Heart Rate Variability (HRV) in Prediabetics – A Cross Sectional Comparative Study in North India

D. Santhanalakshmi¹, Sujata Gautam¹*, Asha Gandhi¹, Debasish Chaudhury², Binita Goswami³ and Sunita Mondal¹

Departments of Physiology¹, Medicine² and Biochemistry³
Lady Hardinge Medical College & Associated Hospital, New Delhi.

Abstract

Background: Cardiac autonomic dysfunction (CAD) and neuropathy is common in diabetes mellitus but the abnormalities in Autonomic nervous system (ANS) and the influence of altered glycaemic indices on cardiovascular parameters by using HRV has not been elucidated in prediabetics. Hence, the present study was aimed to measure HRV and to find out the association, if any, between the parameters of HRV and glycaemic index in Prediabetics.

Methods: Recording of short term HRV in thirty prediabetics and thirty apparently healthy controls of either sex in the age group of 40 to 65 years were done. The subjects were enrolled as per American Diabetes Association (ADA) criteria on the basis of their glycaemic indices viz: Fasting blood sugar (FBS), 2h Oral glucose tolerance test (OGTT) and Glycated haemoglobin (HbA1c).

Result: Prediabetic subjects showed a significant decrease (p=0.007) in SDNN (Time Domain parameter of HRV) when compared with the control group, whereas the RMSSD and other frequency domain parameters of HRV did not show any significant difference in the two groups. However, the correlation analysis between various parameters of HRV and glycaemic indices showed a significant negative association.

Conclusion: A significant decrease in SDNN along with significant negative association between HRV parameters and glycaemic indices indicates towards a decrease in parasympathetic activity of cardiac autonomic function and hence the possibility of initiation of CAD in Prediabetic stage itself.
Introduction

Prediabetes, typically defined as blood glucose levels above normal but below diabetes thresholds, is a risk state that defines a high chance of developing diabetes. According to the World Health Organization (WHO), high risk for developing diabetes relates to two distinct states, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 110–125 mg/dl and impaired glucose tolerance (IGT) defined as post load plasma glucose of 140–199 mg/dl based on 2-h oral glucose tolerance test (OGTT) or a combination of both (1). The American Diabetes Association (ADA), although applying the same thresholds for IGT, uses a lower cut-off value for IFG (FPG 100–125 mg/dl) and has additionally introduced haemoglobin A1c(HbA1c) levels of 5.7–6.4% as a new category of high diabetes risk (2). Over 371 million people have been reported to suffer from prediabetes which is predicted to rise to 470 million by 2030 across the world (1, 3). International Diabetes Federation projects also found that globally, the prevalence will increase up to 471 million by 2035 (4). Also, around 77.2 million prediabetes patients are estimated to exist in India (5).

Though prediabetes is considered as borderline diabetes, it seems that the risks of cardiovascular disease (CVD) as well as vascular complications were high when compared to normal population (6-10). The increased cardiovascular risk in these patients could be attributed to the presence of pro-inflammatory cytokines these in turn has some influence on autonomic nervous system (ANS) (11). Though various hypotheses have been put forward regarding the pathophysiological mechanism of cardiovascular complications in pre-diabetics, the abnormalities in ANS and its influence on cardiovascular parameters by using HRV has not been elucidated in great detail.

Abnormal autonomic control of heart rate is associated with an increased risk of cardiovascular morbidity and mortality (14, 15). Disturbance in ANS leads to cardiac autonomic dysfunction (CAD), which is considered as the important form of diabetic autonomic neuropathy. In diabetic patients the risk of silent myocardial ischemia and mortality are more when the cardiovascular autonomic function is reduced as measured by HRV (16).

The risk for CVD and total mortality is almost twice as high in individuals with prediabetes (17, 18). A study conducted by Ziegler et al using KORA S4 survey has found that the prevalence of CAD was high not only in individuals having T2DM and or impaired glucose tolerance (IGT) but also to a lesser extent in isolated impaired fasting glucose (IFG) (19) Cardiovascular health and prognosis is mainly based on the status of autonomic nervous system (20), although ignored by many clinicians. Early screenings for CAD is recommended for all prediabetic individuals, as there is a possibility of reverting the progression of disease or slow down the disease with the help of effective management such as lifestyle modifications (21).

To date, there are very few studies on HRV with prediabetics. The present study was undertaken to elucidate cardiac autonomic function (parasympathetic and sympathetic) based on short-term HRV in prediabetes compared to healthy individuals and to see its correlation with varying blood glycaemic indices.

Methods

The study was carried out as a cross sectional comparative study in a tertiary care hospital, New Delhi, India. A convenient sample size of thirty prediabetics, in the age group of 40 to 65 years of either gender who attended General Medicine department on out-patient basis were included in the study based on predetermined eligibility criteria as per case definition put forward by ADA. Thirty age and sex matched apparently healthy voluntary participants having normal clinical and blood glucose profiles based on the (ADA 2010) criteria were enrolled in control group. Prediabetic participants
having diseases or disorders such as anaemia, diabetes mellitus, hypertension, hepatic dysfunction, renal disease, hypothyroidism or participants using any long-term medications like oral hypoglycaemic agent, Phenytoin, beta blockers, Amiodarone, Anti-Arrhythmic drugs and seriously ill subjects were excluded from the present study.

Voluntary participation in the study was encouraged and informed written consent from the eligible participants was obtained before including them in the study. All the participants who volunteered for the study were asked to report in department of Physiology after an overnight fast for at least eight hours. The subjects were also instructed not to take tea, coffee or nicotine in any form in the last 24 hours. All the procedures were clearly explained to the participants beforehand. Blood samples were collected from antecubital vein in fasting state and 2 hrs after intake of 75 gms oral glucose. Biochemical analysis was performed centrally in the hospital biochemistry lab for all the subjects using standard procedure (spectrophotometry by glucose oxidase method for determining the blood sugar level and latex agglutination inhibition assay for estimating glycated haemoglobin level). Anthropometric measurements such as height (m), weight (kg) were recorded. Resting blood pressure was measured and resting heart rate was recorded in all the subjects. Institute Ethics Committee’s approval certification for Human Research was sought and obtained before the study was started.

Recording and data extraction of HRV

Short term HRV is considered as a reliable parameter to document the presence of Cardiac Autonomic Neuropathy (CAN). It is a non-invasive, less time-consuming procedure and is proved to be a more sensitive tool than mean heart rate (HR). The study participants were asked to lie down on the couch in supine position and were instructed to close the eyes and rest for 15 minutes. While resting, the ECG electrodes were placed on position (right wrist, left wrist and right foot). The participants were also instructed not to talk or move hands, legs and body during the HRV recording (22). Ambient room temperature was maintained during the test time.

The data was extracted in the form of Lead II ECG using Autonomic Neuropathy Analyzer (RMS Vagus HRV apparatus), HRV/92001/FNL - version 2.1 supplied by Recorders and Medicare Systems, Chandigarh, India, while subjects are resting in supine position with eyes open for duration of 15 min. This was done to make sure that subjects didn’t sleep during the recording.

The heart rate and short term HRV was recorded and stored in system. The extracted ECG data were manually scanned for any artifacts and only artifact free 5 min ECG data were used for analysis. If there were any artifacts, the recordings were repeated on the next day. The data was analysed by using the software Autonomic Neuropathy Analyzer, complying with guidelines recommended by the Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology standards for measurement of HRV (13).

Analysis of HRV

HRV was analysed by the Autonomic Neuropathy Analyzer software, from the calculation of the mean R-R interval and its standard deviation measured on short-term (5 minutes) electrocardiogram, normal-to-normal (NN) R-R interval data was obtained from artefact free sequences of R-wave and QRS complex. Standard deviation of normal R-R intervals (SDNN), square root of mean-squared difference of successive R-R intervals (RMSSD) and NN50 were used for comparison of time-domain parameters. For frequency domain HRV parameters analysis, spectral power was quantified by Fast Fourier transform (FFT) method for the following frequency bands: very low frequency (VLF, 0.003-0.04 Hz), low frequency (LF, 0.04-0.15Hz), high frequency (HF, 0.15-0.4 Hz), Low frequency normalized unit (LFnu), High frequency normalized unit (HFnu) and LF/HF ratio. These parameters were defined in accordance with the 1996 American college of Cardiology (ACC) / American Heart Association (AHA) / European society of Cardiology (ESC) consensus (13). SDNN, RMSSD, HF and HF(nu), reflect parasympathetic activity on heart (cardio vagal tone); LF reflects both sympathetic and parasympathetic activity; VLF component’s physiological explanation is ill defined and it cannot
be interpreted based on short term HRV recordings; LF (nu) and HF (nu) represent controlled and balanced activity of sympathetic and parasympathetic nervous system (PSNS) and LF/HF ratio indicates sympathovagal balance (13).

**Statistical analysis:**

Statistical analysis was performed using IBM SPSS (Statistical Package for Social Sciences) version 21 software; the data were expressed in Means and proportions. Kolmogrov's test was applied for normality distribution and the comparison of continuous variables between the groups was carried out using student unpaired t test for parametric data and Mann Whitney test for nonparametric data. The correlation between the parameters was analyzed using partial correlation test. A p-value of less than 0.05 was considered statistically significant.

**Results**

According to 2010 ADA criteria, 30 prediabetics and 30 controls were recruited; both the groups had 19 females and 11 males. There were no significant differences in age, height, waist circumference between the groups, however, the weight and Body mass index (BMI) were significantly high in prediabetic group when compared to controls (Table I).

All the blood glycaemic parameters were increased significantly in prediabetic group (Table II). Of these, 21 (70%) had impaired fasting glucose (IFG), 27 (90%) had impaired glucose tolerance (IGT) alone, only 25 (83%) had impaired glycated haemoglobin (HbA1c) and 17 (56%) participants had impairment in all the blood glycaemic parameters.

In our study, prediabetic group exhibited a significant reduction (p value - 0.007) in SDNN. The other HRV parameters viz., RMSSD, Low Frequency (LF) in normalized units (nu), High Frequency (HF) in normalized units (nu), LF/HF ratio and pNN50% did not show any significant difference. The change in Total power, Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF) in absolute power (ms²) after logarithmic conversion were also found to non-significant (Table III).

**IQR: Interquartile range**

There was a significant increase in weight and BMI among prediabetics as compared to controls in the present study (Table I). After adjusting for weight and BMI, the time domain parameter (SDNN) demonstrated a significant negative association with

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<th>TABLE I : Comparison of anthropometric measurements.</th>
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<th>TABLE II : Comparison of blood glycaemic parameters.</th>
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<td>FBS (mg/dl)</td>
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<td>HbA1c (%)</td>
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Heart Rate Variability in Prediabetics

2 hr OGTT (r= -0.284, p=0.031). A significant negative correlation was also found when frequency domain parameters; LFms² (r= -0.288, p= 0.028), HFms² (r= -0.305, p=0.020) and total power (r=-0.301, p=0.022) was correlated with 2 hr OGTT. The LF: HF ratio also showed a significant negative association with HbA1c (r= -0.400, p=0.002). A significant negative association was also observed between lnLF (ms²) (r= -0.291, p= 0.027), lnVLF (ms²) and lnTotal Power (ms²) with fasting glucose after logarithmic conversion of Total power, Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF) in absolute power (ms²) (Table IV).

Discussion

Prediabetes is the asymptomatic stage of diabetes mellitus and a useful target for early intervention to prevent the development of the disease and its complications like CAD. The present study was carried out among 40–65 years old healthy controls and prediabetic individuals based of 2010 ADA criteria, to demonstrate the impairment in HRV and its association with blood glycaemic indices. A meta-analysis by Levitan et al. pointed out that prediabetic condition is able to increase the cardiovascular risk profile of individuals (23).

In the present study, SDNN, a time domain parameter of HRV reflecting parasympathetic activity of the heart, was significantly reduced in the prediabetic group (Table III). Our study results were consistent with results obtained in Framingham Heart Study (24), Atherosclerosis Risk in Communities.
Low SDNN is an independent risk factor for congestive heart failure (28), sudden death in myocardial infarction patients (29, 30), predicts mortality from all causes in middle-aged and elderly men (31, 32). Another study by Subbalakshmi et al on type 2 diabetes mellitus patients reported that SDNN could be a marker in quantifying cardiac autonomic dysfunction (33). Wang et al stated that SDNN/RMSSD can act as a surrogate for LF/HF (34). Studies (24-26) also observed a significant decline among frequency domain parameters of HRV viz. LF (nu), HF (nu), LF/HF ratio, LF (ms²), HF (ms²), VLF (ms²) and total power (ms²). However, we did not get any significant changes among frequency domain parameters, though the mean values were reduced in prediabetics group, these may be attributed to a smaller sample size. A decrease in HRV is an earliest clinical indicator of CAN, and independent predictor of cardiovascular mortality (13) and the disease progression begins with parasympathetic denervation, followed by sympathetic tone enhancement and eventually sympathetic denervation (25, 35, 36).

In our study, prediabetes as compared to controls had significantly higher weight and BMI (Table I). Raised BMI and weight were considered as confounders 37, hence were adjusted by performing partial correlation analysis to look for any direct association of blood glycaemic indices with HRV parameters (Table IV). Significant negative association was observed in our study between the HRV parameters (SDNN, LF (ms²), HF (ms²), VLF (ms²) and total power (ms²), InLFms², InVLFms², In total power ms² and LF: HF ratio) and glycaemic index viz. FBS, OGTT and HbA1c (Table IV), which points a decrease in parasympathetic activity and altered sympathovagal balance in prediabetics. Singh et al (24) and Schroeder et al (25) has also observed a significant inverse relationship between plasma glucose levels and HRV parameters such as LF power, HF power, and LF/HF ratio in prediabetics as well as diabetic patients. Subbalakshmi et al demonstrated that duration of diabetes was associated with decline in SDNN parameter (32). There is no evidence available till date in literature to explain the cause of such association. However with respect to findings of correlation analysis, the authors of the present study are of the opinion that, the significant negative association obtained between the blood glycaemic index and the various HRV parameters may have some contribution in deciphering the cause effect relationship. However, more extensive study with appropriate study design to eliminate various confounding factors with a large sample size is required to ascertain any such cause and effect relationship.

The prediabetic stage is associated with a decreased parasympathetic modulation of the heart and a shift toward augmented sympathetic tone. Studies have suggested that Prediabetes is associated with dysfunction of cardiac autonomic activity, reflected by reduced HRV, decreased parasympathetic modulation of the heart and increased prevalence of erectile dysfunction (38, 39). Autonomic dysfunction in prediabetics emphasizes the susceptibility of peripheral autonomic nerve fibres, especially small A delta fibres and C fibres, to relatively mild, short-duration hyperglycaemic changes. Research findings strongly suggest that even prediabetes is a risk factor for autonomic neuropathy (a type of small fibre neuropathy), and that so-called “impaired glucose tolerance neuropathy” may represent the earliest stage of diabetic neuropathy. A dose-response relationship was observed by Sunner et al between the severity of hyperglycaemia and the degree of neuropathy, as the patients with IGT more often had small fibre neuropathy, whereas diabetics had polyneuropathy involving small and large fibres (40).

Pathological mechanism of CAN remains uncertain but is likely to be multifactorial (41). The fundamental pathology in CAN is hyperglycemia (16) and its activation of redox and/or multiple metabolic (Polyol, aldose reductase) pathways because of hyperglycemia induced oxidative stress, alteration of Na⁺/K⁺-ATPase pump function, calcium disturbance and low grade inflammation (16, 25, 42). This, in conjunction with reduced blood flow to nerve fibers, contributes to CAN (35). Though, not proved, yet it can be hypothesised from the results of our study that the disease progression may begin with parasympathetic nerves as demonstrated by a
significant decrease in SDNN. It can also be suggested that with increasing blood glycaemic index there is a probable negative impact on cardiac autonomic nerves leading to CAD as detected by changes in HRV parameters. However, more extensive studies with appropriate study design to eliminate confounders with a large sample size are required to ascertain any such cause and effect relationship. Some of the possible limitation includes physical activity level, occupational stress, personal life problems were not studied.

Conclusion

There is a significant decline in SDNN parameter of HRV depicting a decreased cardiovagal tone in prediabetics. Also, there was a significant negative correlation between various parameters of HRV and blood glycaemic indices, which implicated a decrease in parasympathetic activity and altered sympathovagal balance. Short term HRV test can be used as a screening tool for detecting latent cardiac autonomic dysfunction in asymptomatic prediabetic individuals.

References


