



HEART RATE VARIABILITY IN PREDIABETIC INDIVIDUALS

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ABSTRACT **Background:** The World Health Organisation (WHO) defines Pre-diabetes as a state of intermediate hyperglycemia. In diabetes mellitus, Cardiac autonomic dysfunction (CAD) and neuropathy are common, but the abnormalities in the autonomic nervous system (ANS) and the influence of altered glycaemic indices on cardiovascular parameters by using Heart Rate Variability (HRV) have not been elucidated in prediabetics. This study was aimed at elucidating the effect of hyperglycemia on cardiovascular autonomic function in prediabetic patients using HRV. **Method:** A cross-sectional study was done in 50 prediabetics based on the WHO classification of prediabetics, and 50 age- and sex-matched healthy controls in the age group of 18–40 years were recruited from Coimbatore medical college & Hospital, Coimbatore. After obtaining institutional ethical committee clearance, consent was obtained from the subjects. Subjects who have chronic illnesses, underlying cardiovascular comorbidities, chronic smokers, pregnant women, or have a history of any medications were excluded from this study. Short-term HRV was done in these individuals. The results were tabulated and analysed. **Results:** A statistically significant difference was observed in Heart Rate (HR) and time domain parameters in pre-diabetics compared to healthy controls. Among the prediabetics, males have significantly lower HRV than prediabetic females. Body mass index was significantly higher in prediabetics than controls. **Conclusion:** In prediabetics, lower heart rate variability was observed than in healthy controls. Among the prediabetics, males had significantly lower HRV than females. This may lead to a subclinical level of cardiovascular complications. Thus, lifestyle modifications can be made to reverse the prediabetic state of individuals. Thereby preventing prediabetics from developing further cardiovascular complications.

KEYWORDS : Heart rate variability, prediabetics

INTRODUCTION

World Health Organisation (WHO) defines Pre-diabetes, a state of intermediate hyperglycaemia using these specific parameters

1. Impaired Fasting Glucose (IFG) which is Fasting Plasma Glucose (FPG) of 110–125 mg/dl (6.1-6.9 mmol/L)
2. Impaired Glucose Tolerance (IGT) defined as plasma glucose of 140–199 mg/dl (7.8-11.1 mmol/L) based on 2-h Oral Glucose Tolerance Test (OGTT) or
3. A combination of both.

In diabetes mellitus, Cardiac autonomic dysfunction (CAD) and neuropathy are common but the abnormalities in Autonomic nervous system (ANS) and the influence of altered glycaemic indices on cardiovascular parameters by using HRV have not been elucidated in prediabetics. The risks of cardiovascular disease and vascular complications were comparatively high in prediabetics than normal population. The increased risk in these prediabetics could be due to the presence of pro-inflammatory cytokines which has some influence on autonomic nervous system (ANS).

The role of ANS on heart is important, under normal resting conditions both the sympathetic and parasympathetic chains of ANS are tonically active, with a predominant vagal effect. The main function of ANS is to maintain the homeostasis, by constant modification of heart rate on beat-to-beat basis. Any variations between consecutive heartbeats (RR or NN interval) can be easily accessed by HRV. This beat-to-beat variability is due to continuous changes in the sympathetic and parasympathetic outflow to the heart.

Previous experimental evidences showed the association between lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity. Abnormalities of autonomic activity is reflected through reduced heart rate variability (HRV). It is strongly associated with increased risk for cardiac events, and overall mortality. Diabetic autonomic dysfunction, even when subclinical, is also associated with a high risk of mortality.

In diabetics, the frequency component of HRV, derived from power spectral analysis reflects the autonomic modulation of the heart. Spectral analysis of HRV can partially distinguish parasympathetic from sympathetic influence on the heart and may provide important insights into the pathogenesis of autonomic neuropathy in hyperglycaemia. This study was aimed to study the effect of hyperglycaemia on cardiovascular autonomic function in prediabetic patients, which is evaluated by performing heart rate variability.

MATERIALS AND METHODS

This study was a cross-sectional comparative study done in Coimbatore Medical college and Hospital, Coimbatore, Tamil Nadu. After obtaining Institutional Ethical committee clearance, adult population of age group 18-40 years were recruited. Consent for willingness was obtained from both the cases and controls for the study. 50 prediabetic cases comprising 28 males and 22 females were recruited from the Makkalai Thedi Maruthuvam (MTM) clinic based upon the World Health Organisation (WHO) criteria for prediabetes. They were all newly diagnosed prediabetics. The prediabetic subjects who are less than 18 years and more than 40 years, having any history of chronic illness, underlying cardiovascular comorbidities, chronic smokers, pregnant women, history of any medications were excluded from this study. Attenders of patients attending General medicine outpatient service were recruited for the control group. 50 age and sex matched healthy controls were recruited. Among them 24 were males and 26 were females. A brief history has been taken and the anthropometric measurements such as height in meter and weight in kg were recorded for both the group. Body mass index was calculated by dividing the subject's weight in kg by the square of their height in meter. $BMI = \text{kg}/\text{m}^2$, where 'kg' is the subject's weight in kilograms and 'm' is the subject's height in meters. Basal heart rate was also measured. Heart rate variability procedure has been explained to the subjects and consent was obtained.

Recording Of HRV

Subjects were asked to take rest in supine position for 15 minutes in a quiet room. Heart rate variability was assessed by a portable machine which has a pulse detector and 3 leads connected to the machine through wires. The three leads were stuck by using a micropore to right wrist, left wrist denoted by a red coloured wire and right foot as the ground electrode which is denoted by a green coloured wire. On the other end of the machine, it has a port which was connected to the windows 11 laptop. Short term Heart rate variability has been done for both prediabetics and controls. The recording was done in Audacity app for 10-12 minutes. The recording, which was devoid of any artifacts for a minimum period of 5 minutes, was selected, and the beat-to-beat time difference was calculated and analysed by using Heart Rate Variability (HRV) analysis software in the Windows 11 system. Results of the heart rate variability were tabulated and analysed.

Statistical Analysis

Data were entered and analysed using SPSS software 21.0. continuous variables were represented in mean \pm SD. Paired t-test was used. P value <0.05 was set as significant value.

RESULTS

The study was conducted with the objective of studying the effect of hyperglycemia on cardiovascular autonomic function in prediabetic patients, which was evaluated by performing HRV. The data was collected from a total of 100 study participants, 50 of whom were prediabetes and the other 50 were normal.

Table 1: Comparison Of Anthropometric Measurements.

Parameters	Controls (n = 50)			Prediabetics (n = 50)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
Age (years)	28.30 ± 6.19	28	23-34	29.92 ± 5.29	30	26-34.25	0.163
Height (cm)	1.67 ± 0.10	1.65	1.6-1.73	1.67 ± 0.11	1.66	1.59-1.76	0.889
Weight (kg)	66.94 ± 14.5	65.50	55-80.5	80.28 ± 9.93	82	72-88	0.001*
BMI (kg/m ²)	23.97 ± 4.30	23.80	20.28-26.93	29.58 ± 5.40	29.65	25.47-32.8	0.001*

*Significant P value.

Table 1 presents a comparison of anthropometric measurements between the control group (n = 50) and prediabetic participants (n = 50). The mean age of the control group was 28.30 years (SD = 6.19), with a median age of 28 years and an interquartile range (IQR) of 23–34 years, while prediabetics had a mean age of 29.92 years (SD = 5.29), a median age of 30 years, and an IQR of 26–34.25 years. No statistically significant difference in age was observed between the two groups (p = 0.163). Regarding height, controls had a mean of 1.67 cm (SD = 0.10), with a median of 1.65 cm and an IQR of 1.60-1.73 cm, whereas prediabetic individuals had a mean height of 1.67 cm (SD = 0.11), a median of 1.66 cm, and an IQR of 1.59-1.76 cm, showing no significant difference between groups (p = 0.889). However, notable differences emerged in weight and body mass index (BMI).

Prediabetics exhibited a significantly higher mean weight (80.28 kg, SD = 9.93) compared to controls (66.94 kg, SD = 14.50), with respective medians of 82 kg and 65.50 kg and IQRs of 72-88 kg and 55-80.50 kg (p = 0.001). Similarly, prediabetics had a markedly elevated mean BMI (29.58 kg/m², SD = 5.40) compared to controls (23.97 kg/m², SD = 4.30), with medians of 29.65 kg/m² and 23.80 kg/m² and IQRs of 25.47-32.80 kg/m² and 20.28-26.93 kg/m² (p = 0.001). These findings highlight significant differences in weight and BMI between the prediabetic and control groups, highlighting the association between prediabetes and alterations in anthropometric parameters.

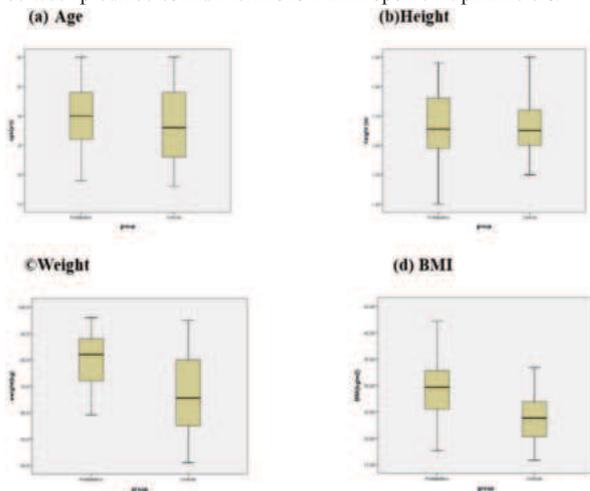


Figure 1: Comparison Of Anthropometric Measurements.

Table 2 presents a comparative analysis of blood glycaemic parameters between the control group (n = 50) and prediabetic subjects (n = 50). For fasting blood sugar (FBS) levels, controls exhibited a mean of 90.96 mg/dl (SD = 9.83), a median of 90 mg/dl, and an interquartile range (IQR) of 83-97.25 mg/dl, while prediabetics showed a significantly higher mean FBS of 116.42 mg/dl (SD = 3.58), a median of 116 mg/dl, and an IQR of 113-119.25 mg/dl (p = 0.001). Similarly, in the 2-hour oral glucose tolerance test (OGTT), controls had a mean of 120.40 mg/dl (SD = 10.44), a median of 122 mg/dl, and an IQR of 115-130 mg/dl, whereas prediabetic participants demonstrated a markedly

elevated mean of 169.22 mg/dl (SD = 13.47), a median of 168 mg/dl, and an IQR of 160-180.50 mg/dl (p = 0.001).

Table 2: Comparison Of Blood Glycaemic Parameters.

Parameters	Controls (n = 50)			Prediabetics (n = 50)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
FBS (mg/dl)	90.96 ± 9.83	90	83-97.25	116.42 ± 3.58	116	113-119.25	0.001*
2 hr OGTT (mg/dl)	120.4 ± 10.44	122	115-130	169.22 ± 13.47	168	160-180.50	0.001*

*Significant P value.

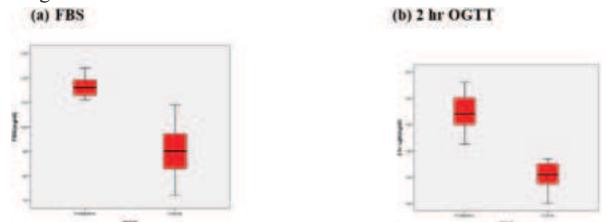


Figure 2: Comparison Of Blood Glycaemic Parameters.

Table 3: Comparison Of HRV Parameters Between Prediabetics And Controls.

Parameters	Controls (n = 50)			Prediabetics (n = 50)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
HR (beats/min)	76.36 ± 7.89	76	69-84	85.12 ± 6.59	85	81.50-91	0.001*
Mean RR interval (ms)	947.90 ± 105.97	934.50	855-1028.25	901.92 ± 97.19	872	837.75-942.50	0.026*
SDNN (ms)	32.67 ± 12.43	30.40	21-48	25.34 ± 15.24	23.14	18.4-48.6	0.01*
RMSSD (ms)	33.08 ± 8.43	34	26.75-38	23.90 ± 4.38	24	20-26.25	0.001*
NN50	19.62 ± 4.63	19	16-23.25	17.30 ± 3.56	16.50	14-20	0.006*
pNN50%	42.95 ± 18.06	41	26.30-57.25	28.22 ± 10.07	27	17.50-35	0.001*
VLF (ms ²)	908.16 ± 96.21	928	834-962	917.90 ± 97.39	934.50	848.25-968	0.616
LF (ms ²)	1462.70 ± 271.46	1361.50	1256-1677.50	1442.66 ± 203.70	1355	1256-1635	0.677
HF (ms ²)	358.06 ± 157.99	345	249.50-489	327.46 ± 121.01	281.50	253-425.25	0.280
LF/HF	5.06 ± 2.60	4.36	2.99-6.65	5.08 ± 2.11	4.80	3.51-6.18	0.961

*Significant P value.

Table 3 outlines a comparative analysis of heart rate variability (HRV) parameters between prediabetic individuals (n = 50) and controls (n = 50). Prediabetics demonstrated significantly altered HRV indices compared to controls across various parameters. Regarding heart rate (HR), prediabetic participants exhibited a notably higher mean HR (85.12 beats/min, SD = 6.59) compared to controls (76.36 beats/min, SD = 7.89), with significant differences observed (p = 0.001). Similarly, the mean RR interval, standard deviation of NN intervals (SDNN), a measure of overall HRV, were significantly lower in prediabetics (901.92 ms, SD = 97.19) compared to controls (947.90 ms, SD = 105.97) (p = 0.026). Root mean square of successive differences (RMSSD), reflecting parasympathetic activity, was markedly reduced in prediabetics (23.90 ms, SD = 4.38) compared to controls (33.08 ms, SD = 8.43) (p = 0.001).

Additionally, the number of pairs of successive NNs differing by more than 50 ms (NN50) and the percentage of NN50 divided by the total number of NNs (pNN50%) were significantly lower in prediabetics compared to controls (p = 0.006 and p = 0.001, respectively), indicating diminished parasympathetic modulation in prediabetics. Notably, no significant differences were observed in the very low-frequency (VLF), low-frequency (LF), high-frequency (HF), and LF/HF ratio between prediabetics and controls (p > 0.05). These

findings underscore the presence of autonomic dysfunction characterised by sympathetic predominance and parasympathetic withdrawal in prediabetic individuals, as reflected by altered HRV parameters.

Table 4: Correlation Between Blood Glycaemic Indices With HRV Parameters After Adjusting For Weight And BMI.

Parameters	FBS		2 hr OGTT	
	r value	P value	r value	P value
HR (beats/min)	0.455	0.001*	0.503	0.001*
Mean RR interval	-0.138	0.171	-0.158	0.117
SDNN (ms)	-0.023	0.116	-0.342	0.024
RMSSD (ms)	-0.443	0.001*	-0.504	0.001*
NN50	-0.167	0.096	-0.232	0.020*
pNN50%	-0.402	0.001*	-0.475	0.001*
LF (ms ²)	-0.095	0.345	-0.085	0.401
HF (ms ²)	-0.119	0.237	-0.113	0.264
LF/HF	0.014	0.894	0.013	0.901

*Significant P value.

Table 4 presents the associations between blood glycaemic indices and heart rate variability (HRV) parameters after adjusting for weight and body mass index (BMI). For fasting blood sugar (FBS), significant positive correlations were found with heart rate (HR) ($r = 0.455, p = 0.001$) and root mean square of successive differences (RMSSD) ($r = -0.443, p = 0.001$), indicating that higher FBS levels were associated with elevated HR and reduced parasympathetic modulation. Similarly, in the 2-hour oral glucose tolerance test (2 hr OGTT), positive correlations were observed with HR ($r = 0.503, p = 0.001$) and RMSSD ($r = -0.504, p = 0.001$), confirming the influence of postprandial glucose levels on autonomic function. Moreover, significant negative correlations were noted between 2 hr OGTT and NN50 ($r = -0.232, p = 0.020$) and pNN50% ($r = -0.475, p = 0.001$), indicating an inverse relationship between postprandial glucose levels and parasympathetic activity.

These results suggest that while elevated blood glucose levels, particularly postprandial, are associated with altered HRV indices indicative of autonomic dysfunction, these associations are independent of weight and BMI adjustments.

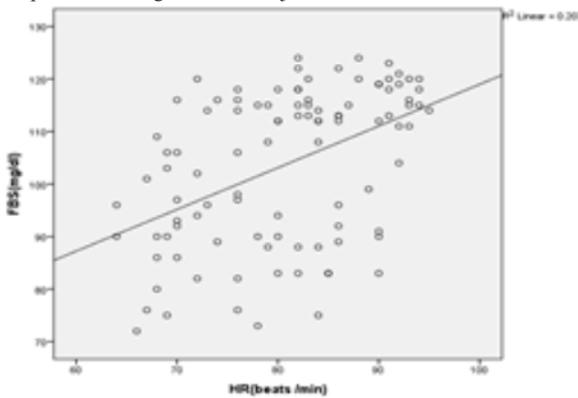


Figure 3: Correlation Between FBS With Heart Rate

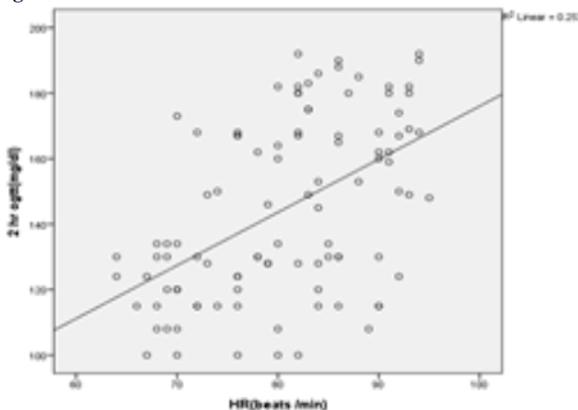


Figure 4: Correlation Between 2 Hr OGTT With Heart Rate.

Table 5: Comparison Of Anthropometric Measurements In Prediabetic Males And Females.

Parameters	Prediabetic males (n = 28)			Prediabetic females (n = 22)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
Age (years)	29.86 ± 5.25	30	25.25-33.50	30 ± 5.46	30	27-35.25	0.926
Height (cm)	1.73 ± 0.07	1.73	1.65-1.80	1.58 ± 0.08	1.58	1.52-1.62	0.001*
Weight (kg)	80.21 ± 10.52	81.50	72-89.50	80.36 ± 9.37	83	71-88	0.959
BMI (kg/m ²)	27.19 ± 4.37	27	24.12-30.55	32.63 ± 5.12	31.80	28.93-36.50	0.001*

*Significant P value.

Table 5 presents the comparison of anthropometric measurements between prediabetic males (n= 28) and prediabetic females(n=22). Prediabetic female had a markedly elevated mean BMI (32.63 kg/m², SD = 5.12) compared to prediabetic male (27.19 kg/m², SD = 4.37)

Table 6: Comparison Of Blood Glycaemic Parameters Between Prediabetic Males And Females.

Parameters	Prediabetic males (n = 28)			Prediabetic females (n = 22)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
FBS (mg/dl)	116.04 ± 3.95	115	112.25-119	116.91 ± 3.05	116	114.7-120	0.397
2 hr OGTT (mg/dl)	170.71 ± 13.47	168.50	162.50-182	167.32 ± 13.53	167	157.5-180	0.382

Table 6 presents the comparison of blood glycaemic parameters between prediabetic males and females. There was no significant change in the blood glycaemic parameters between prediabetic male and female.

Table 7: Comparison Of HRV Parameters Between Prediabetic Males And Females.

Parameters	Prediabetic males (n = 28)			Prediabetic females (n = 22)			P value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
HR (beats/min)	85.93 ± 6	86	82.25-91.75	84.09 ± 7.28	82.50	78.25-91	0.332
Mean RR interval	871.82 ± 72.30	863	834-926.25	940.23 ± 112.13	917	859.50-1032.75	0.012*
SDNN (ms)	23.16 ± 6.34	22.64	18.4-30.2	28.16 ± 10.42	29.2	19.67-48.6	0.041*
RMSSD (ms)	24.21 ± 4.76	24	20-27.75	23.50 ± 3.91	23.50	20.50-26	0.572
NN50	17.25 ± 3.04	17	14.25-20	17.36 ± 4.22	16	14-20.25	0.912
pNN50 %	29.32 ± 9.44	28.50	24-34.75	26.81 ± 10.88	25.50	15.75-35.75	0.388
LF (ms ²)	1532.82 ± 212.98	1212.98	1278-1674	1327.91 ± 117.72	1268	1256-1354.50	0.001*
HF (ms ²)	332.79 ± 120.64	265	247-425.75	320.68 ± 123.97	295.50	262.75-396	0.729
LF/HF	5.22 ± 1.98	5.19	3.50-6.34	4.90 ± 2.29	4.80	3.38-5.54	0.589

*Significant P value.

Table 7 presents the comparison of HRV parameters between prediabetic males and prediabetic females. Prediabetic males have statistically significant lower heart rate variability parameters like mean RR interval, SDNN in time domain parameter, and LF in frequency domain parameter compared to prediabetic females. This signifies that lower heart rate variability is more pronounced in prediabetic males than females, as all these parameters reflect the parasympathetic activity of the heart.

DISCUSSION

HRV is a tool to find cardiac autonomic activity. The time domain parameter SDNN shows the overall vagal modulation of the heart.

RMSSD shows the vagal modulation of cardiac functions on a short-term basis. NN50 signifies the short-term variability of vagal modulation. In the frequency domain parameter, low frequency (LF) reflects the sympathetic activity of the heart, and high frequency (HF) reflects the parasympathetic activity of the heart. The LF/HF ratio shows the sympatho-vagal balance of the heart. In our study, there is a significant decrease in SDNN along with a significant negative association between HRV parameters and glycaemic indices. This indicates a decrease in the parasympathetic activity of cardiac autonomic function. Hence, there is a possibility of CAD initiation in the prediabetic stage itself. This is in accordance with the study done by Santhanalakshmi et al.

In our study, we observed an inverse relationship between HRV and impaired fasting glucose levels and 2-hour OGTT glucose values. This is in accordance with the study done by Jagmeet P. Singh et al., which stated that HRV is inversely associated with plasma glucose levels and is reduced in diabetics as well as in subjects with impaired fasting glucose levels.

Charlotte Coopmans and Tan Lai Zhou et al. stated that both prediabetes and type 2 diabetes were associated with lower HRV. This reveals the association between hyperglycemic status and lower HRV, which is in accordance with our study. This data strongly suggests that CAD is already present in prediabetic individuals.

In our study, there was a statistically significant increase in BMI in prediabetics compared to the control group. Yao Shan Zhang et al., study also indicated that overweight was a risk factor for prediabetes and diabetes.

Yi Huang et al., study showed that prediabetes was associated with increased cardiovascular mortality. Thus, prediabetics were at increased risk for cardiovascular disorders than normoglycemic individuals. A study by Subbulakshmi NK et al. on type 2 diabetics showed that higher HR, diastolic blood pressure, prolonged Q-T interval, and duration of diabetes were associated with reduced SDNN.

Shah et al. study showed that young adults with youth-onset Type 2 diabetes mellitus show evidence of cardiac autonomic dysfunction with both parasympathetic and sympathetic impairments that are associated with higher HbA1c. This shows the relationship between sympathetic and parasympathetic imbalances in pre-diabetic and diabetic patients.

CONCLUSION

There is a significant difference in the SDNN parameter in prediabetics compared to normal individuals, indicating sympathetic dominance in pre-diabetic individuals. Among the prediabetics, males have significantly lower heart rate variability than females. This lower heart rate variability may lead to a subclinical level of cardiovascular complications. Thus, Heart rate variability can be routinely measured in prediabetics to predict the early onset of cardiovascular pathology.

As prediabetes is a reversible state, preventive measures like lifestyle modifications should be taken to reverse the prediabetic state of the individuals, thereby preventing them from developing further cardiovascular complications.

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