Olfactory Dysfunction in Iranian Diabetic Patients

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Abstract- Olfactory dysfunction is a known complication of diabetes and, despite its importance in the quality of life, is usually neglected due to its gradual progression. In this study, we aim to determine the prevalence and severity of olfactory dysfunction in diabetics and its association with microangiopathic complications of the disease (neuropathy, nephropathy, and retinopathy). Excluding the confounding factors, a case-control study of 60 eligible subjects, divided into a group of 30 diabetic patients and a group of 30 control subjects was performed. We used "absorbent perfumer's paper strips" method to test the olfactory threshold. In our study, 60% of diabetics were found to have some degree of olfactory dysfunction and a significant difference (P<0.01) between the olfactory threshold of the case and control groups was observed. There were no significant associations between the olfactory dysfunction and age, sex, treatment duration and microangiopathic complications.

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Keywords: Diabetic; Iran; Olfactory Dysfunction; Complication

Introduction

Olfactory impairment is often undetected in the general population due to its gradual progression. Self-reported incidence of 1-3% and 15.3% were observed in different studies (1,2). Self-report, however, significantly underestimate the prevalence rates of olfactory dysfunction compared to the results of olfaction testing (3,4) and even in a population-based survey with an olfaction test, an incidence of 24.5% was reported (against self-report of 9.5%) (5).

Olfactory dysfunction in diabetic patients and its pathophysiology were reviewed in many previous studies (6-9). Besides, olfaction and gustation in diabetics are of great importance regarding quality of life and possible hazards that their impairment may bring about (10). Hence, using a standard technique and excluding the confounding factors, we aim to determine the prevalence and severity of olfactory dysfunction in diabetic patients and its association with microangiopathic complications of diabetes, duration of the disease and level of glycemic control.

Materials and Methods

An Observational-Analytical Case-Control Study was conducted in 30 diabetic patients referred to the Diabetes Clinic of Imam Khomeini hospital and 30 controls cases visited in ENT Clinic of Amir Aalam hospital. The sample size was determined based on a comparison of two proportions formula (α=0.05, β=0.2, P=0.66, and OR=4). One hundred cases were selected initially and 40 were omitted by means of a detailed exclusion criteria of cigarette smoking, chronic alcohol use, substance abuse in the past 6 months, abnormal ENT physical exam (congestion, infection, chronic rhinitis), asthma, head trauma, history of head and neck radiation, history of cerebrovascular accident or Parkinson's disease, pregnancy, upper respiratory infections in the past 2 weeks, psychosis or schizophrenia, environmental toxins exposure, antibiotics, antihistamines, antidepressants, anticonvulsants or antineoplastic drugs usage, other endocrine disorders (hypothyroidism, hypogonadism and adrenal insufficiency) and autoimmune disease like Sjogren's Syndrome. A questionnaire encompassing personal data (age and sex), disease characteristics (duration, nephropathy, neuropathy, retinopathy, HbA1C and treatment regimen), endoscopic findings and olfactory threshold test result was prepared. Nephropathy was defined as 30-300mg albumin in 24-hour urine. Retinopathy and neuropathy were assumed

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to be present after the ophthalmology and neurology consults, respectively. Treatment regimen was divided into two categories of insulin therapy and oral antihyperglycemic agents.

In this study "absorbent perfumer's paper strips" method was used. We chose phenyl ethyl alcohol as the odorant and Propylene glycol ($C_3H_8O_2$) as the solvent. The phenyl ethyl alcohol was diluted, according to Tsukatani study (11), in 8 stepwise concentrations from 6.44×10^{-1} to 6.44×10^{-8} g/cm3 in 8 numbered glass test tubes. Then an absorbent paper strip was inserted into the test tube 8 (most diluted), and the subject was asked to smell the strip 3 to 4 times. The test continues with higher dilution steps.

Wherever the subject could smell the odorant, the corresponding dilution step was recorded as the subject's olfactory threshold. A series of conditions were considered before carrying out the test: The testing room should be well ventilated and the subjects should not have used any fragrances (this even includes fragrant soaps or shampoos), the test should not be performed within 30 minutes after a meal or a drink (except water), each strip should be used once and disposed of in a can distant to the subject, and the examiner should wear odorless gloves during the test. The eligible participants gave written consent. Endoscopy was performed after the olfactory threshold testing because the mesh soaked with phenylephrine and lidocaine used prior to the endoscopy can interfere with the test results.

Finally, data was analyzed for cases (diabetic subjects) and control (subjects without diabetes) through central tendency indices, standard deviation, Chi2, Pearson Correlation, *t*-test, ANOVA and non-parametric tests (Mann-Whitney) in SPSS v17.0 software. Statistical significance of $P < 0.05$ was set.

Results

A total of 60 subjects divided into the case group of 30 diabetic patients and the control group of 30 nondiabetic subjects were investigated in this study. The mean age of total participants was 44.5 (SD 5.7; range 18-65) and 27 (45%) were male. The characteristics of the diabetic group were as follows: Mean age=47 (range 25-65), 12 (40%) male. Endoscopic findings: Normal; 12 (40%), Unilateral septal deviation; 7 (23.3%), Bilateral septal deviation; 5 (16.7%), Unilateral spur; 5 (16.7%), Bilateral Spur; 1 (3.3%).

Treatment regimen: Oral agents; 20 (66.7%), Insulin therapy; 10 (33.3%). Mean duration of treatment: 65 months (range 1-240). HbA1c: Mean; 8.4 (range 5.8-12.2). Neuropathy frequency: 17 subjects (56.1%). Nephropathy: 8 subjects (26.4%). Retinopathy: 6 subjects (19.8%). Olfactory threshold: Step 0 (pure liquid); 2subjects, step 8; 1 subjects, median; step 3.5 (SD 1.5), mode; step 3 the characteristics of the control group were as follows: Mean age=42 (range 20-60), 15 (50%) male. Endoscopic findings: Normal; 10 (33.3%), Unilateral septal deviation; 14 (46.2%), Unilateral spur; 4 (13.2%), Bilateral spur; 2 (6.6%). Olfactory threshold: range; step 3-8, median: step 5, mode; step 4.

There was a significant difference between the mean age of the two groups (P=0.00). Since the age is a confounding factor in olfactory threshold, we broke down the participants into the groups of 40 year-olds and under and over 40 year-olds to avoid its impact on our test results. Afterward, we analyzed the data from these groups using non-parametric (Mann-Whitney) test. There was no significant association between the median of olfactory threshold and age in the case group (Sig (2-tailed)=0.177), nor is between olfactory threshold and treatment duration (Sig (2-tailed)=0.58). However, there is a significant difference between the median of olfactory thresholds of the two groups (P<0.01). In other words, the olfactory threshold in diabetic patients is higher than the control group.

The median of olfactory threshold in the control group was determined to be step 5. Therefore, higher thresholds (step 1-4) are considered hyposmia, step 0 anosmia and generally step <5 is considered olfactory disorder. Accordingly, in the case group, 18 subjects (60%) assumed to have olfactory disorder (anosmia; 2 subjects (6.7%) and hyposmia; 16 subjects (53.3%)). There were no statistically significant association between olfactory disorder and sex (case group: Exact Sig (2-sided)=0.709, control group: Exact Sig (2-sided)= 0.462), age (case group: Exact Sig (2-sided)=0.662, control group: Exact Sig (2-sided)= 0.515), treatment duration (Exact Sig (2-sided)=10.415), nephropathy (Exact Sig (2-sided)=1.000), neuropathy (Exact Sig (2- sided)= 0.26) or retinopathy (Exact Sig (2-sided)= 1.000).

Discussion

The aim of this study was to assess the olfactory threshold of diabetic patients in comparison to non-diabetics. A significant difference (P<0.01) in, both median and mode of, olfactory threshold between the two groups was observed and, as a result, 60% of the diabetic group falls into the category of olfactory dysfunction. Regarding the pathophysiology of olfactory dysfunction in diabetic patients, previous studies

manifested contradictory results. Naka et al. concluded that there is no correlation between micro- or macroangiopathic complications of DM and olfactory dysfunction. In this study only the diabetic patients with other co-morbidities (hypo- or hyperthyroidism, chronic intake of antidepressant, antiepileptic or antirheumatic drugs, disease of the liver, kidney or central nervous system) had diminished olfactory function (12). Contrarily, Le Floch et al. associated olfactory dysfunction with microalbuminuria ($P<0.05$) and peripheral neuropathy ($P<0.01$) and suggested a degenerative mechanism related to DM (7). Besides, Weinstock et al. somewhat correlated macrovascular disease with olfactory impairment (9). In our study, there is no association between olfactory dysfunction and neuropathy (Exact Sig (2-sided)=0.26), nephropathy (Exact Sig (2-sided)=1.000) and retinopathy (Exact Sig (2-sided)= 1.000). It may be postulated that olfactory impairment in diabetic patients is multi-factorial and microvascular complications of DM alone, do not account for it, As nutritional and occupational factors, depression, menopause, body mass index, steroid use, oral medications for cardiovascular disease or protease inhibitors have been mentioned in previous surveys to affect the chemosensory function (5,13-16).

The present data indicate that the olfactory impairment is not correlated with the duration of the disease or the level of glycemic control, which is congruent with previous studies (9,12). We also found no association between olfactory threshold and age in neither of the groups. In summary, our study revealed a significant difference between the olfactory threshold of diabetic and nondiabetic patients. The impaired sense of smell was neither correlated with the microvascular complications of DM nor duration of the disease or level of glycemic control. Perhaps, larger case and control groups and considering more variables including pathologic variables and co-morbidities can help to recognize the pathophysiology of olfactory dysfunction in diabetic patients.

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