Original Article

Cognitive Deficit is Linked to Cardiovascular Risk in Type 2 Diabetes Mellitus

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Abstract

Background and Aim: Diabetes has been reported to be caused by sympathovagal imbalance and is associated with cardiovascular (CV) risks and a wide variety of cognitive loss. The present study was designed to assess the link of cognitive deficit with CV risks in diabetic patients. **Methods:** Eighty participants (forty type 2 diabetic patients and forty controls) were included in this case–control study. The rate-pressure product (RPP), heart rate variability, event-related potential (P300), and biochemical parameters were recorded in both groups. Association of various factors with RPP was studied by Pearson's correlation analysis, and the independent contribution of factors to RPP was assessed by univariate regression analysis. **Results:** RPP and low-frequency-to-high-frequency (LF-HF) ratio were increased in patients with diabetes. The latency of P300 was significantly prolonged in patients with diabetes and P300 latency was positively correlated with RPP, the marker of myocardial oxygen stress, in hypertensives. The Homeostatic Model Assessment of Insulin Resistance and malondialdehyde significantly correlated with RPP. The P300 had independent contribution to RPP in diabetic group. **Conclusion:** Type 2 diabetic patients have sympathovagal imbalance, myocardial oxygen stress, oxidative stress, and considerable cognitive impairment. The cognitive impairment could be associated with CV risks in these patients.

Keywords: Cardiovascular risks, cognitive deficit, oxidative stress, rate-pressure product, sympathovagal imbalance, type 2 diabetes mellitus

Received: 03rd May, 2018; ***Revised*:** 25th May, 2018; ***Accepted:*** 27th May, 2018

Introduction

Diabetes mellitus (DM) is a known risk factor for premature cognitive impairment.[1,2] India is presently the epicenter diabetes in the world, with more than 62 million population suffering from the disease.[3] In the general population of India, type 2 DM (T2DM) has been found to be quite prevalent even in younger age group, which is considered to be the future pillar of the nation.[4] Therefore, premature dementia in such a younger population due to diabetes poses a serious threat to the socioeconomic development in the Indian subcontinent. Although the pathophysiology of memory impairment in T2DM is not fully understood, the levels of hyperglycemia, hyperinsulinemia, insulin resistance, and increased formation of advanced glycation end products (AGEs) have been proposed to be the possible mechanisms.[5,6]

Autonomic imbalance has been implicated in the pathophysiology of diabetes.[7-9] Sympathovagal imbalance has been reported to predict the cardiovascular (CV) risk and mortality in T2DM.[10] Cognitive deficit is defined as an average cognitive performance at around the 35th to 45th percentiles of normative data affecting one or multiple domains of cognition, though the cutoff to detect cognitive deficit is at 5th to 10th percentiles.[2] Although there are various sophisticated techniques for determining cognitive impairment, recently, the event-related potential (ERP) recorded in the form of positive wave at 300 ms (P300) has been considered as a better tool for assessing cognitive deficit.[11] P300 is closely related to cognition-related brain functions such as attention, intelligence, and working memory as P300 activates multiple

Access this article online

Quick Response Code:

Website: www.ijcep.org

DOI: 10.4103/ijcep.ijcep_36_18

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How to cite this article: Pal A, Sahoo JP, Venugopal L, Sirisha A, Pal GK. Cognitive deficit is linked to cardiovascular risk in type 2 diabetes mellitus. Int J Clin Exp Physiol 2018;5:94-8.

brain cortical areas which include frontal, prefrontal, and parietal regions.[12,13]

Rate-pressure product (RPP), a physiological marker of myocardial oxygen demand and myocardial work stress, is reported to be increased in prehypertension and hypertension that usually occur in diabetes.[14] Increased RPP is a known indicator of CV risk. However, till date, no study has been conducted to assess the link of increased RPP with cognitive deficit in T2DM patients in Indian population. Therefore, the present study was designed to assess the association of increased RPP, the marker of myocardial oxygen stress, with cognitive deficit in patients with T2DM.

Materials and Methods

The present study was conducted as a research project of the first author, as part of Undergraduate Golden Jubilee Straus Research Grant of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. After obtaining the approval of Undergraduate Research Monitoring Committee and Institutional Ethics Committee of JIPMER, eighty individuals (forty controls and forty diabetic patients) were recruited from the medicine outpatient department, diabetes clinic, and among the staff of JIPMER.

Sample size calculation

The total sample size was calculated to be 80, with 40 participants in each group. As the primary objective of this study was to measure and compare the association of RPP with P300, using previous reference,[15] considering the mean and standard deviation (SD) values of RPP, accepting power as 80%, and keeping the level of significance at 5%, the total sample size calculated by Open Epi software was 80.

Estimation of biochemical parameters

Written informed consent was obtained from all the participants prior to commencement of the clinical and laboratory investigations. From each participant, 5 ml of fasting blood sugar (FBS) sample was collected and blood glucose and malondialdehyde (MDA) were estimated by an autoanalyzer (AU400, Olympus, Orlando, FL, USA). Plasma insulin was assayed by chemiluminescence method using the kits of Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA. For determination of insulin resistance (IR), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated by using the following formula: HOMA-IR = FBS (mMol) × insulin (μIU/L)/22.5.

Grouping of subjects

Based on the fasting blood glucose (FBG) level, participants were classified into two groups, as per the American Diabetes Association criteria.[16]

1. Control group ($n = 40$): Normal healthy subjects, having FBG at 3.3–5.4 mmol/l
2. Diabetic group ($n = 40$): Freshly diagnosed, treatment-naïve, apparently healthy diabetic patients having FBG at 6.9 mmol/l or above.

The age of the participants of both the groups was between 18 and 44 years, of both the genders.

Exclusion criteria

1. Individuals having any acute illness
2. Individuals receiving any medications for any form of health problem
3. History of smoking, alcoholism, hypertension, other endocrinal disorders, CV diseases, and neurological disorders
4. Individuals practicing regular athletic activities or yoga.

Recording of anthropometric and basal cardiovascular parameters

The participants were asked to report to the Electrophysiology Laboratory of Physiology Department at about 9 AM following a light breakfast, without tea or coffee. After obtaining the informed consent, their age, height, body weight, and body mass index (BMI) were recorded. Blood pressure (BP) of all the participants was recorded in autonomic function testing (AFT) laboratory. The temperature of the Electrophysiology Laboratory was maintained at 25°C for all the recordings. Omron (SEM 1 Model), the automatic BP monitor (Omron Healthcare Co. Ltd, Kyoto, Japan), was used for BP recording. Systolic BP (SBP), diastolic BP (DBP), and basal heart rate were recorded.

Recording of P300 event-related potential

As ERP has long been established as a tool for the assessment of cognitive function,[17] in the present study, cognitive ERPs were recorded following the recommendation of the International Federation of Clinical Neurophysiology[18] and using the protocol of recording in Indian laboratory setup.[19] The participants were asked to come with cleaned oil-free scalp (shampoo head bath) with light breakfast. Before recording, they were checked and ruled out for ear wax. They were asked to sit for 10 min for getting adapted to the laboratory environment, during which the procedure of recording was explained to them. The scalp was cleaned with alcohol and the electrode placements were done according to the 10–20 international system of electroencephalography. The active recording electrode was placed at Cz (central 0 point on scalp), the midpoint between both the tragus and the midpoint between nasion and occipital protuberance. Two electrodes, one each on the two mastoids, were placed and connected with a jumper electrode that served as the reference electrode. The ground electrode was placed at Fz. The auditory stimulus was given binaurally through a headphone. The stimuli were given with the intensity of 40 dB with the "tone" as continuous stimulus and "click" as rare stimulus. The participants were asked to relax totally and asked to concentrate on the rare stimulus. During the recording, total silence was ensured and only the investigator and the participants were present in the laboratory. The rare stimuli were applied randomly, and the percentage of rare stimuli was set at 20% of the regular stimuli.

The appearance of negative waves is defined as N and positive waves as P. Two negative waves and two positive waves are recorded in the ERP tracing. They are designated in numbers according to the time taken in ms from the application of stimulus. Thus, N1 is the negative wave at 100 ms, N2 is the negative wave at 200 ms, P2 is the positive wave at 200 ms, and P3 is the positive wave at 300 ms. Among these waves, P300 (also known as P3), i.e., the positive wave at 300 ms, is documented as the marker of cognition. The procedure of recording was repeated for reproducibility of P3 and the marking was done for the latencies of N1, P2, N2, and P3 in milliseconds and the amplitudes of N1-P2, P2-N2, and N2-P3 in microvolts.

Recording of heart rate variability

The participants were shifted to autonomic function testing laboratory for heart rate variability (HRV) recording. After 15 min of supine rest on a couch in AFT laboratory, electrocardiogram (ECG) was recorded for 5 min for short-term HRV analysis following the standard procedure as per the recommendation of the Task Force on HRV.[20] For the purpose, ECG electrodes were connected and Lead II ECG was acquired at a rate of 1000 samples/second during supine rest using BIOPAC MP 150 data acquisition system (BIOPAC Inc., Goleta, CA, USA). The data were transferred from BIOPAC to a Windows-based PC with AcqKnowledge software version 4.2 (BIOPAC Inc., Goleta, CA, USA). HRV analysis was done using the HRV analysis software version 2.0 (Bio-signal Analysis group, Kuopio, Finland). Frequency domain indices such as total power (TP) of HRV, normalized LF power (LFnu), normalized HF power (HFnu), ratio of low-frequency to high-frequency power (LF-HF ratio), and time domain indices such as mean heart rate (mean RR), square root of the mean squared differences of successive normal-to-normal intervals (RMSSD), SD of normal-to-normal interval (SDNN), the number of interval differences of successive NN intervals greater than 50 ms (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) were calculated.

Statistical analysis of data

SPSS software version 16 (SPSS Inc., Chicago, IL, USA) and GraphPad InStat software (GraphPad Inc., San Diego, CA, USA) were used for statistical analysis. All the data were presented as mean ± SD. Normality of data was tested by Kolmogorov–Smirnov test. For parametric data, the level of significance between control and diabetic groups was tested by Student's unpaired "*t*" test and for nonparametric data, the Welch's corrected *t*-test was used. The association of RPP with BMI, HOMA-IR, MDA, LF-HF ratio, and P300 was assessed by Pearson's correlation analysis. The independent contribution of various factors such as P300 to RPP was assessed by univariate regression analysis. $P < 0.05$ was considered statistically significant.

Results

There was no significant difference in age between controls and diabetic patients [Table 1]. The BMI was significantly more ($P = 0.027$) in diabetic group compared to control group. Basal heart rate, SBP and DBP, and mean arterial pressure were significantly increased in diabetic patients ($P < 0.001$) compared to controls. All time domain indices of HRV (SDNN, RMSSD, NN50, and pNN50) significantly decreased in diabetic group compared to control group. Among frequency domain indices, HRV, TP, and HFnu were significantly decreased ($P < 0.001$) and LFnu and LF-HF ratio significantly increased ($P < 0.001$) in diabetic group compared to that of control group. In ERP recording, the latency of P300 was prolonged ($P < 0.001$) and amplitude of P300 was decreased ($P < 0.001$) in diabetic group compared to control group [Table 1].

Table 1: Comparison of parameters between control group and diabetes group

Parameters	Control group ($n=40$)	Diabetes group ($n=40$)	*P*
Age, BMI, and BP parameters			
Age (years)	37.30±4.47	38.904±5.32	0.141
BMI (kg/m^2)	24.28±3.85	28.66±5.70	0.027
BHR (beats per min)	70.12±5.10	79.55±4.62	<0.001
SBP (mmHg)	110.60±4.74	124.30±7.86	<0.001
DBP (mmHg)	68.10±6.35	76.12±5.34	<0.001
MAP (mmHg)	82.20±8.20	92.15±8.45	<0.001
RPP (mmHg/min)	78.25±8.36	99.14±9.70	<0.001
TDI of HRV			
RMSSD (ms)	30.10±12.20	20.12±10.26	<0.001
SDNN (ms)	30.85±11.65	23.12±9.72	<0.001
NN50	28.34±11.31	15.21±5.70	<0.001
PNN50	8.50±4.21	3.60±1.31	<0.001
FDI of HRV			
TP (ms^2)	856.30±454.20	520.16±380.10	<0.001
LFnu	36.80±10.40	64.10±20.15	<0.001
HFnu	63.20±18.32	35.90±16.90	<0.001
LF:HF	0.63±0.28	2.10±1.25	<0.001
P3 values of ERP			
P300 latency	308.12±22.17	333.85±24.40	<0.001
P300 amplitude	11.80±4.45	7.32±2.77	<0.001

Data expressed as mean±SD. $P<0.05$ was considered statistically significant. HRV: Heart rate variability, ERP: Event-related potential, BMI: Body mass index, BHR: Basal heart rate, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, RPP: Rate-pressure product, RMSSD: The square root of the mean of the sum of the squares of the differences between adjacent NN intervals, SDNN: Standard deviation of normal-to-normal interval, NN50: The number of interval differences of successive NN intervals >50, pNN50: The proportion derived by dividing NN50 by the total number of NN intervals, TP: Total power of HRV, LFnu: Normalized low-frequency (LF) power of HRV, HFnu: Normalized high-frequency (HF) power, LF-HF ratio: Ratio of low-frequency-to-high-frequency power of HRV, P300 (P3): Positive wave that appears in 300 ms from application of stimulus in ERP tracing, SD: Standard deviation, MAP: Mean arterial pressure, FDI: Frequency domain index, TDI: Time domain index

The levels of FBG, plasma insulin, HOMA-IR, and MDA significantly increased in diabetic group compared to control group [Table 2]. The BMI, HOMA-IR, MDA, and P300

significantly correlated with RPP in diabetic group, but not in control group [Table 3]. Simple regression analysis demonstrated significant independent contribution of RPP to P300 in diabetic group [Table 4].

Discussion

In the present study, a significant prolongation of P300 latency in diabetic group [Table 1] indicates significant cognitive impairment in T2DM, as ERP is an established marker of higher cognitive function that correlates with our recent report.[21] We have also recently reported autonomic imbalance and increased CV risks in patients with diabetes and their first-degree relatives.[15,22] However, there are no reports till date to correlate cognitive deficit with CV risks in T2DM. All the time domain indices of HRV (mean RR, RMSSD, SDNN, NN50, and pNN50) significantly reduced in diabetic group compared to control group, indicating that parasympathetic autonomic modulation was considerably less in diabetic patients as these HRV indices represent cardiac vagal drive,[15,22] which was supplemented by reduction in HFnu and TP of HRV. In addition, the basal heart rate was more in diabetic patients compared to controls, indicating the poor vagal tone in these individuals as resting tachycardia indicates decreased vagal tone and increased CV risks in these individuals.[23] Thus, these findings indicate that diabetic patients have poor vagal tone.

The sympathetic drive of diabetic patients was increased as LFnu was significantly more in diabetic group compared to control group, LFnu being the index of sympathetic modulation of cardiac functions.[15,22] LF-HF ratio, the marker of sympathovagal imbalance, was significantly correlated with RPP in diabetic group, but not in control group [Table 3], depicting the significant association of sympathovagal imbalance with CV risks. Further, P300, the marker of cognitive impairment, was also correlated with RPP in T2DM, which indicates the link of memory impairment with CV risks. RPP was substantially increased in diabetic patients [Table 1]. Increase in RPP indicates myocardial work stress and is an established marker of CV risks. In diabetic group, further, P300 had independent contribution to RPP as demonstrated by regression analysis [Table 4]. Thus, findings of the present study indicate the close link of memory loss with CV risks, in T2DM.

The exact mechanism of cognitive impairment in T2DM is not known. Although high BMI in diabetes has been suggested as a plausible contributor to memory loss, as obesity is reported to be associated with dementia,[24,25] BMI was not significantly associated with P300 in diabetic group in our previous study.[21] Thus, contribution of high BMI to memory loss in diabetic patients could be negligible. Metabolic derangements in diabetes are common. There is also report of decline in cognitive function in conditions of metabolic derangements such as dyslipidemia, IR, and oxidative stress.[26-28] However, there are no reports demonstrating cognitive impairment in diabetes, especially in Indian population. In the present study, FBS, insulin, and HOMA-IR significantly increased in hypertensives compared to normotensives [Table 2]. Persistent hyperglycemia, AGEs, and hyperinsulinemia have been implicated in the genesis of memory loss, brain aging, and Alzheimer's disease.[26,27] IR has also been strongly implicated in the development of cognitive impairment in Alzheimer's disease.[28] Thus, these metabolic derangements could be the potential contributor to memory loss in diabetes. Nevertheless, further studies should be conducted to ascertain these possible links.

In the present study, the levels of HOMA-IR were significantly high in diabetic patients compared to controls [Table 2], and HOMA-IR was significantly correlated with RPP in

Table 2: Comparison of biochemical parameters between control group and diabetes group

Parameter	Control group ($n=40$)	Diabetes group ($n=40$)	*P*
FBG (mmol/l)	4.40±0.55	10.62±3.158	<0.001
Plasma insulin (μIU/ml)	11.12±3.37	29.97±8.45	<0.001
HOMA-IR	2.15±0.78	13.52±5.64	<0.001
MDA (μM/ml)	9.53±4.15	34.20±12.62	<0.001

Data expressed as mean±SD. $P<0.05$ was considered statistically significant. HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, MDA: Malondialdehyde, SD: Standard deviation, FBG: Fasting blood glucose

Table 3: Correlation of rate-pressure product with various important parameters of control and diabetes groups

Parameters	Control group ($n=40$)		Diabetes group ($n=40$)	
	r	*P*	*r*	*P*
BMI	0.088	0.140	0.350	0.005
HOMA-IR	0.040	0.182	0.456	0.000
MDA	0.038	0.210	0.298	0.013
LF-HF ratio	0.035	0.230	0.380	0.000
P300	0.102	0.122	0.292	0.012

The $P<0.05$ was considered statistically significant. P300: Positive wave at 300 ms in event-related potential tracing, BMI: Body mass index, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, MDA: Malondialdehyde, LF-HF ratio: Ratio of low frequency-to-high frequency power of heart rate variability

Table 4: Single regression analysis to assess the independent association of rate-pressure product (as dependable variable) with P300 (as independent variables) in diabetes group, after adjusting for body mass index and gender

Standardized regression coefficient beta	95% CI		*P*
	Lower limit	Upper limit	
0.260	0.003	1.532	0.012

$P<0.05$ considered statistically significant. P300: Positive wave at 300 ms in event-related potential tracing, BMI: Body mass index, CI: Confidence interval

these individuals [Table 3]. Thus, IR could be a potential contributor to CV risks in these individuals. Another major linking mechanism of CV risks in diabetic patients could be the oxidative stress, as the level of MDA was significantly increased in diabetic group compared to control groups [Table 2], and MDA was significantly correlated with RPP in diabetic group [Table 3]. Therefore, oxidative stress could be a plausible link between the cognitive loss and CV risks.

In summary, in the present study, increased heart rate, increased RPP, and decreased TP (that depicts reduced HRV) were prominently noted in diabetic patients, and these factors have been documented to be associated with CV risks. Among them, RPP is considered as a physiological marker of CV risk as increased RPP depicts myocardial work stress. Further, as P300 was positively correlated with RPP and had an independent association with RPP, it is clearly evident that the cognitive loss in T2DM is linked to CV risk.

Limitations of the study

In the present study, we have not assessed other measures of CV risks such as baroreflex sensitivity and echocardiographic parameters. Further, the sample size was modest in the present study.

Conclusion

The novelty of the present study is that this is the first report linking cognitive deficit with CV risk in diabetic patients in the Indian subcontinent. This is also the first report from India linking cardiometabolic risks with increased RPP in T2DM. The findings of the present study demonstrate that diabetic patients have considerable cognitive impairment, which could probably be linked to their CV risks.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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