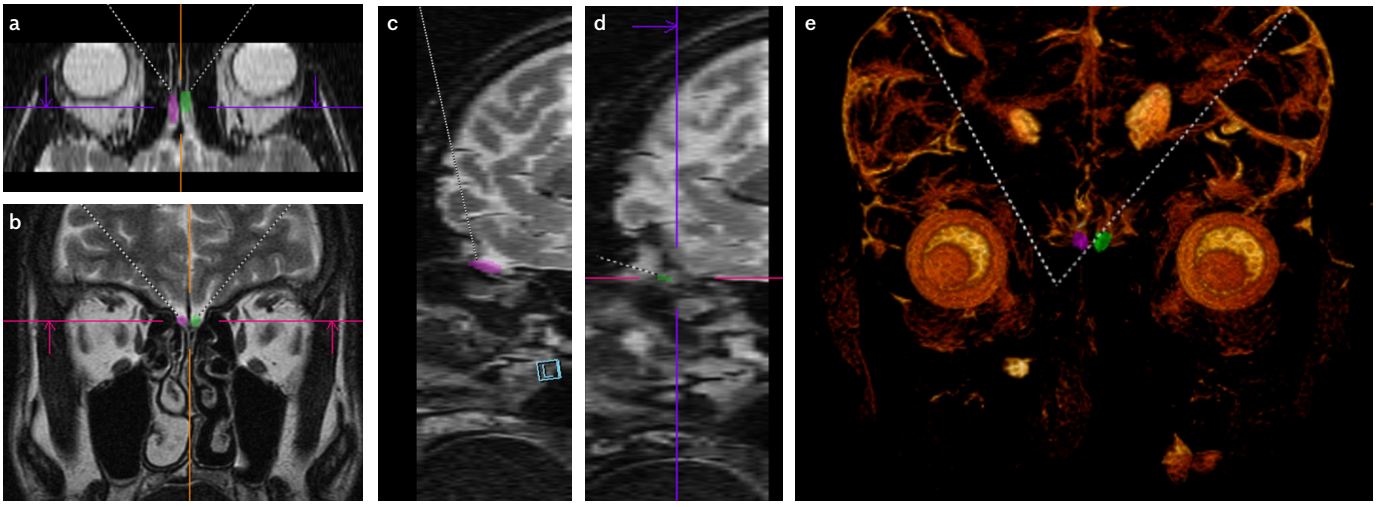

Figure 1. a-e. Right and left olfactory bulb volume (OBV) T2-weighted magnetic resonance (MR) sections and volume rendering technique (VRT) MR images of a patient with diabetic olfactopathy. In this patient, OBV measurements are 62 mm^3 on the right and 69 mm^3 on the left:
(a) Right and left OBV measurements in axial T2-weighted MR sections and VRT.
(b) Right and left OBV measurements in coronal T2-weighted MR sections and VRT.
(c) Right OBV measurements in sagittal T2-weighted MR sections and VRT.
(d) Left OBV measurements in sagittal T2-weighted MR sections and VRT.
(e) Right and left OBV measurements in VRT.

Table 2. Descriptive statistics

	Group 1 (n = 12)				Group 2 (n = 13)				Combined (n = 25)			
Variables	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Age (year)	54.25	3.96	53	[50–61]	55.23	4.23	54	[50–63]	54.76	4.04	54	[50–63]
CCCRC	4.27	0.67	4.25	[2.75–5.25]	6.42	0.31	6.5	[5.75–7]	5.39	1.21	5.75	[2.75–7]
OBV	65.04	6.97	62.75	[56.5–76.5]	76.46	11.36	77	[57.5–93.5]	70.98	10.98	68.5	[56.5–93.5]

Abbreviations: OBV: Olfactory bulb volume; CCCRC: Connecticut Chemosensory Clinical Research Center test score; Group 1: Patients with Diabetes Mellitus; Group 2: Control Group

Wilcoxon-Mann-Whitney test also confirmed that the CCCRC and OBV were statistically significantly lower ($p < 0.01$) for patients with DM than those of the control group (Figure 2).

Results

Total CCCRC scores were 4.27 ± 0.67 in Group 1 and 6.42 ± 0.31 in Group 2; these scores significantly differed between the groups ($p < 0.01$). The mean CCCRC scores in Groups 1 and 2 were moderately hyposmic and normosmic, respectively. In Group 1, one patient was anosmic, two were severely hyposmic, six were moderately hyposmic, and three were mildly hyposmic; in Group 2, one individual was mildly hyposmic, and the remaining 12 were normosmic. The mean OBV values were 65.04 ± 6.97 mm^3 and 76.46 ± 11.36 mm^3 in Groups 1 and 2, respectively (Table 2); these values significantly differed between the groups ($p < 0.01$).

Discussion

Olfactory dysfunction most often occurs after sinonasal diseases and head injuries. Olfactory dysfunctions have also been diagnosed in relation to post-infectious olfactory loss, toxic chemical exposure, alcoholism, endocrine diseases (e.g., DM and hypothyroidism), neurodegenerative diseases (e.g., Parkinson's disease, multiple sclerosis, and Alzheimer's disease), psychiatric disorders (e.g., major depression and schizophrenia), intracranial tumors, and nasal and sinus surgeries. If no cause is identified, the condition is regarded as idiopathic olfactory dysfunction (13, 15). In epidemiological studies, the prevalence of olfactory dysfunction has been reported to range from 19% to 24%; however, many individuals are unaware of olfactory dysfunction and thus are not diagnosed (16).

The incidence of T2DM is gradually increasing and, accordingly, increased incidences have also been observed in morbidities and complications related to DM, leading to reduced quality of life among affected patients. In a study by Weinstock et al. (5), the olfactory function of 111 adults with T1DM and T2DM was evaluated by a detailed olfactory test using an odorant confusion matrix, which measured olfactory function according to the number of odorants correctly defined. In general, participants exhibited a reduced ability to identify odorants (67.8% correct identification). This reduction was significantly associated with older age and the existence of macrovascular disease (e.g., peripheral vascular disease and coronary artery disease); however, it was not related to glycemic control, DM type, duration of disease, or microvascular complications of DM (e.g., neuropathy, retinopathy, and nephropathy) (5).

DM is often complicated with severe medical conditions that may be associated with the development of reduced olfactory

ability. Microvascular complications (e.g., peripheral neuropathy and retinopathy) contribute to this situation in individuals with T1DM and T2DM (17). Although many studies have investigated visual impairment caused by microvascular complications in patients with DM, the relationship between olfactory dysfunction and DM is not well understood (18).

Olfactory tests have been used as early indicators to predict the onset and progress of diseases such as Parkinson's disease, multiple infarction dementia, multiple sclerosis, and Alzheimer's disease (19-21). Sequelae associated with macrovascular disease, such as ischemia, are presumed to adversely affect olfactory ability (5). In addition to the coexistence of DM and olfactory dysfunction, olfactory scores are reportedly lower in the context of DM-related complications (22). Although cranial neuropathies are relatively uncommon, they exhibit a clear relationship with diabetic neuropathy. The reported incidence of cranial nerve involvement is 1% in patients with DM (23). Olfactory dysfunction in patients with DM may be owing to olfactory nerve damage, which is an indicator of central neuropathy. Olfactory dysfunction has been associated with diabetic retinopathy and peripheral neuropathy (23). Patients' abilities to identify odorants have been shown to decrease with increasing severity of peripheral neuropathy (24). Olfactory tests are therefore recommended for the early diagnosis of diabetic complications (7).

Olfactory dysfunction because of DM has been known for many years, and many studies have been conducted regarding this relationship. However, it is unclear whether olfactory dysfunction has a mucosal or neural pathology in patients with DM or whether DM interacts with the OBV. Diabetic neuropathy comprises peripheral nervous system disorders caused by neuropathy. Olfactory dysfunction observed in patients with diabetic neuropathy is regarded as diabetic olfactopathy. Hyperbaric oxygen therapy has been reported to improve olfactory ability in patients with diabetic olfactopathy (25).

Mononeuropathy has been described as weakness of the cranial nerves. The incidence of cranial neuropathy is higher in elderly patients who have exhibited DM for a long period. Many of these patients have various comorbidities and poor glycemic control (26). Diabetic neuropathy is characterized by isolated paralysis (palsy) of the third, fourth, and sixth nerves (27).

Olfactory dysfunction in patients with DM may occur because of conductive or sensorineural problems (28). Conductive dysfunction can be a consequence of nasal pathologies. In this study, a detailed nasal examination was performed, and conductive etiology was discarded. Sensorineural olfactory dysfunction could be owing to defects in the olfactory nerve fibers, receptors, olfactory bulb, and orbitofrontal cortex (28). The olfactory sensory neurons extend axons only to the olfactory bulb. The olfactory bulb is the most important link that connects the peripheral and cortical structures and reflects afferent neural activity, which preserves the plasticity of the olfactory system (29). The OBV is reportedly associated with measured olfactory function and varies as a function of age in healthy individuals (30).

Various theories have been proposed regarding the underlying mechanisms, including microvascular and macrovascular changes and their direct effects on the olfactory nerve or central DM owing to other abnormalities (5, 6, 23). Furthermore, the olfactory system is connected to endocrine systems that regulate or alter the energy balance of the body (31). Olfactory dysfunction may progress because of glucose toxicity and oxidative stress underlying micro- and macrovascular complications. Gouveri et al. (6) also suggested a mechanism whereby central manifestations of diabetic neuropathy affect the olfactory nerve. Vascular lesions and brain atrophy have been reported to cause central nervous system dysfunction and may play a role in T2DM-related cognitive impairment in patients with DM (32).

An important effect of olfactory deprivation in animals is the reduction in OBV because of a reduced number of cells (4). Magnetic resonance imaging is regarded as the gold standard in OBV measurements. OBV reflects the functionality of the olfactory system in humans because of the plasticity of this structure. OBV has been investigated in patients with post-traumatic olfactory deficiency, neurodegenerative diseases, and normal olfactory function (12, 33, 34). The high prevalence of cranial nerve involvement in patients with DM shows that the olfactory nerve, which is the first cranial nerve, can be affected by DM to a similar degree as other cranial nerves. Olfactory dysfunction in patients with DM may occur because of the weakened olfactory nerve. Thus, it can be considered an indicator of central neuropathy (23). In our study, we believe that olfactory nerve nutrition was impaired by microvascular or macrovascular mechanisms in patients with DM, and therefore, OBV decreased owing to olfactory atrophy.

Consistent with the literature, both mean OBV values and total CCCRC scores were significantly lower in the diabetic olfactopathy group in this study, indicating that the olfactory nerve was affected by DM in a manner similar to that of other cranial nerves. Furthermore, there is a need for additional studies regarding existing findings to determine whether the olfactory test and OBV measurement can be used as a tool for the early diagnosis of central diabetic neuropathy, including DM-related cognitive impairment. We believe that they can be used as a marker of DM in the future.

In our study, a significant reduction was observed in the olfactory function of patients with T2DM compared with that of healthy individuals. Moreover, OBV was significantly lower in patients with diabetic olfactopathy than in healthy individuals. To the best of our knowledge, this is the first study to show that the olfactory bulb is affected in patients with diabetic olfactopathy.

Ethics Committee Approval: This study was approved by Ethics committee of İstinye University, (Approval No: 2017-KAEK-120/2/2020.G-068).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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H.Ö.D.; Data Collection and/or Processing – D.G., M.C.K., A.M.B., H.Ö.D.; Analysis and/or Interpretation – D.G., M.C.K., A.M.B., H.Ö.D.; Literature Search – D.G., M.C.K., A.M.B., H.Ö.D.; Writing Manuscript – D.G., M.C.K., A.M.B., H.Ö.D.; Critical Review – D.G., M.C.K., A.M.B., H.Ö.D.

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