Original Research Article

The Association Between Time Domain Analysis Of Heart Rate Variability With Glycated Hemoglobin And Duration Of Type 2 Diabetes Mellites

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Abstract

Aim:The aim of present study was to investigate the association of impairment heart rate variability with glycatedhaemoglobin and duration of diabetes in type 2 Diabetes Mellitus (T 2 DM) subjects. **Material and Methods**: The present study was a cross sectional study carried out in 60 age and gender matched individuals selected after proper screening with inclusion and exclusion criteria, out of them 30 were T 2 DM and control group consisted of 30 healthy non-diabetic individuals. All the participants of study were subjected to measurement of 5 minutes ECG using Niviqure data acquisition system and time domain analysis of heart rate variability was done. HbA1c levels were estimated by high performance liquid chromatography. Statistical analysis was done using MS office excel 2020 software. **Results**: The study revealed that time domain analysis parameters of Heart rate variability (HRV)were significantly (P<0.05) reduced in diabetic patients viz., standard deviation of normal to normal R-R interval (SDNN 22.7±6.6), Root mean square of successive difference between normal to normal beat (RMSSD 19.84±4.22) and percentage of adjacent NN intervals that differ from each other by more than 50 ms (pNN50 1.81±1.14), and respectively) compared to non-diabetic (SDNN,RMSSD,pNN50 30.89±7.6, 22.7±2.85 and 3.19±2.12 respectively). It was also found that there is a negative correlation between HbA1c values of subjects and parameters of HRV. **Conclusion:** chronic elevated hyperglycaemia leads to cardiac autonomic neuropathy that can be screened and detected by simple, yet sensitive tests measuring heart rate variability

Keywords: diabetes mellites, heart rate variability, SDNN, RMSSD, pNN50

Introduction

Most common cause of mortality and morbidity in type 2 diabetes mellitus (T 2 DM) are Cardiovascular disease and its largest contributor to the expenditure of managing complications of T2 DM [1,2].Despite significant improvement on risk management of coronary heart disease over the past decade many patients with T2 DM have not achieved overall target of multifactorial risk factor in preventing it [3]. Cardiovascular autonomic neuropathy (CAN) is common, but mostly underestimated complication in patients with T2DM. It is impairment of autonomic control of cardiovascular system and its prevalence has been reported to be about 50% among T2DM patients. Clinically it might manifest as resting tachycardia, exercise intolerance, orthostatic hypotension, and silent myocardial infarction (MI) [4,5,6]. henceforth, current ADA guidelines recommend screening for CAN at early stage for preventing its complications, reducing cardiovascular morbidity and mortality[7].

The methods of study for CAN evolved from simple bedside test [8] to power spectral analysis of HRV which has frequency domain measures and time domain measures[9]. Among this time domain analysis is a simple and easy to interpret tool. Time-domain indices of HRV quantify the amount of variability in measurements of the inter beat interval (IBI), which is the time between successive heartbeats, they arethe standard deviation of the inter beat interval of normal sinus beats (SDNN) is measured in ms. Both parasympathetic and sympathetic activities have been found to contribute to SDNN [10]**;**the percentage of adjacent NN intervals that differ from each other by more than 50 ms (pNN50). Androot mean square of successive differences between normal heartbeats (RMSSD). Both pNN50 and RMSSD reflect the vagally mediated changes reflected in HRV [11,12]. Task force of European society of cardiology, the North American society of pacing electrophysiology has recommended use of these measures. as a diagnostic method to detect early CAN in patients with type 2 diabetes [13].

Previous studies have reported the Association between impaired HRV and CAN in patients with type one diabetes and type 2 diabetes mellitus at tertiary care hospitals in urban population [14]. Therefore, this study analysed HRV in type II DM patients attending the out-patient department (OPD) of hospital attached to Medical College in the rural part of India.

Material and Methods

This study was cross sectional study done at department of physiology and diabetes out-patient department of Mahatma Gandhi memorial hospital, attached to Kakatiya medical college at Warangal, Telangana state, India, on T 2 DM subjects and non-diabetics subjects from January 2011 to June 2014 after approval from ethical committee clearance. 30 patients were selected and grouped under diabetic subjects according to inclusion and exclusion criteria, and normal healthy individuals were considered as controls.

Determination of diabetic status

The criteria for diagnosis of T2DM are as follows. Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200mg/dl) (OR) Fasting plasma Glucose ≥ 7.0mmol/L (126mg/dl)

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(OR) Two- hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl) during an oral glucose tolerance test[15]. The same procedure was followed in control subjects to exclude the asymptomatic diabetic subjects in control group.

Inclusion criteria

1. Only normal healthy subjects, without any family history of diabetes mellitus, known chronic disease and not using any medicine for any reason, were included in the study as control group. 2. Established diabetic patients of both type I and type II were included in case group. 3. Confirmed diabetic patients whose blood sugar level was controlled on taking oral hypoglycaemic were also included.

Exclusion Criteria

1. History of Hypertension (sitting blood pressure > 140/90 mmHg). 2. History of alcohol / smoking, intercurrent illness (e.g.- Pyrexia, Diarrhoea), drug intake. 3. Ages below 17 years and above 70 years. Informed consent was taken from both groups by explaining what this study is meant for and ethical committee clearance was taken. Both groups were clinically examined to rule out cardiovascular, respiratory, neurological, and endocrine disorders. Along with routine general examination, blood pressure was taken. The basal recording of systolic blood pressure (S.B.P.) and diastolic blood pressure (D.B.P.) in mm of Hg was done using sphygmomanometer by standard Riva Rocci method.

Recording of heart rate variability

The subjects were instructed to abstain from smoking and caffeine for 2 hrs. and alcohol for 36 hr. prior to the experiment, have adequate rest, get at least 8 hours of uninterrupted sleep on the night prior to the experiment, have a normal breakfast on the morning of the experiment and to void urine prior to the recording. All recordings were conducted between 10:30 A.M. to 1:00 P.M. After comfortable strapping, at ambient temperature and rest for 5 min on the couch in supine position, ECG was recorded using disposable Ag/AgCl electrodes in standard lead II configuration using portable ECG acquisition equipment (NiviqureMeditech Systems, Bangalore, India). From this recording data was edited manually for artifacts and ectopic beats and suitable sections were taken. The data gathered was subjected to time domain analysis of HRV using non-parametric method of Fast Fourier Transformation with HRV software (NIVIQURE ECG SOFTWARE for HRV studies Ver. 52.0.0).

Biochemical Tests

Blood samples were collected from both groups and Estimation of HBA1C was done by high performance liquid chromatography. HBA1C values are expressed as %. Normal value of HBA1C - <7% is considered normal [15].

Statistical Analysis

Statistical analysis was performed with a Microsoft excel 2020 software. Data are expressed as mean ± SD. The procedure of testing the hypothesis was concluded by accepting the hypothesis or rejecting it. Data between the study group and control group were compared using student T-test. When the statistic t value is computed, we found p value corresponding to it from the tables. If p value of <0.05 it is considered significant, Pearson's correlation coefficient was used.

Results

Table 1:Comparison of heart rate variability parameters in diabetics and normal individuals Parameters Controls Cases Mean S.D.± Mean S.D.± t-value p-value

Parameter	Non-diabetic subjects		Diabetic subjects		P-Value
	Mean	S.D. ±	Mean	S.D. ±	
Age (yrs)	52.33	4.17	56.2	3.78	0.0014
HbA1C (%)	6.1	0.44	8.29	0.90	≤ 0.0001
S.B.P.(mm Hg)	119.74	8.52	136.66	8.61	< 0.005
D.B.P.(mm Hg)	78.32	4.84	82.73	3.21	< 0.05
Mean H.R. (/min)	77.03	6.65	85.33	8.15	≤ 0.00017
SDNN (ms)	30.8	7.6	22.7	6.6	0.000066
RMSSD (/min)	22.7	2.85	19.84	4.22	0.002
pNN50 (%)	3.19	2.12	1.81	1.14	0.004

HbA1C – glycated haemoglobin; F.B.S. fasting blood sugar; P.L.B.S. post lunch blood sugar; S.B.P. -systolic blood pressure; D.B.P. – diastolic blood pressure; M.H.R.- mean heart rate; SDNN- standard deviation of normal-to-normal R-R interval; RMSSD- Root Mean Square of the Successive Differences; pNN50 - proportion of NN50 divided by the total number of NN (R-R) intervals

Table 2:Correlation of heart rate variability parameters with HbA1C in both diabetics andnormal individuals

Parameter	Mean H.R.	SDNN	RMSSD	pNN50
HbA1C	r-value = 0.49	r-value = -0.43	r-value = -0.48	r-value = -0.39
Duration	r-value = 0.42	r-value= - 0.28	r-value = - 0.03	r-value = - 0.2

Pearson's correlation r-value ; $0 < r \leq 1$ –

The study was done in 60 subjects with mean age of 56.2±3.78 yrs among diabetic subjects and 52.33±4.17 yrs among normal subjects. The cardiovascular parameters like S.B.P. and D.B.P. were higher 136.66±8.61 and 82.73±3.21 mm hg among diabetics compared with normal subjects 119.74±8.52 and 78.32±4.84 mm of hg respectively and mean Heart rate is found to be 85.33±8.15, 77.03±6.65 beats per minute among T2DM and normal subjects respectively. The time domain analysis parameters of HRV, SDNN, RMSSD and pNN50 are 22.7±6.6, 19.84±4.22 and 1.81±1.14 respectively in diabetic patient and 30.8±7.6, 22.7±2.85 and 3.19±2.12 in normal subjects as shown in table 1.

There is positive correlation in mean heart rate with both duration of diabetes and HbA1C but all other parameters of HRV show a significant negative correlation with duration and glycated haemoglobin as shown in table 2.

Discussion

Previous studies consistently reported cardiac autonomic neuropathy is a major cause for cardiovascular risk and sudden death due to silent M.I. in T 2 D.M. patients [16,17].In the present study time domain analysis parameters of HRV were selected in accordance with the recommendations of Task force of European society of cardiology, the North American society of pacing electrophysiology [13].It was observed that all glycaemic indices and duration of diabetes had considerable impact on cardiac autonomic functions predicted by SDNN, RMSSD and pNN50 values of time domain analysis of heart rate variability.Among the parameters of time domain analysis of HRV, SDNN representing overall autonomic neural activity [10],was observed to be reduced in diabetic patients

(22.7±6.71 ms) when compared with normal subjects (30.80±7.64 ms with p-value 0.00003) depicted in table 1. It is in concurrence with Framingham study of 1919 individuals that showed lower recordings among diabetic subjects [18].And alsosimilar results were found instudy done atDepartment of Cardiology and Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey [20,21]**.**Additionally, in this study other parameters of time domain analysis viz pNN50 and RMSSD reflecting vagal activity of autonomic nervous system[11] were observed and found to be significantly reduced in T 2 DM patients (1.81±1.14 and 22.77±2.85 ms respectively) when compared with controls (3.19±2.12 and 19.84±4.29 ms) with p-value is ≤ 0.002 as it is was depicted in table 1, which is consistent with study done in 10 consecutive, newly diagnosed non-insulin dependent diabetics mellitus (NIDDM), 10 with NIDDM with diabetic autonomic neuropathy (DAN), and 10 age matched normal controls[19,20].The most significant factor correlating with incidence and progression of diabetic neuropathy is the status of glycemic control (HBA_1C) and it reflects the status of glycemia over a period of 3months [28]. In this study HbA1C levels in diabetic individuals are significantly raised and there is negative correlation of HbA1c with pNN50 (r =-0.48), RMSSD (r=-0.45) and low negative correlation with SDNN (r=-0.29)) as shown in table 2 This is consistent with study done on 105 type 1 DM and 27 type 2 DM subjects at midwestern medical centre[23].In their study The Association of HRV With Cardiovascular Risk Factors and Coronary Artery Calcification in type 1 diabetes mellitus patientsshowed that HbA1C levels in diabetic patients and non-diabetic individuals are negatively associated with HRV parameters and they concluded that reduced HRV parameters may be an early feature of insulin resistance and loss of glycaemic control. It is consistent with results of our study, as seen by negative correlation for SDNN r-value is -0.28, for RMSSD r -value is -0.03 and pNN50 it is -0.3 with HbA1C shown in table 2[22].The effect of duration of T 2 DM on HRV in was studied on 60 T2 DM subjects at maulanaazad medical college, New Delhi, India found significant negative correlation of HRV parameters RMSSD, pNN50 and SDNN which was also like observation in this study shown in table 2[24-26].

The probable pathogenesis behind the above observations of reduced HRV in diabetic patients and negative corelation with HbA1C and duration could be axonal damage caused by elevated blood glucose levels which causes productions of advanced glycation end products (AGE) [27].

Conclusion

chronic elevated blood glucose levels may lead to sustained degeneration of autonomic nerves. Major complication of type 2 diabetes mellitus and one of the leading causes of cardiac diseases in diabetics is CAN. It is concealed for a long time before it reaches the stage of clinical diagnosis. This study has shown that HRV is a simple yet sensitive method of assessing cardiac autonomic neuropathy at an early stage in diabetics. This provides an opportunity so that proper lifestyle interventions and glycaemic control can be undertaken to improve the condition of patient.

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