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Original Article

The Relationship between Non-Linear Analysis of Heart Rate Variability, QTc Interval and Cardiovascular Risk Factors in Young Individuals with Pre-Diabetes

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Abstract

Introduction: Cardiac autonomic functions and cardiovascular risk factors are closely associated with each other. This study aimed to evaluate the cardiac autonomic status employing the Poincaré plot and QTc in young pre-diabetic individuals and correlate it with the cardiovascular risk factors. **Material and Methods:** This was a cross-sectional study. The students participating in the health check-up program organized by the college were the study participants. Basal anthropometric measurements, detailed family, and personal medical history were documented. Autonomic functions were evaluated. Plasma glucose and lipid profile were evaluated biochemically. Based on the impaired fasting plasma glucose and impaired glucose tolerance values, subjects were classified as normal and pre-diabetes mellitus groups. **Results:** A total of 295 subjects (198 normal and 97 pre-diabetes mellitus), were evaluated. Standard descriptor 1 and 2 in the pre-diabetes mellitus group reported a significant decrease, p<0.0001, (95% CI 15.98, 19.07) (95%CI 31.73 37.26) compared to the normal group (95% CI 26.33, 30.27) (95% CI 48.39, 52.71). QTc was significantly increased in the pre-diabetes mellitus group, p<0.0001, (95% CI 415.62, 423.99). Body mass index, fasting plasma glucose, and lipid parameters reported as being significant independent variables were associated with autonomic function test parameters. **Conclusion:** Cardiac autonomic dysfunction starts appearing in the pre-diabetic stage itself. Body mass index and altered lipid profiles showed a significant association with increased blood glucose levels. Early detection at a young age can help to plan better prevention and treatment strategies.

Keywords: Impaired fasting glucose, Oral glucose tolerance, QTc interval, Heart rate variability.

Introduction

In India, 69.1 million individuals have diabetes, making it the Diabetic Capital of the world [1]. The reasons for the alarming increase may be due to rapid socio-economic and nutritional transition, lack of self-awareness, and follow-up programs in the society. As per the "ticking clock hypothesis", the microvascular disease manifestation appears in the precursor stage, before the expression of full-blown clinical type 2 diabetes mellitus [2]. According to the American Diabetes Association, pre-diabetes is Impaired Fasting Glucose (IFG) ranging from 100–125 mg/dL or Impaired Glucose Tolerance (IGT) of 140– 199 mg/dL [3]. Pre-diabetes is related to increased cardiovascular (CV) disease and mortality [4]. Evaluation strategies targeting the younger candidates with increased risk will be a potential boon for the society to plan early interventional strategies.

The autonomic nervous system, with its sympathetic and parasympathetic limbs, orchestrates numerous physiological and pathological cardiovascular responses. The sympathovagal imbalance is an indicator of increased cardiovascular risk. A variety of markers have been provided to reflect autonomic activity and cardiovascular risk, that includes heart rate, heart rate variability (HRV), [5] QT interval lengthening, and QTc (Corrected QT interval) [6].

Early diagnoses of autonomic dysfunction employing the Ewing test battery are outdated. HRV has been widely accepted as a non-invasive marker of autonomic control [5]. HRV represents the variation in time between successive heartbeats. The traditionally employed linear analysis method (time and frequency domain) is prone to interference by ectopic rhythms and assumes that the analyzed R-R segments are stationary, and variations occur in a harmonic fashion. Considering the fact that the cardiovascular system exhibits non-linear dynamics, the newly explored non-linear methods of HRV analysis provide better insights into the autonomic control of the cardiovascular system. Poincare plot is a geometric, semi-quantitative method, used for identifying the non-linear patterns within the electrocardiograph (ECG) data [7].

QT interval is an ECG measurement that represents the duration between ventricular depolarization to ventricular repolarization. It is affected by heart rate, so QTc calculated using Bazett's square root formula is the accepted gold standard that reflects autonomic activity.

With this perspective, the current study was aimed to evaluate the cardiac autonomic status employing Poincare plot and QTc in young pre-diabetic individuals. Also, we sought to identify the cardiovascular risk factors that contribute to autonomic dysfunction.

Material and Methods

Study design and patients

This was a cross-sectional study. Bachelor of Medicine, Bachelor of Surgery students participating in the health check-up program organized by the institution, were the study participants. The study was approved by the Institute Ethics Committee of the Sri Manakula Vinayagar Medical College and Hospital.

A total of 403 participants from the 18-25 age group were screened during the medical health check-up program. Sociodemographic details, personal history, general examination, systemic examination, family history of diabetes, and blood investigations (fasting blood glucose and lipid profile) were evaluated in all individuals on the day of the health check-up program. Seventy-six participants were excluded due to a history of any medication intake, any form of medical illness, athletes, fasting glucose more than 125mg/dL, or if they reported having cardiovascular diseases. Among the remaining 327 subjects, 32 participants were not willing to participate after hearing the protocol procedures. The remaining 295 subjects were the study participants. Based on their fasting pasma glucose (FPG) and IGT values, the subjects were divided into two groups; Group I (n=198) included subjects who had FPG and IGT in the range of 60-99 mg/dL and >140 mg/dL respectively; Group II (n=97) included subjects with FPG and IGT ranging from 100-125 mg/dL or 140–199 mg/dL, respectively.

Cardiovascular autonomic function test: HRV Analysis - Poincare plot

The study was carried in the Autonomic Laboratory, Department of Physiology, Sri Manakula Vinayagar Medical College and Hospital, between 07.00 to 8:30 A.M. The Task Force guidelines on HRV were followed. The subject was given rest for 10 minutes, and lead II ECG was obtained using Recorders and Medicare (RMS) polyrite D hardware, version 1.0, India. The sampling rate of 500Hz and bandpass filter of 2Hz to 40Hz was followed. The readings were taken thrice each with a five minutes interval, and the last 5 minutes ECG was performed, digitalized, and stored for HRV analysis. From the ECG reading, the RR series were extracted with maximum amplitude and sharpness. Analysis of the RR series was done using the Finland version 1.1 software for HRV (Bio-Signal Analysis Group, University of Kuopio, Finland).

The Poincaré plot represents a time series on a cartesian plane. It is a scatter plot of RRn vs. RRn+1. The time between two successive R peaks is represented by RRn, and the time between the next two successive R peaks is represented by RRn+1.Employing the ellipse-fitting technique on the plot, two main indices are depicted: the standard deviation of instantaneous beat-to-beat interval variability (SD1), and the continuous long-term R/R interval variability (SD2). On the Poincaré plot, SD1 is the width and SD2 the length of the ellipse. The line of identity (LOI) is the 45° imaginary diagonal line on the Poincaré plot. SD1 depicts short-term HRV and measures the dispersion of points

along the line perpendicular to the LOI and is considered as an indicator of parasympathetic activity, whereas SD2 portrays both long and short-term HRV and overall variability and assesses dispersion of points along with the LOI [8].

ECG Analysis

A 12 lead ECG recording was obtained using automated ECG, RMS Vesta 302i. ECG paper speed was kept at 25 mm/sec. The QT interval represents the duration from the beginning of the QRS complex to the end of the T wave. QTc was measured using the Bazett formula: QT / √RR.

Body composition analysis

Body composition was analyzed using the HBF-375, Karada Scan Body Composition Monitor. The subjects were asked to stand barefooted on the foot electrodes and hands holding the grip electrodes in such a way that the arms and the body are kept at 90°. Body mass index (BMI), body fat, and visceral fat were evaluated automatically based on bioelectric impedance.

Biochemical Investigations

Five ml of venous blood were withdrawn, and biochemical investigations were carried out.

Serum glucose

The subjects were instructed for 8 hours of overnight fasting, and a blood sample was collected for estimating fasting blood glucose (FBG) levels. The subjects were then administered 75 g of anhydrous glucose in 250 to 300 mL, and a blood sample was collected again 2 hours after the test load. The FBG and oral glucose tolerance test values were measured using the glucose oxidase-peroxidase method using reagent kits supplied by Accurex Biomedical Pvt Limited, Mumbai, adapted to the Cobas Mira Plus Automated Chemistry analyzer.

Lipid profile

Serum total cholesterol (TC) was evaluated by the cholesterol oxidase method, and triglyceride (TG) levels were measured by the glycerol kinase- peroxidase method. High-density lipoprotein cholesterol (HDL-c) was measured by the divalent cation precipitation method using reagent kits adapted to an automated blood analyzer. Very low-density lipoprotein cholesterol (VLDL-c) was calculated by dividing the triacylglycerol concentration by 5 and low-density lipoprotein cholesterol (LDL-c) by using Friedwald's equation [TC-(VLDL+HDL)].

Statistical analysis

Continuous data were expressed as mean (Standard Deviation) and categorical data as frequencies. Frequency distributions between the groups were compared using the $\chi 2$ test.

The comparison of basic physiological parameters, cardiovascular autonomic function test parameters, and biochemical parameters for normally distributed data was made using the student t-test. The association was evaluated using Pearson correlation analysis. Univariate regression analysis was used to evaluate the contribution of various CV risk factors on the autonomic function.

Statistical package for social sciences (SPSS) version 19.0 for Windows (SPSS Inc., USA) was used for data analysis. A p-value of less than 0.05 was considered statistically significant.

Results

Out of the 295 individuals, 198 were normal, and 97 were pre-diabetic. The pre-diabetic subjects had significantly higher BMI; [95% CI (22.01, 22.95) vs. (28.45, 30.18) (p=<0.0001)], when compared to the normal group (Table 1).

The SD1 and SD2 was found to be significantly decreased among the pre-diabetic group: [95%CI (26.33, 30.27) vs. (15.98, 19.07)], [95%CI (48.39, 52.71) vs. (31.73, 37.26)], [95%CI (20.05, 20.95) vs. (14.03, 15.16)], respectively compared to the normal group. QTc was significantly prolonged among the pre-diabetic group compared to the normal. [95%CI (383.93, 391.20) vs. (415.62, 423.99)] (Table 2).

TC, TG, LDLc, VLDLc, BF, and VF reported a significant increase among the pre-diabetic group, while HDLc showed a decrease (Table 3). A significant correlation was reported between autonomic function, age, FPG, and BMI. SD1 and SD2 were negatively correlated to age, FPG, and BMI. QTc showed positive correlation with age (r=0.24), FPG (r=0.49) and BMI (r=0.37) (Table 4).

Univariate regression analysis showed that age, FPG, BMI, and lipid profile parameters were significantly associated with SD1, SD2, and QTc (Tables 5 and 6).

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Table 1: Basal anthropometric measurements and BP among the two groups.

Parameters	Control (n=198)	preDM (n=97)	p-value
	Mean (SD)	Mean (SD)	
Age, yr	19.19 (1.19)	20.33 (1.32)	<0.0001
FPG, mg/dL	80.94 (3.29)	110.66 (5.75)	<0.0001
IFG, mg/dL	97.21 (21.6)	150.44 (13.12)	<0.0001
SBP, mmHg	109.51 (6.51)	119.39 (9.55)	<0.0001
DBP, mmHg	66.84 (6.57)	71.45 (8.17)	<0.0001
HR, beats/min	76.01 (6.67)	77.81 (8.16)	0.04
WC, cms	82.52 (9.66)	86.12 (22.88)	0.05

Note: Values are expressed as mean (SD). P value less than 0.05 was considered to be significant. PreDM, Prediabetic; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WC, waist circumference; HC, hip circumference; BMI, body mass index.

Table 2: Autonomic function evaluated using the Poincaré plot and QTc among the two groups.

Parameters	Control n=198		PreDM n=97		p-value
	Mean(SD)	95%CI	Mean(SD)	95%CI	
SD1 (ms)	28.30 (14.04)	26.33, 30.27	17.53 (7.66)	15.98, 19.07	<0.0001
SD2 (ms)	50.55 (15.38)	48.39, 52.71	34.49 (13.71)	31.73, 37.26	<0.0001
QRS (ms)	97.67 (17.16)	95.26, 100.07	102.76 (23.37)	98.05, 107.47	0.03
QT (ms)	345.58 (32.65)	341.01, 350.16	364.41 (39.91)	356.10, 372.19	<0.0001
QTc (ms)	387.56 (25.93)	383.93, 391.20	419.80 (20.78)	415.62, 423.99	<0.0001

Note: Values are expressed as mean±SD. P-value less than 0.05 was considered to be significant. SD1, standard descriptor 1; SD2, standard descriptor 2; QTc, corrected QT interval.

Table 3: Lipid profile, body fat and visceral fat among the two groups.

Parameters	Control n=198		preDM n=97		p-value
	Mean (SD)	95% CI	Mean (SD)	95%CI	
TC	133.76 (16.38)	131.47,136.06	172.94 (12.18)	169.92, 176.60	<0.0001
TG	77.42 (24.85)	73.94, 80.91	103.68 (39.25)	95.77, 111.59	<0.0001
HDLc	37.56 (3.47)	36.85, 38.25	35.65 (4.52)	35.01, 36.28	<0.0001
LDLc	77.49 (9.91)	76.53, 79.01	84.95 (9.96)	82.94, 86.95	<0.0001
VLDLc	15.48 (4.97)	14.78, 16.18	20.73 (7.85)	19.15, 22.31	<0.0001
BodyFat (%)	28.66 (7.02)	27.67, 29.64	31.38 (7.13)	29.74, 32.50	0.002
Visceral Fat	4.35 (2.84)	3.95, 4.74	10.71 (4.91)	9.73, 11.71	<0.0001

Note: P value less than 0.05 was considered to be significant. TC, total cholesterol; TG, trilycerides; HDLc, high density lipid cholesterol; LDLc, low density lipid cholesterol; VLDLc, very low density lipid cholesterol.

Table 4: Pearson's correlation between autonomic function, age, FPG, IGT, BMI and HR.

	SD1		SD2		QTc	
	r	p	r	p	r	p
Age	-0.21	0.0001	-0.22	0.0001	0.24	0.0001
FPG	-0.42	0.0001	-0.46	0.0001	0.49	0.0001
IGT	-0.14	NS	-0.17	NS	0.12	NS
BMI	-0.42	0.0001	-0.47	0.0001	0.37	0.0001
Heart rate	-0.12	0.03	-0.09	0.11	0.15	0.08

Note: P-value less than 0.05 was considered to be significant.

Table 5: Univariate regression analysis with SD1 and SD2 as dependent variables and age, FPG, BMI and lipid profile as independent variables.

Independent variables	Standardized Beta coefficients	95% CI		p-value
		Lower bound	Upper bound	
SD1 as Dependent Variable				
Age	-0.21	-3.21	-0.98	0.0001
FPG	-0.41	-0.47	-0.28	0.0001
BMI	-0.42	-1.34	-0.81	0.0001
TC	-0.23	-0.18	-0.06	0.0001
TG	-0.12	-0.09	-0.01	0.04
HDLc	0.08	-0.11	0.61	0.17
LDLc	-0.31	-0.56	-0.27	0.0001
SD2 as Dependent Variable				
Age	-0.21	-3.95	-1.16	0.0001
FPG	-0.46	-0.64	-0.41	0.0001
BMI	-0.47	-1.84	-1.19	0.0001
TC	-0.35	-0.30	-0.16	0.0001
TG	-0.19	-0.16	-0.04	0.0001
HDLc	-0.01	-0.48	0.41	0.88
LDLc	-0.29	-0.69	-0.31	0.0001

Note: P-value less than 0.05 was considered to be significant.

Table 6: Univariate regression analysis with QTc as dependent variable and age, FPG, BMI and lipid profile as independent variables.

Independent variables	Standardized Beta coefficients	95% CI		p-value
		Lower bound	Upper bound	
QTc as Dependent Variable				
Age	0.24	2.78	7.53	0.0001

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FPG	0.49	0.77	1.16	0.0001
BMI	0.36	1.42	2.61	0.0001
TC	0.45	3.39	0.63	0.0001
TG	0.32	0.19	0.38	0.0001
HDLc	0.11	-0.02	1.51	0.05
LDLc	0.16	0.13	0.79	0.01

Note: P-value less than 0.05 was considered to be significant.

Figure 1 represents the Poincaré plot among the normal and preDM groups, with its numerical descriptors SD1 and SD2.

Discussion

In the present study, the prevalence of prediabetes was observed to be 32.88%, with 66% of males, indicating an alarming increase in the pre-diabetic population. A previous study from India, comparing the risk factors in the Indian and U.S. population, reported a prevalence of prediabetes of 24% [9]. The CV risk factors showed significant changes among the pre-diabetic group compared to the normal group, further supporting the "ticking clock hypothesis" [2].

In our study, BMI, which represents general obesity, and visceral fat and waist circumference (WC), that represents central obesity, were significantly increased in the preDM group. This is in agreement with other studies from the literature, which report that BMI is a significant risk factor for diabetes [10] and is also correlated to preDM [11]. It was found that BMI was significantly positively correlated to QTc and negatively correlated to the SD1 and SD2 parameters. Similar findings were reported by Ravikumar et al., where BMI was positively correlated to QTc [12].

We found significant differences in SD1 and SD2 among the two groups. The lower SD1 in the preDM group indicates weakened parasympathetic regulation, and lower SD2 indicates increased sympathetic activity depicting that there is a pronounced vagal withdrawal and sympathetic augmentation in the pre-diabetic stage. Also, in our study, SD1 and SD2 reported a significant moderate correlation with BMI and FPG. Univariate regression analysis revealed that FPG causes a 17% variation in SD1 and a 21% variation in SD2. A study among diabetic patients employing the non-linear analysis of HRV suggested decreased parasympathetic modulation and suggested using non-linear methods to evaluate autonomic dysfunction in diabetic individuals [13]. Autonomic impairment is reported even before the alteration in glucose homeostasis becomes clinically apparent [14]. A study conducted on 400 subjects to find the role of isolated IFG on the pathogenesis of cardiac autonomic neuropathy (CAN), investigating HRV and heart rate turbulence observed that autonomic dysfunction is present in the isolated IFG subtype of preDM [15]. A recent update on diabetes has put forward the putative mechanisms for CAN, which include tachycardia, QT interval, impaired HRV, reverse dipping, and orthostatic hypotension [16]. A review suggests that since CAN is a predictor of adverse cardiac functioning, an improvement in ANS can thus help to reduce CV events in the future [17].

QTc showed a significant increase among the preDM group compared to the normal group, but the increase was within the normal limits, not clinically significant. The QTc interval showed a significant positive correlation with FPG and a moderate correlation with BMI. QTc prolongation may be due to the sympathetic dominance among the preDM group. It is observed that prolonged QTc duration and QTc dispersion is related to increased glycemic variability [18]. Increased long-term variability of postprandial glucose is an independent risk factor for QTc prolongation in type 2 diabetes [19]. A study on the Chinese population in 2012 showed that postprandial glucose level was an independent risk factor for prolongation of QTc interval, and the underlying mechanism may be due to increased reactive oxygen species, increased calcium concentration, and sympathovagal imbalance [20]. The exact basis of QTc prolongation in the preDM group and the effect of hyperglycemia is multifactorial.

This study reported cardiac autonomic dysfunction in younger individuals employing the Poincaré plot analysis and QTc. The limitations include the small sample size and the fact that gender-based analysis of autonomic function was not carried out; also, dietary practices and physical activity were not taken

into account, and since it is a cross-sectional study, the exact cause and pathophysiological link behind IFG and autonomic functions could not be elucidated. Future longitudinal studies are required to explain the link between hyperglycemia and impaired autonomic function.

Conclusion

Autonomic dysfunction appears in the pre-diabetic stage, in the form of parasympathetic withdrawal and sympathetic dominance. Gender, BMI, and FPG were reported to show a significant association with SD1, SD2, and QTc. This study emphasizes glucose monitoring and evaluating autonomic functions, in younger individuals to know the extent of alterations caused and to plan early interventional strategies.

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Conflict of Interest

The authors declare no conflict of interest.

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