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Assessment of olfactory functions in diabetes mellitus

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ABSTRACT

Background: The prevalence of Type 2 Diabetes Mellitus (T2DM) is increasing all over the world and is a major public health problem in India. Studies have been done on diabetes and associated complications like, retinopathy, nephropathy, neuropathy etc, but there is a paucity of research on olfactory functions in T2DM.
Aim: Assessment of olfactory functions in T2DM.
Materials and Methods: This was a cross-sectional study done on 105 subjects; 35 T2DM patients ≤ 5 years disease duration and 35 T2DM patients > 5 years disease duration, and 35 controls. Ethical clearance was obtained from the Institute's Ethics Committee, and a written informed consent was obtained from all the subjects. Assessment of olfactory functions was done by olfactory evoked potentials (OEP).
Results: The study showed that the latencies of the OEP waves in T2DM patients showed a trend towards significance both with increased duration of the disease, and higher HbA1c levels. This can be interpreted as deviation from the normal pattern of OEP, seen in normal individuals. This opens opportunities for further research in this field.
Conclusion: Changes in the central processing of the olfactory functions with increasing duration of T2DM and greater HbA1c levels may occur. Early detection smell impairment and meticulous control of blood sugar levels are required to prevent complications of T2DM affecting the olfactory sensation.

1. Introduction

The history of diabetes mellitus dates back to ancient Egypt, where its symptoms were first described around 2000 B.C. Mellitus means honey and depicts one of the early signs of diabetes, sugar in the urine.[1] Over the past few decades, the number of patients with diabetes mellitus has more than doubled globally, making it one of the most important public health challenges worldwide. India is amongst the epicentres of the worldwide diabetes mellitus pandemic. The age of onset in India has been shifting towards younger people even within the past decade.[2]

Less is known about the impact of diabetes on special senses such as olfaction. Only a limited number of studies have explored the relationship between olfaction and diabetes. The objective of the study is to assess olfactory functions in T2DM. The hypothesis is, that olfactory functions may be impaired in T2DM and probably worsen with longer disease duration and increasing HBA1C levels.

1.1. Diabetes and olfactory dysfunction

Several hypotheses have been proposed for the development and progression of olfactory dysfunction in diabetes. Patterson D.S. et al. linked the olfactory system to the endocrine system, suggesting various metabolic

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and endocrine pathways related to food intake, energy balance, insulin resistance, low-grade chronic inflammation, and modification of hypothalamus–pituitary–adrenal axis, which influences the modulation of olfactory pathways.[3] Glucose toxicity and oxidative stress underlying micro and macro vascular complications may cause olfactory nerve impairment.[4] Naka A et al. stated isolated cranial neuropathy as a well-established manifestation of diabetic neuropathy[5] and Palouzier-Paulignan B et al. proposed midbrain ischaemia as a cause of multiple cranial nerve palsies in diabetes.[6]

1.2. Olfactory evoked potential

Olfaction is the oldest sensory modality in the evolutionary history of mammals.[7] Evoked potentials are time locked electrical response of the central nervous system to external stimuli which can be of somatosensory, auditory, gustatory, visual or olfactory modalities. These electrical activities occur within a large number of pyramidal cortical neurons that are oriented similarly.

Evoked potentials are defined as EEG-derived polyphasic signals which can be used in diagnosis of a wide variety of neurological diseases. They provide stable monitoring of sensory, peripheral and central nervous systems functioning in clinical context. They also help to define anatomic distribution of a disease over time.[8] The first quantitative EEG changes in adults upon odour stimulation was published by Van Toller.[9] In 1966, Finkenzeller was the first discoverer of olfactory evoked potentials (OEP).

OEPs are a valid electrophysiological technique for study of the olfactory system.

This method allows to observe changes in olfactory function in an objective way. Presence of OEP is a strong indicator of good olfactory function; conversely, its absence suggests olfactory loss. It consists of a large negative component, called N1, followed by a large positive component, called P2.[10] The early component N1 reflect the exogenous cortical activity related to sensory input detection and primary sensory processing while the late components P2 reflect endogenous cortical activity related to secondary cognitive processing.[11,12] Latency of N1 and P2 components is a measure of the time required for sensory and cognitive processing of odour stimuli, respectively. A study of olfactory cortical evoked potentials performed by Whittet HB and Royston R.displayed a well-defined cortical response by normosmic control group. On an average, the latency of the first peak appeared in the range of 170-240 ms, and the final peak was observed in the range of 360-500 ms.[13]

2. Materials and Methods

2.1. Study design

The present study was a cross sectional study. After determining the subjects and controls, assessment of various variables of the study were done and compared.

2.2. Sample source

Subjects included in the sample consisted of patients selected from the Department of Endocrinology and age and sex matched controls from the neighbourhood.

2.3. Sample size

The sample used in this study consisted of 105 subjects - 35 T2DM patients with duration of disease upto 5 years, 35 T2DM patients with duration of disease more than 5 years, and 35 age and gender matched controls

2.4. Age group

Subjects selected were of the age range of 25 to 50 years

2.5. Determination of sample size

Sample size is calculated based on previous study conducted by Gouveri et al. in which it was found that among diabetics the lower odour threshold was 6.51 ± 2.52 and 8.7 ± 2.96 among controls. In the present study considering effect size of 0.72, and considering power of 80% and confidence level of 95%, sample size is calculated to be 35 in each group.

2.6. Inclusion criteria

The study group comprised of patients with T2DM and controls, in the age group of 25 to 50 years.

1. Patients with equal to or less than 5 years T2DM (Group I)
2. Patients with more than 5 years T2DM (Group II)
3. Age and sex matched controls (Group III)

2.7. Exclusion criteria

1. Past or present history of psychiatric or neurodegenerative disorders
2. History of head/ oral/ nasal trauma or surgery
3. Patients with a known history of nasal polyps, severe deviated nasal septum, respiratory tract infections
4. Those who have had COVID in the past 6 months.
5. Patients on treatment with sedatives drugs, antiepileptic drugs
6. Alcoholics, smokers or substance abusers
7. Patients with known taste disorders due to any reason
8. Patients with hypothyroidism or hyperthyroidism
9. Patients with chronic liver or kidney disease

10. Pregnancy

2.8. Method of collection of data

Subjects fulfilling the inclusion and exclusion criteria described above were recruited for the study. A written informed consent was obtained from the participating subjects. Ethical clearance to conduct the study was obtained from the Institute's Ethics Committee for Human Research. HBA1C levels were determined for all subjects. The procedure for evaluating OEP was described in detail to the subjects and were given the right to terminate their participation during the study, if they chose to do so. No monetary expenditure was done by the subject for any of the tests in the study.

2.9. Olfactory evoked potentials recordings

Olfactory function was assessed objectively by recording olfactory evoked potentials. Prior to the test, the subject was instructed to avoid applying hair oil after their last hair wash, and was told not to use and perfume / eu de toillete or any other scents. Olfactory evoked potentials were recorded with the subjects awake, comfortably sitting on a chair in a semi darkened, quiet and well ventilated room and were requested to remain calm and quiet avoiding bodily movements during the test. The eyes were kept closed to avoid electro- oculographic artefacts due to eye movements and improve the attention to the stimuli presented. The OEP recordings were performed using Ag/ AgCl disc electrodes. The sites chosen for electrode placement were cleaned with Nuprep EEG and ECG abrasive skin prepping gel. The recording electrodes were placed at Fz and Cz using the Ten 20 conductive electrode paste as per the 10-20 international system of EEG electrode placement. The reference electrode was placed at A1 and the ground electrode was placed at FPz. All electrodes were plugged to a junction box and skin to electrode impedance was kept below 5 K Ohm. Signals picked up by the electrodes were band –pass filtered between 1 to 30 Hz, amplified, averaged and displayed on the screen of GALILEO NT Evoked Potential Recorder. The waves N1 and P2 were measured from the Fz and Cz electrodes in response to the stimuli presented binasally. The recommended montage for olfactory evoked potential recordings were Channel 1: Fz-A1 and Channel 2: Cz-A1. Stimulus was presented with the help of a customized olfactometer. It had an air flow rate of 7.4 L/m of humidified air, with ambient temperature. Air and the odorant stimulus, amyl acetate (1% v/v) were delivered to the nostrils by a plastic duct through Teflon tube. Stimulus was presented for 200 ms each, corresponding to the inspiration of the subject. Interstimulus interval was kept at 30 seconds to avoid habituation/ adaptation. Samples contaminated with artefacts were auto discarded. The responses to the stimuli were averaged and 1000 averages were recorded. The waveform pattern was replicated. The sampling frequency was kept at 128 Hz. Amplitude was measured from the peak of one polarity to the baseline. The latency was calculated as the difference between the time of stimulus to the peak point of the waveform. The different wave form latencies were calculated.

2.10. Statistical analysis

The Statistical software SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. One-way analysis of variance (ANOVA) is employed to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Pearson correlation /Spearman Correlation between study variables was performed to find the degree of relationship. In all the above tests, P value of less than 0.05 was accepted as indicating statistical significance.

3. Results

The smell functions were compared between the normal subjects and those who had T2DM. Also, the association of HbA1c and the duration of T2DM with smell functions was studied.

Mean age (in years) was 40.00±7.60, 42.17±5.51 and 39.20±7.90 in Groups I, II and III respectively. Gender distribution in the three groups was not statistically significant (P = 0.765). Mean BMI in the three groups were 23.72±1.22, 23.95±1.72, 23.52±1.68 kg/m^2 respectively. Mean duration of T2DM (in years) in Group I was 2.27±1.2 and in Group II was 9.22±4.86. HbA1c % distribution in three groups of subjects was done using the Fisher Exact Test (P <0.001). (Table 1). HbA1c % distribution amongst Group I vs. Group II was also statistically significant (P=0.022).

A comparison of Mean ±SD of OEP N1 and P2 Latencies at Fz-A1 and Cz-A1 in the three groups of subjects was done by the ANOVA test. There was no statistical significance observed amongst the three groups (p> 0.05). (Table 2)

A comparison of OEP Latencies in relation to HbA1C % of subjects was also done. Within the respective groups, the subjects were distributed by HbA1c % values up to 6, 6 to 7 and ≥ 7. There was no statistically significant difference seen except for N1 latency at Cz. (Table 3)

Table 1: HbA1c% distribution in groups studied

HbA1c%	Group I	Group II	Group III	Total
Up to 6	0(0%)	0(0%)	35(100.0%)	35(33.3%)
6-7	16(45.7%)	7(20%)	0(0%)	23(21.9%)
7 & more	19(54.3%)	28(80%)	0(0%)	47(44.8%)
Total	35(100%)	35(100%)	35(100%)	105(100%)

Table 2: Comparison of OEP latencies in the groups studied

V ariables	Group I	Group II	Group III	Total	P value
N1 Latency (Fz)	211.09±4.93	210.37±5.30	212.12±3.37	211.19±4.62	0.283
N1 Latency (Cz)	210.68±4.08	209.98±5.66	212.37±3.53	211.01±4.58	0.080
P2 Latency (Fz)	408.02±5.00	406.12±10.56	406.64±10.07	406.92±8.86	0.655
P2 Latency (Cz)	406.24±5.46	395.21±68.73	406.98±10.19	402.81±40.22	0.394

Table 3: Comparison of OEP latencies in relation to HbA1c% of subjects studied

OEP Latency	HbA1c%			Total	P value
	Up to 6	6-7	7 & more		
N1 Latency (Fz)	212.11±3.42	212.17±5.54	210.07±4.73	211.19±4.62	0.074+
N1 Latency (Cz)	212.34±3.58	211.66±5.03	209.76±4.74	211.01±4.58	0.029*
P2 Latency (Fz)	406.29±10.01	407.84±8.10	406.93±8.47	406.92±8.86	0.813
P2 Latency (Cz)	406.61±10.10	390.38±84.44	406.07±8.52	402.81±40.22	0.247

Pearson correlation test was done to study correlation between HbA1c and the OEP latencies. The correlation between HbA1c % and N1 latency (Fz) was not significant in the groups. However, it was found there was a negative correlation (r = 0.204, p = 0.037*) with statistical significance for the entire population. The correlation between HbA1c and N1 latency (Cz) was also studied and found to be not significant in the groups. However, it was found there was a negative correlation (r = -0.265, p = 0.006**) with statistical significance for the entire population. The correlation between HbA1c and P2 latency (Fz) was not significant in the groups. It was found that there was a negative correlation (r = -0.019, p = 0.850) for the entire population. The correlation between HbA1c and P2 latency (Cz) was not significant in the groups. However, it was found there was a negative correlation(r = -0.012, p= 0.902) for the entire population. (Table 4)

A Comparison of the Means of OEP Latencies (N1 and P2) in relation to the duration of T2DM of was done. It was not found to be statistically significance. (P > 0.05) (Table 5)

4. Discussion

The sense of smell is an important component of flavour and an impairment, be it of acute onset or a chronic one will falter a person's ability to relish a normal diet. Olfaction may get altered either in an acute condition or slowly in chronic conditions like T2DM, where they may go unnoticed by the patients in the early stages. Alterations in smell may cause a decline in the quality of life or expose the affected individual to situations which might be hazardous to health. People who experience a subtle loss of taste might increase the intake of a particular tastant in their diet, like sugar, salt or sour substances. This can be especially detrimental to their health if they suffer from conditions like diabetes, hypertension, renal disorders, peptic ulcer disease etc. Affected individuals may not take proper quantity or quality of food if there is no flavour to it, leading to weight loss, or overeat in the pursuit of palatable taste. Both these conditions are perilous for a healthy lifestyle. The olfactory function was tested by recording OEP which is an objective assessment tool. Assessment of olfactory function done by other methods in different studies showed that olfactory sensation may be impaired in T2DM. Gouveri et al. conducted a study on 154 adults and found that T2DM patients had a lower odour threshold, odour discrimination and odour identification, and thus a lower TDI scores compared to controls. It was also observed that the treatment modality (insulin vs. oral hypoglycaemic agents), BMI, duration of diabetes and levels of HbA1c were not associated with olfactory dysfunction in diabetics.[14] In another study by Seraj J M et al, no association, significant enough was found between olfactory disturbances and any chronic complication of diabetes.[15]

Seta N et al. conducted a study to evaluate the components of chemosensory evoked potentials in normosmic subjects. Amyl acetate was used as an odorant gas and the trigeminal stimulant was odourless air.[16] They claimed to separate the evoked potentials obtained into two parts. Thus concluding that the earlier components of the evoked potential were trigeminal, and the later components were olfactory in nature. The olfactory evoked potential

Table 4: Correlation between OEP latencies and HbA1c% in the groups studied

Pair	Group I		Group II		Group III		Total	
	r value	P value	r value	P value	r value	P value	r value	P value
HbA1c% vs. N1 Latency (Fz)	-0.138	0.428	-0.267	0.121	-0.017	0.921	-0.204	0.037*
HbA1c% vs. N1 Latency (Cz)	-0.179	0.305	-0.232	0.179	-0.017	0.924	-0.265	0.006*
HbA1c% vs. P2 Latency (Fz)	-0.268	0.120	-0.016	0.927	-0.007	0.966	-0.019	0.850
HbA1c% vs. P2 Latency (Cz)	-0.300	0.080+	0.328	0.054+	-0.035	0.840	-0.012	0.902

Table 5: Comparison of OEP latencies according to duration of T2DM of subjects studied

Variables	Duration of DM		Total	P value
	≤5yrs	>5yrs		
N1 Latency (Fz)	211.09±4.93	210.42±5.23	210.75±5.06	0.581
N1 Latency (Cz)	210.68±4.08	210.08±5.60	210.37±4.89	0.606
P2 Latency (Fz)	408.02±5.00	406.46±10.61	407.23±8.31	0.434
P2 Latency (Cz)	406.24±5.46	395.88±67.87	400.99±48.42	0.372

peaks were in the range of 200.73 ± 28.9 ms and 353.64 ± 32.8 ms respectively. Thus, the components with longer latencies are the potentials evoked by olfactory stimulants and not the earlier ones.

A study by Han P et al investigated the influence of air flow rate and odorant concentration on olfactory potentials, on the previous study by Hummel et al. (2000). They mentioned components P1, N1, and P2. The largest negative peak N1 ranged between 200 and 700 ms, and the P2 peak was measured between 300 and 800 ms. thus indicating that the olfactory potentials fall in the late latencies, and they have a wider range of distribution.[17]

Whittet HB and Royston R. performed a study on olfactory cortical evoked potentials, post traumatic anosmic patients and found out that the controls displayed a well-defined cortical response.[18] On an average, the latency of the first peak appeared in the range of 170-240 ms, and the final peak was observed in the range of 360-500 ms. Air administration alone produced no cortical response, suggesting that the initial response was olfactory.

Not many studies have assessed olfactory function in diabetic individuals using OEP recordings. In this study OEP of all the subjects were recorded, also the latencies of the OEP waves were compared based on duration of diabetes in the T2DM patients. The latencies of waves N1 and P2 at Cz showed a trend towards decrease as the duration of diabetes increases. Correlation of OEP wave latencies and HbA1c levels of the subjects were also studied. A weak negative correlation of N1 wave latency was seen with HbA1c levels. These are suggestive of some changes in

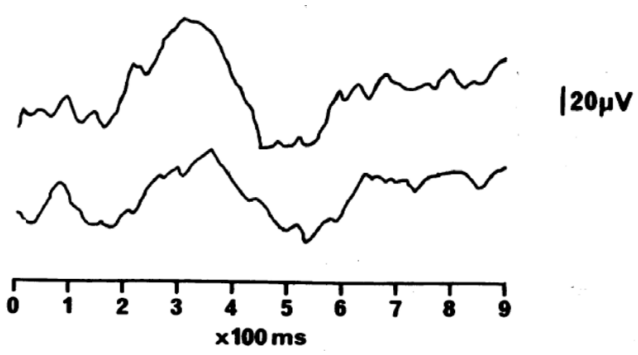

Fig. 1: Recording of response to olfactory stimulus presentation in control[18]

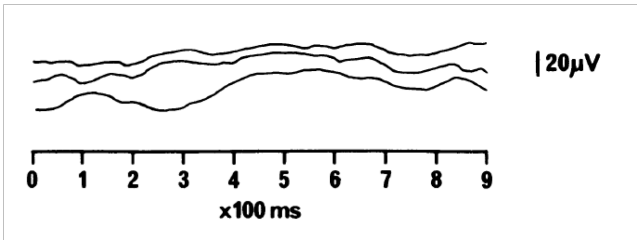

Fig. 2: Recording of response to olfactory stimulus presentation in congenital anosmic patient[18]

the processing of olfactory signals in the T2DM individuals which calls for further evaluation. Only latencies of the OEP waves were considered in this study. Amplitudes were not taken into consideration during the evoked potential test because amplitude values are of considerably variable nature.[19]

5. Limitations of the Study

The study had various limitations, as the sampling was done from a single source from the general outpatient department of only one tertiary care facility rather than the community; hence a potential bias would be likely to occur. Due to the relatively smaller sample size, some potential predictors of olfactory potential latencies in the study population were not statistically significant. The turnout of the findings in our study are most likely to be different if a larger sample size is considered.

6. Conclusion

This study concluded that olfactory functions of diabetic individuals show a trend towards being affected with the increase in disease duration and higher levels of HBA1C, though not at statistically significant levels. The results of the study are suggestive of some changes in the processing of olfactory signals in the T2DM individuals which calls for further evaluation. Future studies can be done to correlate the olfactory impairment of in T2DM with other factors like prehypertension, medicines and biochemical markers.

7. Source of Funding

None.

8. Conflict of Interest

None.

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