Original Article

Impact of Cardiac Autonomic Dysfunction on Cognitive Event-Related Potential in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition that is responsible for various long-term complications. Cognitive impairment is one of the most common complications, but the underlying mechanisms are still undetermined. The autonomic imbalance is a major cause for CVS morbidity in T2DM which could also potentially affect cognition. But there is sparse data available in the literature to prove the association between autonomic dysfunction and cognitive impairment. **Methodology:** We recruited 40 T2DM patients and 40 healthy controls. The assessment of cognitive functions was done by cognitive P300 event-related potential (ERP) and MoCA. Heart rate variability (HRV) was done to assess autonomic function. **Results:** The P300 ERP latency in Fz, Cz and Pz sites was significantly prolonged in T2DM patients ($P < 0.001$). We found moderate correlation is present between P300 latency and total power ($r = -0.466$, $P < 0.01$) and LFnu ($r = -0.423$, $P < 0.01$) in T2DM patients. The total power and HbA1C show independent association with P300 latency after adjustment for confounding factors like age and duration of diabetes ($P < 0.05$). **Conclusion:** As the incidence of Alzheimer's disease is rising among T2DM patients increasing their dependency, making necessary lifestyle measures at earliest to improve autonomic balance may prevent or delay the onset of cognitive decline and alleviate its consequences and improve the quality of life in T2DM patients.

Keywords: Autonomic imbalance, cognitive impairment, cognitive P300 event-related potential, heart rate variability, type 2 diabetes mellitus

Introduction

Globally, diabetes mellitus is recognized as the most prevailing and fastest growing metabolic condition. The International Diabetes Federation (IDF) reported that 463 million have people diabetes worldwide, and this may rise to 700 million by 2045.[1] Chronic hyperglycaemia leads to various microvascular and macrovascular complications that affect organs like the heart, kidney, eyes and peripheral nerves. The various end-organ complications and its consequences are well established in T2DM, whereas the presence of mild cognitive impairment in T2DM is often overlooked due to the lack of clear signs and unavailability of standard techniques to diagnose cognitive decline at the earliest. According to a recent systematic review by Pais *et al*.[2] in 2020, the global prevalence of cognitive impairment ranged from 5.1% to 41% with a median of 19.0%. It has been observed that the presence of diabetes increases the rate of cognitive deficit by 19% compared to those without diabetes.[3] Diabetes is one of the major causes of vascular and non-vascular dementia.[4-6]

Cognitive impairment will affect the domains of daily activities like general intelligence, attention, learning, memory and executive function leading to increased dependence. Self-care in diabetes has an important role in the successful management of the patients for a good outcome.[7] Cognitive

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deficit in T2DM hampers self-care leading to non-compliance to treatment and loss of control over blood glucose. Chronic uncontrolled hyperglycaemia has been shown to worsen cognitive functions and accelerates the progression from mild cognitive deficit to more advanced conditions like Alzheimer's disease (AD).[8-10] This intrigued the need for the detection of pathogenic mechanisms that could lead to cognitive decline in T2DM.

The major cardiovascular morbidity in T2DM has been attributed to cardiac autonomic neuropathy.[11] The autonomic imbalance in T2DM has various delirious effects increasing mortality. Heart rate variability (HRV) is the gold standard method to assess cardiac autonomic function. Previous evidence reported that there is reduced HRV among T2DM patients.[12] Decreased HRV has been shown to be associated with cognitive dysfunction in older adults. Most previous studies have explored the association of HRV and cognition in young and older individuals.[13] The Irish Longitudinal Study on Ageing (mean age 61.7 years) reported a cross-sectional association between time domain measures of HRV like SDNN and MOCA.[14] Moreover, a Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) with a mean age of 75 years has reported a longitudinal and cross-sectional correlation between HRV with processing speed and executive function.[15] But the data correlating HRV with cognitive function in T2DM patients are limited.

MoCA is one of the most sensitive screening tests that is widely employed for assessing cognitive function.[16] However, this test has a relatively high rate of intrasubject variability that lowers their capability to identify cognitive impairment.[17] This drawback can be overcome by using an objective test like cognitive P300 event-related potential with an auditory oddball paradigm to assess the neural events linked to short-term memory and attention. In an "oddball" paradigm, the patient concentrates on an infrequent "target" stimulus in a train of frequent "non-target" stimulus. The hippocampus and numerous associated regions of the neocortex involved in memory are thought to contribute to the P300 ERP.[18] The latency of the cognitive P300 ERP has shown to be a promising marker for cognitive dysfunction as it correlates well with various neuropsychological tests.[19] Golob *et al*.[20] demonstrated prolonged P300 latency in a group of asymptomatic familial AD patients with presenilin-1 or amyloid precursor protein mutations which proves that P300 ERP has the potential to detect sub-clinical cognitive deficit even before the emergence of obvious neurological manifestations.

The autonomic imbalance in T2DM has been frequently reported, but its association with cognitive decline in T2DM is largely undetermined. There is also a dearth of literature on utilizing cognitive P300 ERP as a screening tool for cognitive deficit in T2DM patients. In this background, the present study aims to determine cognitive function in T2DM patients using P300 ERP and Montreal cognitive assessment (MoCA). Further, an attempt is made to study the correlation between HRV and P300 ERP.

Methods

Study design

This was a cross-sectional study done on patients with type 2 diabetes mellitus to evaluate the association between heart rate variability and cognitive event-related potential. A total of 80 patients aged 18–60 years were included in our study. Of 80, 40 were T2DM patients and 40 were age and gender matched healthy individuals. The T2DM patients were recruited from the Department of Endocrinology. The details of the procedure were explained in the patient's native language, and informed written consent was obtained before taking up the patient for the study. This study was conducted in the clinical physiology laboratory, Department of Physiology. Inclusion criteria are BMI between 18.5 to 22.9 Kg/m^2. Exclusion criteria are type-1 diabetes mellitus, gestational diabetes mellitus, patients with major central nervous system disorders like dementia and Parkinson's disease, past history of head injury, stroke, current major psychiatric disorders like schizophrenia and bipolar disorder, peripheral neuropathy, alcoholics and smokers. We also excluded patients with clinical evidence of coronary artery disease, hypertension and severe multi-organ disease as these conditions have influence on autonomic function. The study was approved by the Institute Research Council and Institute Ethics Committee for human studies with reference no. T/IM-F/18-19/24 before the commencement of the study.

A brief medical history including age, duration of diabetes, symptoms associated with cognitive dysfunction, history of associated co-morbidities and treatment history was obtained from all the participants. Anthropometric parameters like height, weight, waist and hip circumference were measured. The body mass index (BMI) was calculated as Quetelet's index. Systolic and diastolic blood pressure were recorded from the right arm in sitting position after 10 mins of rest. After an overnight fast of approximately 8 hrs, blood samples were collected and the serum levels of fasting blood sugar, post-prandial blood sugar, glycated haemoglobin, serum triglycerides, high density lipoprotein, urea and creatinine were measured.

Assessment of cognitive functions

Montreal cognitive assessment (MoCA): The cognitive function was evaluated by MoCA in all the participants, which addresses the following cognitive domains like visuospatial abilities, executive functions, immediate and delayed memory, working memory, language, attention and orientation to time and place. The total MoCA score is 30, and a score less than 26 was considered to be cognitive impairment.

Event-related potential (ERP): The P300 ERP was recorded using NIHON KOHDEN-NEURO PACK EPEMG MACHINE (model: MEB-2300). The study participants were instructed to come to the electrophysiology lab around 9 am with an oil-free scalp. The test was carried out in sitting posture

in a quiet room after 10 mins of rest. The 10–20 international system was followed for electrode placement. The recording sites over the scalp were initially scrubbed with mild abrasive gel followed by cleaning with spirit to decrease the impedance. The electrodes were placed over the recording sites and secured with the micropore. The active electrodes were placed over Cz, Pz and Fz. The reference electrodes were placed one on each mastoid, and the ground was placed over the forehead. The impedance was kept ≤2 kΩ, and the bandpass filter was set at the range of 0.1–50 Hz. [Figure 1].

The participants were given clear explanations of the procedure before the recording. The standard auditory oddball paradigm technique was used with the binaural auditory stimulus through a headphone with the "tone" as the target or rare stimulus and "click" as a non-target or frequent stimulus. The rare stimuli were set at 20% and the frequent stimuli at 80% random. The participants were asked to concentrate on the rare stimuli. The stimuli were given at 1 Hz with a click duration of 0.1 ms. The signals were analysed using Neuro workbench Software. The parameters like latency and amplitude were obtained for analysis.

Recording of heart rate variability

All the subjects were asked to report 2 hrs after light breakfast. The patients were instructed to avoid exercise, smoking, alcohol and caffeinated drinks one day before the test. The European task force guidelines were followed for HRV recording and analysis. The study participants were given 20 mins of rest in supine position before commencement of the recording. A lead II ECG was recorded for 5 mins to obtain an R-R tachogram. The lab chart 8 data acquisition system and lab chart pro software were used for recording HRV. The time-domain and frequency-domain parameters were obtained for analysis.

Statistical analysis

The data were analysed by SPSS version 20.0. The distribution of the data was analysed by the Kolmogorov–Smirnov test.

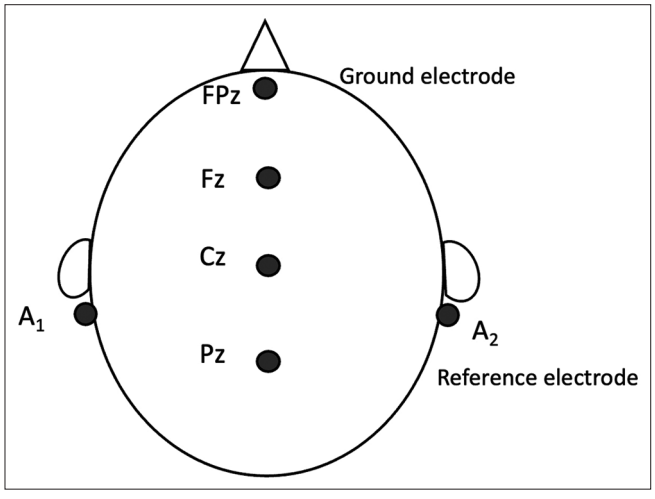

Figure 1: Schematic representation for electrode placement for P300 ERP

Data were expressed as mean ± S.D. The comparison of the mean for HRV parameters and cognitive function parameters was done by unpaired t-test. Pearson correlation was done to correlate between HRV and P300 latency. The multiple linear regression analysis with P300 latency as a dependent variable was done after adjusting for confounding factors like age and duration of diabetes. A *P* value of <0.05 is considered statistically significant.

Ethical Clearance Statement

The study was approved by the Institute Ethics Committee, All India Institute of Medical Sciences, Bhubaneswar for Human Studies vide approval number: T/IM-NF/Physio/19/24 dated 02-03-2022. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for the clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity. The procedures in the study follow the guidelines laid down in the Declaration of Helsinki 2008.

Result

Table 1 shows a comparison of baseline characteristics and biochemical parameters between the groups. The pulse rate was significantly higher in T2DM patients (*P* 0.001). The HbA1C is significantly higher in T2DM patients compared to controls (*P* < 0.001). MoCA shows a significant difference between the groups (*P* < 0.001).

Table 1: Comparison of baseline characteristics and biochemical parameters between the groups

	Type 2 diabetes mellitus (*n*=40)	Heathy controls (*n*=40)	*P*
Age	49.4±6.8	47.9±8.4	0.382
Duration (months)	12.28±6.09	-	
Height (cms)	156.2±12.4	157.4±10.6	0.643
Weight (kg)	58.2±12.7	56.4±14.8	0.561
BMI (kg/m^2)	22.2±3.4	21.2±2.8	0.155
W/H ratio	0.86±0.08	0.88±0.04	0.161
SBP (mmHg)	111.1±5.4	109.2±5.6	0.107
DBP (mmHg)	74.9±3.5	73.5±3.4	0.079
PR (beats/min)	81.8±10.6	74.5±8.9	0.001
HDL cholesterol (mg/dL)	47.8±8.4	52.8±13.8	0.059
Triglyceride (mg/dL)	207.9±32.1	189.5±43.9	0.567
FBS (mg/dL)	100.4±28.1	95.8±19.4	0.396
PPBS (mg/dL)	152±41.7	133.3±23.5	0.01
HbA1c (%)	7.08±1.2	5.3±0.51	0.000
S. Cr (mg/dL)	1±0.5	0.9±0.3	0.349
MoCA	26.4±2.4	29.0±1.0	0.000

Notes: Data expressed as mean±standard deviation. Data analysed by Student *t*-test. *P* value less than <0.05 is statistically significant. Abbreviations: BMI, body mass index; W/H ratio, waist/hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; HDL, high density lipoprotein; FBS, fasting blood sugar; PPBS, post-prandial blood sugar; HbA1C, glycated haemoglobin; S. Cr, serum creatinine; MoCA, Montreal cognitive assessment

Table 2 shows a comparison of heart rate variability parameters between the groups. The time domain parameter SDNN shows a highly significant decrease in T2DM patients compared to healthy controls ($P < 0.001$). The other time domain parameters like RMSSD, NN50 and pNN50 were observed to be significantly decreased in T2DM patients compared to controls ($P < 0.05$). The frequency domain parameters like total power and HFnu were found to be significantly reduced in T2DM patients ($P < 0.001$). The LFnu and LF/HF ratio were significantly higher in T2DM patients compared to controls ($P < 0.001$).

Figure 2 shows a comparison of P300 latency and amplitude between groups. The P300 ERP latency in Fz, Cz and Pz sites in T2DM patients was significantly prolonged with a mean ± SD of 351.4 ± 38.9, 356.6 ± 40.4 and 360.4 ± 42.1, respectively, compared to healthy controls with mean ± SD of 298.6 ± 22.6, 300.6 ± 20.7 and 308.4 ± 20.4, respectively ($P < 0.001$).

Table 2: Comparison of heart rate variability parameters between the groups

	Type 2 diabetes mellitus ($n=40$)	Heathy controls ($n=40$)	*P*
Mean RR (ms)	779.8±126.7	828.2±79.9	0.044
SDNN (ms)	21.75±11.5	31.6±10.6	0.000
RMSSD (ms)	24.1±13.2	30.9±9.9	0.012
NN50	22.1±11.1	26.9±7.1	0.023
pNN50 (%)	7.2±2.4	9.3±3.9	0.007
TP (ms^2)	899.4±165.2	1309.8±257.2	0.000
LFnu	69.9±10.5	44.3±10.7	0.000
HFnu	47.08±10.06	63.3±10.3	0.000
LF/HF ratio	1.6±0.4	0.9±0.3	0.000

Notes: Data expressed as mean±standard deviation. Data analysed by Student *t*-test. *P* value less than <0.05 is statistically significant. Abbreviations: Mean RR, mean RR interval; SDNN: standard deviation of normal to normal interval; RMSSD: square root of the mean squared differences of successive normal to normal intervals; NN50: the number of interval differences of successive NN intervals greater than 50 ms; pNN50: the proportion derived by dividing NN50 by the total number of NN intervals; TP: total power; LFnu: low-frequency component expressed as normalized unit; HFnu: high-frequency component expressed as normalized unit; LF-HF ratio: ratio of low-frequency power to high-frequency power of heart rate variability

The P300 ERP amplitude shows a significant decrease in Cz site in T2DM patients with a mean ± SD of 9.5 ± 4.2 compared to healthy controls with a mean ± SD of 11.03 ± 1.9 (P 0.02). No significant difference in amplitude was observed in Fz and Pz sites between the groups.

Figure 3 shows a scatterplot graph showing correlation between HRV metrics and P300 latency. Moderate correlation is present between P300 latency and total power (r = -0.466, P 0.002) and LFnu (r = -0.423, P 0.006) in T2DM patients. Weak correlation is observed between P300 latency and HFnu (r = -0.313, P 0.04), RMSSD (r = -0.34, P 0.03) and mean RR (r = -0.365, P 0.02) in T2DM patients. We found positive correlation between P300 latency and HbA1C (r = 0.34, P 0.03). (not shown in the figure).

Table 3 shows multiple linear regression analysis with P300 latency as a dependent variable in type 2 diabetes mellitus patients. The model could explain the variance by 30%. The total power and HbA1C show independent association with P300 latency after adjustment for confounding factors like age and duration of diabetes. ($P < 0.01$).

Discussion

A cross-sectional study conducted in 2017 in Punjab revealed a higher prevalence of cognitive impairment in T2DM of around 33%.[21] In the present study, we observed prolonged P300 latency in T2DM patients compared to controls. Anandhalakshmi *et al*.[22] observed similar results in T2DM patients in the south Indian population and showed a significant correlation between P300 latency and the duration of diabetes. We did not find correlation with duration in our study which is in concordance with Singh *et al*.[23] We found a positive correlation between HbA1C and P300 latency which supports the findings of other studies that have shown hyperglycaemia to be a risk factor for development of cognitive impairment. We found a significant decrease in the amplitude in the CZ region, and the result is similar to a study conducted by Teede *et al*.[24] In support of our result, a functional magnetic resonance imaging study at rest revealed bilateral decrease in hippocampal connections in T2DM patients.[25]

The P300 ERP used for the evaluation of cognitive deficit in our study is an objective method. It reflects the attention,

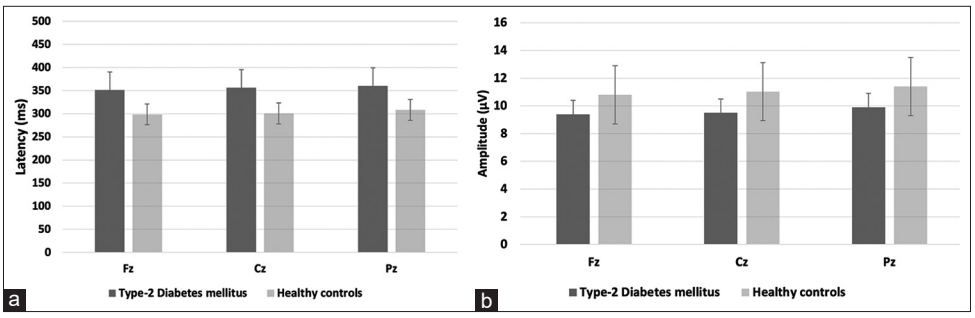

Figure 2: Comparison of P300 latency and amplitude between groups a. Clustered bar graph showing P300 latency in diabetic and control group b. Clustered bar graph showing P300 amplitude in diabetic and control group. Bar graph displays mean (standard deviation). *P* value less than <0.05 is considered to be statistically significant

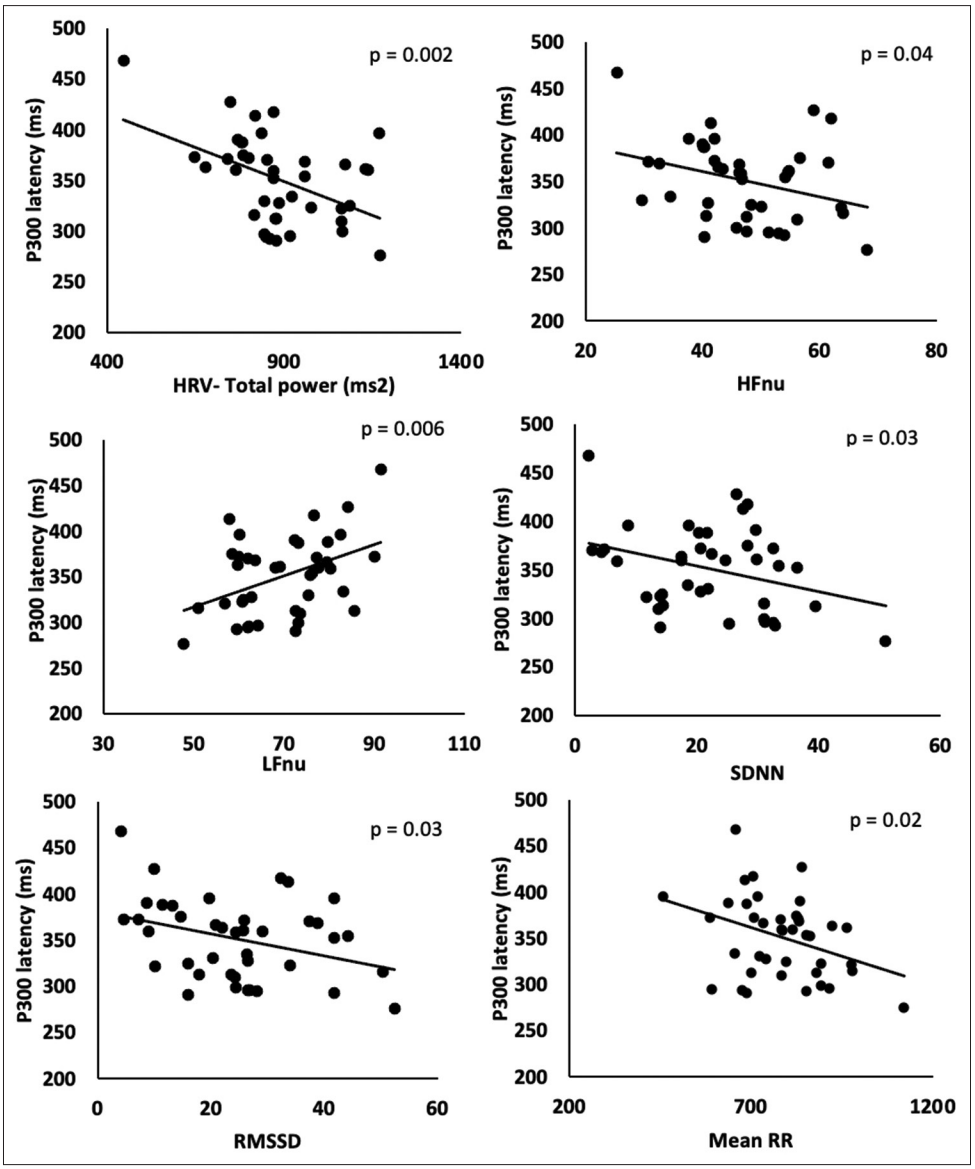

Figure 3: Scatterplot graph showing correlation between HRV metrics and P300 latency in type 2 diabetes mellitus patients. TP: total power; LFnu: low-frequency component expressed as normalized unit; HFnu: high-frequency component expressed as normalized unit; SDNN: standard deviation of normal to normal interval; RMSSD: square root of the mean squared differences of successive normal to normal intervals; Mean RR, mean RR interval. *P* value less than <0.05 is considered to be statistically significant

Table 3: Multiple linear regression analysis with P300 latency as dependent variable in Type 2 diabetes mellitus patients

Variable	Unstandardized B	Standardized co-efficient Beta	*P*	95% CI
Total power	-0.114	-0.393	0.013	-0.203 to -0.26
Age	0.089	0.03	0.828	0.96-10.19
Duration of diabetes	0.769	0.105	0.491	-1.436 to 2.973
HbA1C	10.218	0.296	0.04	-0.008 to 20.445

Notes: *P* values are derived from multiple linear regression analysis; adjusted for age, duration of diabetes and HbA1C. Abbreviations: B, regression coefficient; CI, confidence interval; HbA1C, glycated haemoglobin

working memory and processing speed of an individual. The cognitive P300 ERPs are produced in response to the auditory stimulus and are generated in the superior temporal lobe, especially the hippocampus and insula which are involved in cognitive processing.[26] Various studies in the past had shown a significant correlation between mild cognitive impairment and P300 latency and amplitude.[27,28] The latency of P300 ERP correlates well with the test scores of various neuropsychological test scores like MMSE and MoCA.[29] We also found a significant difference in MoCA score between the

groups which is in concordance with other studies.[29] But the major drawback of these tests is that age and education level might affect the results of these neuropsychological tests.[30] Hence, P300 is a simple, most sensitive and non-invasive method to screen for cognitive impairment.

The cognitive impairment in diabetes may be attributed to various pathogenetic mechanisms like abnormalities in insulin signalling, neuronal inflammation and mitochondrial dysfunction that affects the process of neuronal plasticity.[31] It also favours deposition of tau protein leading to progression towards Alzheimer's disease.[32] Apart from the above-mentioned causes, reduced cardiovagal modulation in T2DM could possibly lead to cognitive decline. The role of autonomic imbalance as the pathogenic factor in development of cognitive impairment has been explored recently in older adults with mild cognitive impairment.[33] However, sparse evidence is available in the literature regarding this association in T2DM patients.

In our study, we found a significant decrease in the time domain parameters of HRV in T2DM patients as compared to healthy controls. We also observed increased sympathetic activity via an increase in LF and reduced parasympathetic activity with a decrease in HF in T2DM patients. Similar findings of sympathovagal imbalance with heightened sympathetic activity and blunted parasympathetic activity were observed in previous studies conducted in T2DM patients and were associated with hyperglycaemia and duration of diabetes. Tarvainen and colleagues had demonstrated increased basal heart rate in T2DM which was associated with hyperglycaemia.[34] Kudat. *et al*. observed lower HRV in T2DM patients with microvascular complications than those without complications.[35]

We found a significant correlation between P300 latency and HRV parameters. We found an independent association between total power and P300 latency in T2DM patients. The decreased cardiovagal modulation in T2DM could lead to cognitive decline. This was supported by the neurovisceral integration model which demonstrates an association between vagal tone and the functioning of the brain areas involved in attention and emotional processing.[36] One of the experimental models demonstrated the presence of a complex neural circuit in the brain, in which the sympathetic hyperactivation leads to disinhibition of amygdala via circuitry through the prefrontal cortex which is involved in memory.[37]

Chronic autonomic dysfunction with sympathetic overactivity leads to hypertrophy of the vascular wall and narrowing of the vessel wall which subsequently results in decreased cerebral perfusion. If perfusion is compromised in the areas of the brain involved in memory, it leads to cognitive deficit.[38] In addition, the orthostatic hypotension that occurs due to autonomic dysfunction leads to episodes of transient cerebral hypoperfusion due to fall in BP. Such frequent hypotensive episodes have been correlated with development of dementia.[14]

As cognitive deficit could range from mild cognitive impairment to dementia which affects the activities of daily living, identifying all the plausible pathogenic mechanisms that could lead to cognitive deficit is essential in order to design appropriate preventive and therapeutic measures.[4] The assessment of autonomic function with a 5 min short-term HRV test could also serve as an early marker for cognitive decline. The lifestyle measures taken to improve the autonomic balance like the incorporation of breathing exercises, physical exercise, and yogic practices could prevent or delay the onset of cognitive impairment which in turn would improve the quality of life in these patients.

The strength of our study was the use of an objective method for assessing cognition, like event-related P300 potential, along with a validated cognitive screening instrument like MoCA. Our study has limitations, including relatively small sample size, lack of brain imaging and lack of molecular studies that help in assessing the pathophysiological basis involved in the process of cognitive decline in autonomic dysfunction. In our study, the participants were in an older age group with a longer duration of diabetes. It will be interesting to see if studies like this conducted in a younger population, as ageing has an impact on cognition. As this is a cross-sectional study, the causal relationship between autonomic imbalance and cognitive impairment could not be determined. Additional longitudinal studies in a larger population with a diverse ethnicity are needed to elucidate possible causal factors between autonomic dysfunction and cognitive impairment.

In conclusion, our study showed a significant association between autonomic imbalances with cognitive functions in T2DM. Recent evidence suggests that diabetic individuals are at greater risk of developing Alzheimer's disease, which increases mortality. Hence, incorporating necessary lifestyle modifications such as tailored dietary changes to control blood glucose levels and practising yoga and aerobic exercise would offer the benefit of improving autonomic balance. Improving autonomic dysfunction through lifestyle interventions will prevent or delay the onset of cognitive impairment and also alleviate the consequences of cognitive decline in T2DM patients.

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Conflicts of interest

There are no conflicts of interest.

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