Original Research Article

Evaluation of Autonomic Function in newly diagnosed Type 2 Diabetes Mellitus using Heart Rate Variability

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Abstract:

Introduction: Cardiovascular autonomic neuropathy (CAN) is a serious complication of type 2 diabetes mellitus (T2DM) which is often underdiagnosed. CAN constitutes the chief cause for silent myocardial infarction and sudden death in type 2 diabetes mellitus patients. Heart Rate Variability (HRV) is a sensitive and non-invasive tool to assess the autonomic functions. **Aim:** To evaluate the effectiveness of heart rate variability as a tool to assess the autonomic functions in newly diagnosed T2DM patients. **Methodology:** 30 newly diagnosed T2DM patients in the age group of 18 – 45 years were recruited. ECG was recorded for 20 minutes to determine the HRV at supine rest with eyes closed. Instantaneous heart rate at RR intervals were plotted using RMS 2.5.2 software. **Results:** There was a significant reduction in the values of SDNN (ms), RMSSD (ms), NN50 count, pNN50% (time domain measures) and HF (ms^2) (frequency domain measure). LF (ms^2) levels and LF/HF ratio were significantly elevated in T2DM patients. **Conclusion:** HRV could detect cardiac autonomic neuropathy in newly diagnosed T2DM cases in the earlier stages and hence HRV can be used as an investigative tool to assess CAN in T2DM patients.

Key Words: Cardiac autonomic neuropathy, type 2 Diabetes Mellitus, silent myocardial infarction, Heart rate variability

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Introduction :

According to World Health Organization (WHO), diabetes mellitus is defined as a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads over time to damage to the heart, vasculature, eyes, kidneys and nerves.[1] Over 90% of diabetes mellitus cases are T2DM, a condition marked by deficiency of insulin secretion by pancreatic islet cells, insulin resistance and an inadequate compensatory insulin secretory response.[2]

About 537 million adults in the age group of 20 - 79 years which represents 10.5 % of the world's population are currently living with diabetes and this number is projected to reach 643 million by 2030, and 783 million by 2045. It is also estimated that over 6.7 million people in the age group of 20 - 79 years will die from diabetes-related causes in

2021. Modern sedentary lifestyle in both personal and professional life is the major risk factor.[3]

Cardiac autonomic neuropathy (CAN) is defined as the abnormalities associated with heart rate control and vascular dynamics. It is a serious complication that affects one-third of patients with Type 2 DM and is associated with five-fold increased risk of developing cardiovascular mortality. CAN is often underdiagnosed and can lead to silent myocardial infarction, severe morbidity, fatal arrhythmias, and sudden death. The cardiovascular mortality associated with CAN was found to be the primary cause of death in patients with Type 2 DM.[4]

Several methods have been described to detect autonomic neuropathy. The assessment of heart rate variability (HRV) is a well-accepted method to evaluate the status of autonomic control on the heart.[5,6] Although many studies have been conducted to evaluate the autonomic functions in established cases of Type 2 Diabetes Mellitus, the data on CAN in newly diagnosed T2DM is scarce.

Aim:

To evaluate the effectiveness of heart rate variability as a tool to assess the autonomic functions in newly diagnosed T2DM patients.

Objectives:

To compare the usefulness of Heart Rate Variability during supine rest of 20 minutes as a measure of autonomic function between T2DM and Controls.

Materials and Methods:

Our study design was analytical cross-sectional study. Thirty patients with newly diagnosed T2DM according to WHO criteria (FBS ≥ 126mg/dl, PPBS ≥ 200mg/dl & HbA1C > 6.5%), were recruited from non-communicable disease outpatient department (OPD).[7] The Sample size was calculated using open epi software taking consideration of the mean difference in the SDNN values between T2DM and healthy controls in the study by Kudat et al.[8] The study sample size arrived was 11 in each group. In order to obtain normally distributed data, minimum sample size of 30 was chosen in each group.

Inclusion criteria were newly diagnosed T2DM patients of age 18 – 45 years of both genders. Exclusion criteria included patients with established diagnosis of DM on treatment, co-morbid conditions such as cardiovascular diseases, renal failure, cerebrovascular diseases, COPD, hypertension, hypothyroidism, history of other acute or chronic illness, history of smoking, alcoholism and intake of any other medications. Thirty age, gender & BMI matched apparently healthy volunteers were selected from Master Health Check-up OPD as control group.

The study was approved by Institutional Ethical Committee (IEC No. 1/2023 dt 28.03.2023). The purpose, risks and benefits of the study were explained to all the participants and informed consent was obtained from each of them. The study was conducted in the autonomic function lab of the Department of Physiology.

Methodology:

Acquisition of Heart Rate Variability:

The Individuals were instructed to come in empty stomach or 2 hrs after a light breakfast to the autonomic function lab by 9 AM. They were instructed not to perform any intense exercise and were advised to avoid intake of any hot or cold beverages 30 mins before the procedure. Anthropometric measurements (height, weight, BMI) were acquired. The subjects were asked to empty their bladder before the procedure. After 10 mins rest, basic cardiovascular parameters like heart rate & blood pressure were recorded.

The recommendations of the Task Force 1996 (9) were followed for acquisition of HRV. ECG was acquired using RMS Polyrite D hardware (India), and instantaneous heart rate at RR intervals were plotted using RMS 5.0.8 software on a Microsoft window-based PC. ECG was recorded for 20 minutes to determine the HRV at supine rest with eyes closed with normal quiet respiratory movements. Electrodes were fixed in the following positions after cleaning the skin with spirit to record the ECG.

Electrode	Position
Exploring Electrode	Left shoulder
Exploring Electrode	Right shoulder
Reference Electrode	Right leg

An RR series was extracted from ECG using maximum amplitude and sharpness for the peaks for R wave detection. After exclusion of artifacts and ectopic, a stationary 256s RR series was chosen and analyzed using software on a window-based PC. Time domain analysis was used for long term HRV changes and frequency analysis was used for short term HRV changes.

Respiratory movements were recorded using respiratory belt which was tied around the chest at the level of the nipple. It analyses inspiration and expiration. The electrodes and the respiratory belt were connected to RMS Polyrite D equipment.

Parameters assessed:

I. Body Mass Index, Fasting blood sugar, Post prandial blood sugar & Heart rate.

II. HRV Parameters

a. Time domain measures - SDNN in ms, RMSSD in ms, SDANN in ms, NN50 count, pNN50%

b. Frequency domain measures - LF in ms^2, HF in ms^2, LF/HF ratio, Total power in ms^2, HF in n.u., LF in n.u.

Statistical analysis:

Data entry:

The collected study data were entered in Microsoft Office Excel 2013 and analyzed **using SPSS software version 26.**

Descriptive statistics:

Continuous variables were expressed as mean and standard deviation. Description of categorical variables were expressed as frequency and proportion.

Tests of significance :

Unpaired t test was used to compare the means of variables. All tests were two-tailed, with results considered statistically significant if the p-value is less than 0.05.

Results:

In our study, 18 were males and 12 were females among the cases. The mean age, height and BMI were comparable among the two groups, whereas the weight of diabetics was significantly lower when compared to that of non-diabetic individuals (Table 1).

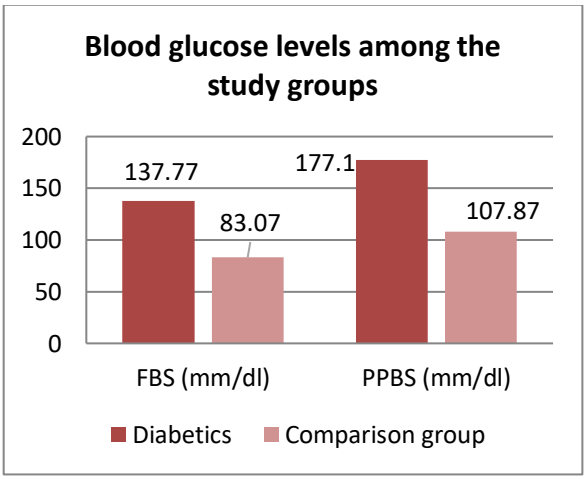
Further, it was observed that the fasting and post prandial blood sugar levels were significantly higher among the diabetic population when compared to the comparison group (p value < 0.001 in both cases) (Figure 1).

Table 1: Baseline characteristics and anthropometric measurements of the T2DM patients and control group

Sl. No.	Parameter	T2DM patients (n = 30)		Control group (n = 30)		p value
		Mean (95% CI)	SD (95% CI)	Mean (95% CI)	SD (95% CI)	
1	Age (years)	29.2 (27.4-31)	5.03 (3.93-5.83)	29.23 (27.50-30.90)	4.95 (3.97-5.74)	0.959
2	Height (cms)	156.9 (153.9-159.43)	7.87 (6.01-9.20)	160.30 (158.03-162.83)	6.77 (4.49-8.49)	0.075
3	Weight (kgs)	54.67 (52.33-56.90)	6.53 (4.78-7.81)	58.57 (56.50-60.80)	5.88 (4.43-6.83)	0.018*
4	Body Mass Index	22.26 (21.34-23.11)	2.47 (1.62-3.15)	22.78 (22.13-23.38)	1.70 (1.18-2.16)	0.344

*p value < 0.05 is significant, **p value < 0.001 is highly significant

Figure 1: Comparison of blood glucose levels between the study groups



On comparing the heart rate variation among the study groups, both heart rate (beats per minute) and R-R interval (in seconds) were found to be distributed normally among both groups. It was also observed that there was significant increase in the mean heart rate among the diabetic patients on comparison with their non-diabetic counterparts and vice versa in case of mean R-R interval (Table 2).

Table 2: Comparison of heart rate variation between T2DM patients and control group

Sl. No.	HRV Parameters	T2DM patients (n = 30) Mean (SD)	Control group (n = 30) Mean (SD)	p value
1	RR interval (seconds)	0.72 (0.086)	0.808 (0.124)	0.002*
2	Heart Rate (bests per minute)	85.97 (8.93)	75.93 (11.55)	**< 0.001****

*p value < 0.05 is significant, **p value < 0.001 is highly significant

Among the time domain measures described, only SDNN was distributed normally so the other parameters of the time domain were described using median and interquartile range (IQR). All the time domain parameters were significantly lower among the diabetic subjects when compared to the control group (Table 3).

Table 3: Comparison of time domain measures in HRV between T2DM patients and control group

Sl.No.	HRV Parameters	T2DM patients (n = 30) Median (IQR)	Control group (n = 30) Median (IQR)	p value
1	SDNN (in milliseconds)	27.68 (13.68)[#]	60.32 (23.92)[#]	**< 0.001****
2	RMSSD (in milliseconds)	15.2 (11.12 - 34.78)	66.58 (45.27 - 88.96)	**< 0.001****
3	NN50 count	3 (0.00 - 9.5)	144 (60 -177.25)	**< 0.001****
4	PNN50%	0.75 (0.00 – 1.9)	42.05 (14.9 – 58.9)	**< 0.001****

*p value <0.05 is significant, **p value < 0.001 is highly significant, [#]- Mean value with Standard Deviation (SD)

All the frequency domain measures were significantly different among the two study groups except for the total power. While both the low frequency domain (LF in ms^2) and the low frequency Normalized Units (LF in N.U.) were significantly higher in diabetic group, the high frequency parameters were higher in the comparison group. Only the low frequency and high frequency in normalized units were normally distributed. Also, LF-HF ratio was also found to be higher in the diabetic subjects (Table 4).

Table 4: Comparison of frequency domain measures in HRV between T2DM patients and control group

Sl. No.	Frequency domain Parameters	T2DM patients (n = 30) Median (IQR)	Control group (n = 30) Median (IQR)	p value
1	LF (in ms^2)	18.3 (13 – 28.35)	11.55 (5 – 20.8)	**0.015***
2	HF (in ms^2)	5.74 (3.22 – 8.18)	13.75 (5.82 – 24.35)	**< 0.001****
3	LF/HF	3.05 (2.42 – 3.88)	0.86 (0.68 – 1.24)	**< 0.001****
4	LF (in N.U.)	74.0 (10.57) [#]	47.25 (12.48) [#]	**< 0.001****
5	HF (in N.U.)	25.82 (10.59) [#]	52.64 (12.42) [#]	**< 0.001****
6	Total power (in ms^2)	22.85 (18.62 – 44.3)	28.65 (10.47 – 45.2)	0.801

*p value <0.05 is significant, **p value < 0.001 is highly significant, [#]Mean value with Standard Deviation (SD)

As described in the Table 4, only the LF and HF in normalized units were normally distributed among the different frequency domain measures.

Discussion:

The Incidence and prevalence of the global epidemic diabetes mellitus is increasing due to modern sedentary lifestyle. Chronic hyperglycemia has been linked to mitochondrial dysfunction, membrane permeability, and endothelial dysfunction.[4]

The increasing mortality in young diabetes mellitus patients is most probably due to cardiovascular autonomic neuropathy. CAN has been detected at the time of diagnosis of diabetes in patients with either T1DM or T2DM irrespective of age, suggesting that its presentation is not limited by age or type of diabetes and can occur before DM is evident clinically.[10]

HRV is a sensitive, noninvasive and easily measurable tool to assess the cardiac autonomic dysfunction. Previously, John APP et al has documented a significant reduction of HRV as indicated by a significant reduction of SDNN in the diabetics compared to the healthy controls.[4] Also, Janet Sugantha et al has documented a significant reduction of HRV in Type 1 DM as indicated by significant reduction of SDNN and elevated LF/HF ratio compared to the healthy controls.[11] Many studies have been conducted both in known Type 1 DM & Type 2 DM cases, but there is a scarcity of studies evaluating HRV in newly diagnosed Type 2 DM.

In our study, we observed that the SDNN in ms was significantly reduced in the newly diagnosed Type 2 DM compared to the controls ($p < 0.001$). Our findings were in accordance with the previous studies of John APP et al and Tiftikcioglu BI et al in T2DM.[4,5] We also observed that RMSSD in ms, pNN50% and NN50 count were significantly reduced in the newly diagnosed Type 2 DM compared to the controls ($p < 0.001$). The reduction in time domain measures of HRV could be probably due to reduced parasympathetic activity which is highly suggestive of vagal neuropathy. A possible mechanism for vagal neuropathy could be that hyperglycemia leads to increased formation of advanced glycation end (AGE) products and reactive oxygen species or superoxide in the mitochondria which causes neuronal dysfunction.

Regarding the frequency domain measures of HRV, we observed a significant reduction of HF in ms^2 in the newly diagnosed Type 2 DM patients which also indicates reduced parasympathetic activity. Our findings were in accordance with the previous studies of John APP et al.[4] LF in n.u and LF in ms^2 were elevated in diabetics which suggests increased sympathetic modulation. LF/HF Ratio which is a measure of the sympathovagal balance was significantly elevated in the newly diagnosed Type 2 DM. Altered sympathovagal balance observed in newly diagnosed Type 2 DM patients could be probably due to cardiovascular autonomic neuropathy.

Conclusion:

We observed reduction of HRV in newly diagnosed T2DM patients suggesting early onset of cardiac autonomic neuropathy even at the time of diagnosis of DM. Since HRV could detect autonomic dysfunction at an earlier stage, it can be used as an investigative tool to assess and monitor the severity of CAN which may reduce the morbidity and mortality related to CAN in newly diagnosed type 2 diabetes mellitus patients.

Limitations:

Although the number of subjects in our study is small, the strong differences in statistical analysis between the newly diagnosed type 2 diabetes mellitus and controls validate the conclusions. Also, in our study design we did not estimate and correlate HbA1c levels with the HRV Parameters. We have planned to continue the study in a larger sample group.

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Conflict of interest: Nil

References:

1. Diabetes [Internet]. 2021 [cited 2023 Jan 22]. Available from: https://www.who.int/health topics/ diabetes.
2. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020; 21(17):6275.
3. Magliano DJ, Boyko EJ. IDF diabetes atlas. 10th ed. Brussels: International Diabetes Federation. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK 581934/.

4. John APP, Udupa K, Avangapur S, Sujan MU, Inbaraj G, Vasuki PP, et al. Cardiac autonomic dysfunctions in type 2 diabetes mellitus: an investigative study with heart rate variability measures. Am J Cardiovasc Dis. 2022; 12(4):224–32.
5. Tiftikcioglu BI, Bilgin S, Duksal T, Kose S, Zorlu Y. Autonomic neuropathy and endothelial dysfunction in patients with impaired glucose tolerance or type 2 diabetes mellitus. Medicine. 2016; 95(14):3340.
6. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007; 115(3):387–97.
7. Diagnosis and management of type 2 diabetes [Internet]. 2020 [cited 2023 Jan 22]. Available from: HEARTS D: diagnosis and management of type 2 diabetes (who.int).
8. Kudat H, Akkaya V, Sozen AB, Salman S, Demirel S, Ozcan M, et al. Heart rate variability in diabetes patients. J Int Med Res. 2006; 34(3):291–6.
9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Eur Heart J. 1996; 17:354–81.
10. Dimitro poulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014; 5(1): 17-39.
11. Janet Sugantha M, Balasubramanian K, Rathnavel kumaran M, Muralikrishnan K. Heart rate variability in type 1 diabetes mellitus patients. Indian J. basic appl. med. res. 2016; 6(1):624–33.
12. Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature. 2019; 576(7785):51–60.
13. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: What is defined, what is new, and what is unmet. Diabetes Metab J. 2019; 43(1):3–30.
14. Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study, 1987-1998. Circulation. 2003;107(17): 2190-2195
15. Coopmans C, Zhou TL, Henry RMA, et al. Both prediabetes and type 2 diabetes are associated with lower heart rate variability: the Maastricht study. Diabetes Care. 2020;43(5):1126-1133

Abbreviations:

WHO: World Health Organization
T2DM: Type 2 Diabetes Mellitus
T1DM: Type 1 Diabetes Mellitus
CAN: Cardiovascular Autonomic Neuropathy
HRV: Heart Rate Variability
Resting HRV: Resting Heart Rate Variability
BMI: Body Mass Index
FBS: Fasting Blood Sugar
PPBS: Post Prandial Blood Sugar
LF: Low Frequency
HF: High Frequency
ms^2: Millisecond Square
n.u: Normalized Units
SDNN: Standard deviation of all R-R intervals
NN50: Normal to Normal RR interval deviation more than 50ms:
RMSSD: Root Mean of the Sum of Squares of Difference between adjacent NN intervals
SDANN: The standard deviation of the average NN intervals calculated over short periods, usually 5 minutes.