Original Article

Cardiac Autonomic Neuropathy in Prediabetes: A Case-Control Study

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Abstract

Introduction: Early detection and diagnosis of diabetic autonomic neuropathy, especially cardiac autonomic neuropathy (CAN), have gained attention recently because of their elevated cardiovascular mortality risk. Although the connection between type 2 diabetes mellitus and autonomic neuropathy is well established, evidence is emerging that the association might predate the stage of prediabetes. **Objective:** The present study was undertaken to compare the prevalence of CAN in prediabetes versus that in normoglycemic controls. **Materials and Methods:** The study population was selected by purposive sampling from individuals attending a tertiary care hospital from January 2018 to June 2019. Fifty individuals with prediabetes diagnosed by the American Diabetes Association's glycated haemoglobin criteria and 50 age- and gender-matched healthy controls were recruited. CAN was assessed by standard cardiovascular reflex tests, as described by Ewing and Clarke. Changes in R-R with deep breathing, Valsalva manoeuver, and changes in blood pressure (BP) in response to standing and sustained handgrip were evaluated. Three-time domains [standard deviation of normal-to-normal intervals (SDNN), root mean square of successive RR intervals (rMSSD) and percentage of successive normal to normal R-R (NN) intervals that differ by more than 50 ms (pNN50)] and four frequency domain indices [very low-frequency band (VLF), low-frequency band (LF), high-frequency band (HF), LF/HF ratio) of heart rate variability (HRV)] were examined. **Results:** The mean heart rate was 71.37 ± 7.94 and 65.59 ± 8.73 beats/min in patients with prediabetes and controls, respectively ($P < 0.05$). All three-time-domain indices of HRV were significantly lower in persons with prediabetes compared to controls. The peak frequency of LF, peak power of LF, normalised unit of LF, and LF/HF ratio was significantly lower in subjects with prediabetes than in controls. There was no difference in the traditional cardiovascular autonomic reflex testing. **Conclusion:** Our study demonstrates the presence of subclinical autonomic dysfunction in persons with prediabetes. Early detection of CAN in prediabetes can have future implications for cardiovascular risk reduction.

Keywords: Cardiac autonomic neuropathy, heart rate variability, prediabetes

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is on the rise. With diabetes affecting around 537 million adults worldwide, the morbidity and mortality associated with T2DM and its complications are a global concern.[1] Prediabetes is an intermediate state of hyperglycaemia with glycaemic parameters above normal but below the diabetes threshold. The current thresholds for diagnosing diabetes and prediabetes were defined by the American Diabetes Association in 2010. The cut-offs for fasting plasma glucose (FPG), 2-hour post-glucose load (2-h PG) and glycated haemoglobin (HbA1C) values of 126 mg/dL, 200 mg/dL and 6.5%, respectively, for the diagnosis of diabetes were based on thresholds above which the prevalence of retinopathy increases linearly. An FPG level of 100 to 125 mg/dL, a 2-h PG load of 140–199 mg/dL, or an HbA1c level of 5.7–6.4% is diagnostic of prediabetes. While the FPG and 2-h PG values were derived based on the risk of progression to diabetes, an HbA1C cut-off of 5.7% was chosen as it had the best combination of sensitivity (39%) and specificity (91%) to identify cases with an FPG ≥100 mg/dl.[2] According to data from the population-based US National Health and Nutrition Examination Survey, 50% of Americans over 65 years and

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35% of persons over 20 years in the US have prediabetes.[3] The overall prevalence of prediabetes in 15 states in India is reported to be 10.3%.[4] Apart from the increased risk of progression to diabetes, there is accumulating evidence for a higher prevalence of microvascular and macrovascular complications in prediabetes.[5]

Diabetes is a leading cause of neuropathy worldwide.[6] The presence of symptoms and/or signs of peripheral nerve damage in individuals with diabetes after ruling out other causes is the traditional definition of diabetic neuropathy. Nerves from the autonomic, sensory or motor systems may be involved. Distal symmetric polyneuropathy, which makes up around 75% of diabetic neuropathies, is the most prevalent form of diabetic neuropathy.[7] Diabetic autonomic neuropathy (DAN) has been thought of as a rare occurrence for much of the last century, but it is a serious and frequently ignored complication of diabetes. DAN may involve any tract of the autonomic nervous system, affecting a wide range of organs and significantly increasing morbidity and mortality. It is often asymptomatic in the early stages, delaying diagnosis and treatment.[8] Subclinical DAN has been reported to manifest within a year of diagnosis in T2DM.[9]

Cardiovascular autonomic neuropathy (CAN) is a common and extensively researched form of DAN because of its potentially fatal consequences (arrhythmias, latent myocardial ischemia and sudden death).[10] The diagnosis of CAN should be based on the results of a set of autonomic tests, and the function of both sympathetic and parasympathetic branches should be evaluated.[11] In early subclinical CAN, the cardiovascular autonomic reflex tests may not detect any abnormalities. Persons with subclinical CAN have abnormalities in heart rate variability (HRV), which is followed by changes in baroreflex sensitivity.[12] The treatment of DAN can be difficult, and prevention of its onset or slowing its progression remains the practical approach. CAN is often present at the time of diagnosis of T2DM. For this reason, identifying CAN in the prediabetes stage and establishing an effective screening protocol for DAN could be an effective strategy against the life-threatening consequences of the condition.

To date, there are very few studies on autonomic function in prediabetes. The present study was undertaken to elucidate the prevalence of cardiac autonomic function in prediabetes compared to that in healthy individuals.

Material and Methods

Study population

The study group consisted of 100 subjects attending a tertiary care hospital from January 2018 to June 2019, recruited by purposive sampling. Fifty subjects with prediabetes (diagnosed according to HbA1C criteria) were selected as cases. Subjects without prediabetes or diabetes who underwent a preventive health check-up in the hospital and were found to be clinically and biochemically healthy were recruited as controls. Patients with alcohol use disorder as defined by Diagnostic and Statistical Manual of Mental Disorders criteria,[13] systemic hypertension, a history of smoking, hypertriglyceridemia and patients on long-term medications that can cause peripheral neuropathy were excluded. All participants gave informed consent, and the study protocol was approved by the institutional ethics committee.

Cardiac autonomic neuropathy assessment

CAN was assessed by the standard cardiovascular reflex tests as described by Ewing and Clarke. Changes in R-R with deep breathing, Valsalva manoeuvre as well as changes in BP in response to standing and sustained handgrip were evaluated. The R-R difference with deep breathing was the mean of the difference between the maximum and minimum R-R intervals during six respiratory cycles. The Valsalva ratio was the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during forced exhalation into the mouthpiece of a manometre at 40 mmHg for 15 seconds. An R-R difference ≤10 beats/min and a Valsalva ratio ≤1.10 were considered abnormal. A decrease in BP ≥20 mmHg upon standing and BP elevations in responses to isometric handgrip exercise <10 mmHg were considered abnormal.[14]

Heart rate variability analysis

HRV refers to the variability of the time interval between two consecutive R peaks in electrocardiograms. HRV was acquired using an INCO NIVIQURE digital polygraph. An instantaneous heart rate at RR intervals was continuously plotted using Niviqure software on a Microsoft Window-based computer. Three-time domains SDNN, rMSSD and percentage of successive NN intervals that differ by more than 50 ms (pNN50)] and four frequency domain indices [very low-frequency band (VLF), low-frequency band (LF), high-frequency band (HF), LF/HF ratio) of heart rate variability (HRV)] were examined [Tables 1 and 2].

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 20 Windows software (SPSS Inc., Chicago, USA). The results are given in mean ± SD for all continuous variables and in

Table 1: Time domain indices on spectral analysis

Parameter	Description
SDNN	Standard deviation of NN intervals
RMSSD	Root mean square of successive RR interval differences
pNN50	Percentage of successive RR intervals that differ by more than 50 ms

Table 2: Frequency domain indices on spectral analysis

Parameter	Description
VLF	Very low-frequency band
LF	Low-frequency band
HF	High-frequency band
LF/HF	Ratio of LF to HF power

frequency (percentage) for categorical variables. *P* value <0.05 was taken as significant.

Ethical Clearance Statement

This study conforms to the principles of the Declaration of Helsinki 1964 and relevant ethical guidelines. The current study is approved by the Institutional Ethics Committee of JSS Medical College/Mysore Vide memo no JSSMC/PG/4700/2017-1018 dated 04/11/2017. Before beginning this study, an ethical clearance was obtained from the Institutional Ethics Committee. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes.

Results

A total of 50 cases and 50 controls were analysed. The baseline characteristics of the study population are depicted in table 3. The mean heart rate was 71.37 ± 7.94 and 65.59 ± 8.73 beats in patients with prediabetes and controls, respectively ($P < 0.05$). The results of the standard cardiovascular reflex tests are depicted in Table 4. The mean values of HRV for the deep breathing test were 18.30 ± 5.00 and 27.04 ± 6.98 in cases and controls, respectively. Though the values were significantly different between cases and controls ($P < 0.05$), the heart rate response to deep breathing was normal in both groups. The Valsalva ratio in cases and controls was 1.18 ± 0.104 and 1.19 ± 0.06, respectively. The mean values of the fall in systolic blood pressure on standing were 16.08 ± 7.43 and 15.48 ± 6.23 mm Hg in cases and controls, respectively. The rise in DBP on sustained handgrip was 14.44 ± 5.61 in the prediabetes group and 31.66 ± 12.81 mmHg in the normoglycemic group. None of the above results showed any significant difference between the two groups.

Results of the time domain indices of heart rate variability are depicted in Table 5. All three-time domain indices of HRV were significantly lower in persons with prediabetes as compared to controls. The results of frequency domain indices are depicted in Table 6. The peak frequency of LF, peak power of LF, a normalised unit of LF and LF/HF ratio were significantly lower in subjects with prediabetes as compared to controls.

Table 3 : Baseline characteristics of the study participants

	Cases *n*=50	Controls *n*=50
Age (mean+SD)	53.26±9.81 years	48.56±6.14 years
Sex	35 males 15 females	30 males 20 females
BMI	24.12±1.88 kg/m^2	23.37±2.29 kg/m^2
HbA1C (%)	6.05±0.28	5.16±0.31

Table 4: Results of conventional cardiovascular autonomic reflex tests

	Cases	Controls	*P*
HRV to deep breathing	18.3±5.00	27.04±6.98	<0.05
Valsalva ratio	1.18±0.10	1.19±0.06	0.71
Fall in SBP	16.08±7.43	15.4±6.22	0.66
Rise in DBP	14.44±5.61	31.66±12.68	0.34

HRV: Heart rate variability, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 5: Time domain indices

	Cases	Controls	*P*
SDNN	59.11±9.55	66.91±10.06	<0.05
RMSSD	19.46±11.66	30.66±12.19	<0.05
pNN50	2.06±1.88	6.2±2.72	0.71

Table 6: Frequency domain indices

	Cases	Controls	*P*
Peak frequency VLF	0.017±0.00	0.018±0.00	0.40
Peak frequency LF	0.059±0.02	0.077±0.03	<0.05
Peak frequency HF	0.25±0.14	0.25±0.10	0.99
Peak power VLF	2187±534	2287±343	0.26
Peak power LF	748±277	1100±495	<0.05
Peak power HF	339±174	363±223	0.55
Normalised unit LF	43.03±11.95	49.02±16.78	<0.05
Normalised unit HF	49.87±15.29	48.93±17.53	0.77
Normalised unit LF/HF	0.93±0.36	1.66 48.93±17.530.75	<0.05

Discussion

The elevated risk of cardiovascular mortality associated with DAN calls for its early detection and diagnosis. Although the association between T2DM and autonomic neuropathy is well established, there is growing evidence for the association between CAN and prediabetes. Our study evaluated cardiac autonomic function in individuals with prediabetes and matched controls using both the traditional battery of autonomic function tests and the heart rate variability tests.

CAN can be categorised into three groups based on diagnostic testing: (1) "early involvement" with one abnormal HR test or two borderline findings; (2) "definite involvement" with two or more abnormal results; and (3) "severe involvement" when orthostatic hypotension is evident. The two phases of CAN are subclinical and clinical. Subclinical CAN is categorised according to increases in HRV, baroreflex sensitivity and cardiac imaging demonstrating greater left ventricular torsion without any appreciable alterations on the conventional cardiovascular autonomic reflex tests outlined above. When sympathetic activity is predominant and symptoms like reduced exercise tolerance and resting state tachycardia are noticeable, the clinical stage is diagnosed. Orthostatic hypotension is a marker of overt CAN.[15]

Time-domain indices of HRV quantify the amount of variability in measurements of the inter-beat interval, which is the time period between successive heartbeats.[16] In our

study cohort, the mean time-domain indices represented by RMSSD, SDNN and pNN50, which reflect the parasympathetic activity of the heart, were significantly lower in the prediabetes group when compared to the controls. Among the frequency domain indices, the HF is considered a marker of vagal activity, and the LF includes both sympathetic and vagal activity. In our study cohort, the peak frequency, power and normalised unit of LF were significantly lower among those with prediabetes when compared to controls, which signify dysfunctional sympathetic and parasympathetic activity of the heart in prediabetes. Our results are in line with previous studies, which show impairment in different metrics of heart rate variability. In a review of 14 studies by Spallone, autonomic dysfunction, especially reduced HRV indices that measure cardiovagal function, was present in individuals with prediabetes.[17] This review found that autonomic dysfunction was more prevalent in impaired glucose tolerance (IGT) than impaired fasting glucose (IFG), and the prevalence was more in combined IGT and IFG. In addition to reduced HRV indices, a few studies have found significant differences in heart rate response to deep breathing, Valsalva ratio and BP responses to standing and sustained handgrip but not the 30:15 ratio or HRV measured by the triangular index, between people with normoglycaemia and prediabetes.[18,19] Our study did not show any impairment in the traditional cardiovascular autonomic reflex testing, signifying the presence of subclinical CAN in our cohort with prediabetes.

CAN in prediabetes was most strongly associated with age and use of antihypertensive drugs, as reported in the Hoorn study by Gerritsen *et al*.[20] Autonomic dysfunction in prediabetes is multifactorial. In addition to IGT, there are other independent factors that may contribute to autonomic dysfunction, such as age, body mass index, waist circumference, hypertension, anti-hypertensive drugs and other components of metabolic syndrome.[21] Reduced HRV indices indicate involvement of the parasympathetic nervous system, whereas higher ratios between LF and HF spectral components of HRV indicate involvement of the sympathovagal system with a predominance of the sympathetic nervous system.[22] The vagus is the longest parasympathetic nerve in the body and is affected early in CAN, and the involvement progresses in a length-dependent manner.

Central obesity and hypertriglyceridemia are also found to play a pathophysiological role in the development of CAN, as evident from the Finnish Diabetes Prevention Study.[23] Obstructive sleep apnoea with sympathetic hyperactivity has also been found to contribute to CAN.[24] At a molecular level, endoplasmic reticulum stress due to impaired folding of newly synthesised proteins, defects in mitochondrial stress and oxidative stress are responsible for the development of CAN.[25,26] There is evidence to suggest that the use of antioxidants like alpha-lipoic acid along with angiotensin-converting enzyme inhibitors can improve HRV due to deep breathing in CAN.[27] However, the use of alpha-lipoic acid in CAN still remains controversial.

The presence of CAN in prediabetes increases the risk of sudden cardiac death (SCD). Previous studies have shown that up to 60% of patients with cardiovascular disease have evidence of prediabetes and insulin resistance.[28] The presence of CAN increases the predisposition to cardiac arrhythmias, silent infarction and SCD. Hence, it is imperative to assess for CAN in prediabetes and intervene early to prevent its progression.

Strengths and limitations of our study

Ours is one of the first studies from India to comprehensively assess CAN in prediabetes. However, our study has a few limitations. Firstly, prediabetes was defined only by the HbA1C criteria. The difference in association between IFG, IGT and HbA1C on CAN was also not studied. Secondly, we have not assessed the role of factors in prediabetes like age, body composition, BMI, dyslipidaemia and duration of prediabetes.

Conclusions

Our study shows that subclinical autonomic dysfunction is more prevalent in individuals with prediabetes than in those with normoglycaemia. It is essential to identify such cases in the stage of prediabetes to initiate appropriate measures to mitigate the risk of cardiovascular events.

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Conflicts of interest

There are no conflicts of interest.

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