

Original Article

Cardiac Autonomic Neuropathy in Type II Diabetes Mellitus Patients and its Association with the Age of the Patient, Duration of Disease and Glycemic Control

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Abstract

Objectives: Evaluation of association between age, duration of disease and glycemic control in type II diabetics with the incidence of cardiac autonomic neuropathy (CAN).

Methods: Study includes 50 Type II diabetic patients of 40-60 years age of both the genders with different duration of disease. CAN was evaluated in terms of presence of resting tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver by electrocardiogram (ECG). An R-R variation with respiration of >15 beats per minute was taken normal, while 10-15 beats and <10 beats per minute were taken as borderline and definitive CAN respectively. Valsalva ratio is 1.2 or more taken as normal; Values of 1 to 1.2 & values less or equal to 1 were taken as borderline and definitive CAN respectively. If any two of them found positive, then presence of CAN was confirmed. Correlation between age, duration of disease and glycemic control with incidence of CAN was assessed.

Results: The incidence of CAN in diabetics based on above tests is 16%. There is a significant negative correlation between duration of disease and Glycated hemoglobin with deep breathing difference. ($r = -0.423^{**}$, $p=0.002$) ($r = -0.207^*$, $p = 0.04$).

Conclusion: Poorer the glycemic control and longer the duration of the disease higher the incidence of CAN in type II diabetics.

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Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia occurs either due to decreased insulin level or insulin resistance. The prevalence of Diabetes

Mellitus (DM) for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030 affecting mainly urban population (1). The increased morbidity and mortality in DM is due to its complications like neuropathy, nephropathy, retinopathy etc. A subtype of the peripheral poly neuropathies that accompany diabetes, Diabetic Autonomic Neuropathy (DAN) can involve the entire autonomic nervous system (ANS). It is manifested by dysfunction of one or more organ systems. (e.g., cardiovascular, gastrointestinal, genitourinary, sudomotor, or ocular) (2).

Diabetic CAN, a serious complication found in one fourth of type 1 and one third of type 2 diabetic patients, encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels resulting in abnormalities in heart rate control as well as defect in central and peripheral vascular dynamics. It is associated with poor prognosis and may result in severe orthostasis, postural hypotension, exercise intolerance, and an increased incidence of silent Myocardial infarction (MI) and ischemia (3, 4). Age, duration of diabetes, poor glycemic control, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycemia were shown to be risk factors for developing CAN in diabetes (5). As the clinical importance of Diabetic Autonomic Neuropathy (DAN) has become recognized the need has grown for simple objective tests to confirm its presence or absence. Numerous non-invasive tests which we consider reliable, reproducible and simple have been used for diagnosis of CAN. It may be detected by evaluating resting tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver. If two of these are abnormal, the diagnosis of CAN is established (6, 7).

Correlation between glycaemic control, duration of disease and autonomic function parameters were tested by various investigators. Available studies have highlighted prevalence of CAN increases with age of diabetic patient, duration of diabetes, and poor glycemic control (3, 8).

While some studies showed significant difference in postural BP changes and E/I ratios in diabetics with

no significant correlation between glycaemic control or duration of disease with autonomic function parameters (9). Intensive glycemic controls substantially reduces the prevalence of CAN and slows the progression of R-R variation and Valsalva ratio and improvement in time and frequency domain Heart rate variation (HRV) indexes (10). Many investigators have considered autonomic neuropathies to be irreversible; however, CAN have been shown to regress with good glycemic control. The objective of this study was to determine the frequency of Cardiac Autonomic Neuropathy (CAN) in type II diabetes mellitus patients and its association with the age of patient, duration of disease and glycemic control.

Material and Methods

This is a cross-sectional study conducted in the department of physiology, SDM medical college from June to September 2014 on 50 type II diabetic patients of 40-60 years age of both the genders (males-42 and females- 8) attending the medicine O.P.D. They were selected as subjects randomly. Subjects who are diagnosed as Diabetic from the physician with Glycemic status of fasting serum glucose values > 126 mg/dl, post-prandial blood glucose value >200 mg/dl and glycated hemoglobin (HbA1c values) >7% were included. Clinically they were diagnosed as type II diabetics. The subjects explained regarding the procedure and written informed consent were taken. Enquiry was made about the duration of diabetes mellitus and the therapy. All of them were on oral hypoglycemic drugs.

Exclusion criteria

Patients suffering from cardiac failure, renal failure, alcoholic neuropathy, receiving sympatholytic and vasodilator drugs which can affect autonomic functions were excluded.

Study design

Patients were instructed not to have coffee, tea or cola 12 hours before the tests. They were asked to come to the physiology laboratory at 9 am after having a light breakfast. Detailed history was taken on a standard proforma regarding age of the patient,

duration of the disease, whether he/she on oral hypoglycemic drugs/insulin therapy. Reports of investigation (fasting blood sugar, post prandial blood glucose value and HbA1c value) were noted. Subjects were asked to relax in supine position for 30 minutes.

Presence or absence of CAN is done by performing following 3 different tests on each subject.

1. Resting tachycardia
2. Loss of sinus arrhythmia
3. Heart rate response to Valsava maneuver

If any two of them are positive then presence of CAN confirmed.

Instrument – ECG instrument with paper speed of 25 mm/sec was used for all the above tests.

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Procedure

1. Resting tachycardia

The subjects were asked to relax in supine position for 30 minutes. Resting heart rate was calculated for the evaluation of resting tachycardia under basal conditions; the resting heart rate will be recorded on a standard ECG from lead II. Values of more than 100 beats per minute (b/m) will be considered abnormal.

2. Loss of sinus arrhythmia

Heart rate variation with respiration was observed for loss of sinus arrhythmia.

In sitting position, Patients were asked to take 6 deep breaths per minute. A continuous ECG was recorded for six cycles with marker to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals were measured during each breathing cycle and converted into beats per minute. The

result will be then expressed as mean of the difference between maximum and minimum heart rate for six measured cycles in beats per minute. Normal response is a difference of 15 beats per minute or more, while 10-15 beats and <10 beats per minute were taken as borderline and definitive CAN respectively (5).

3. Heart rate response to Valsava maneuver

Valsalva maneuver was performed in each subject. In sitting position person was asked to blow into a mouthpiece connected to a mercury manometer and holding it at a pressure of 40 mmHg for 15 seconds, simultaneously monitored by the ECG. The ECG will be continued to be recorded even 15 seconds after the release of pressure. The heart rate changes induced by valsalva maneuver will be expressed as ratio of maximal tachycardia during the maneuver to the maximal bradycardia after the manoeuvre. This ratio was defined as valsalva ratio and will be calculated as the ratio of longest R-R interval (during bradycardia)/to the shortest R-R interval (during tachycardia).

Normal Valsalva ratio is 1.2 or more; values less or equal to 1 were taken as evidence of CAN. Values of 1 to 1.2 were taken as borderline (5).

Statistical analysis

It is a cross sectional study done to assess the association between age of the patient, duration of diabetes and glycemic control with the development of CAN in diabetic patients. Statistical analysis was done by using SPSS software version 20. A Pearson's correlation and chi-square tests were used to see the relationship between age of the patient, duration of diabetes and glycemic control with the development of CAN. Values were expressed as mean±SD. p value <0.05 was considered as statistically significant & <0.01 as highly significant.

Results

It is a cross sectional study done to assess incidence of Cardiac autonomic neuropathy in type II

diabetes mellitus patients and its association with the age of the patient, duration of disease and glycemic control. Values were expressed as mean±SD. p value <0.05 was considered as statistically significant & <0.01 as highly significant. Table I shows the demographical characteristics and mean values of study parameters. There are 50 diabetic patients (n=50) which includes both gender (Male=42, Female=8) of mean age group of 51.6±5.4 years. Table II shows the correlation of age of the diabetics with parameters to assess cardiac autonomic neuropathy (CAN). There exist a positive correlation between age of the diabetics with the RHR and VR but not statistically significant. It also shows negative correlation between age of patient and deep breathing difference which is also not

TABLE II: Shows the correlation of age of the diabetics with parameters to assess cardiac autonomic neuropathy (CAN). (n=50)

Parameter	RHR (beats/min)	DBD (beats/min)	VR
Age of diabetics (yrs)	r=0.069 p=0.632	r=-0.186 p=0.195	r=0.048 p=0.328

p<0.05 is considered as significant, p < 0.01 is considered as highly significant.

r =-(negative correlation): r=+(positive correlation)

RHR - Resting heart rate, DBD - Deep Breathing Difference, VR - Valasalva Ratio

TABLE I: Shows the demographical characteristics of subjects and mean values of study parameters. (n=50)

Parameter	Mean±SD values
Age (yrs)	51.6±5.4
Duration of disease (yrs)	6.57±2.3
HbA1c value (%)	9.34±0.28
Resting heart rate (RHR) (beats/min)	80.23±6.89
Deep breathing difference (DBD) (beats/min)	11.62±0.8
Valsalva ratio (VR)	1.1±0.05

significant. Fig. 1 shows the scatter diagram of correlation between age of the diabetics with the parameter to assess CAN.

Table III shows the correlation of duration of diabetes with the parameters to assess cardiac autonomic neuropathy (CAN). There exists positive correlation between duration of diabetes with the RHR and VR which is not statistically significant. There is also negative correlation between duration of diabetes with DBD which is statistically highly significant. (p=0.002) Fig. 2 shows the scatter diagram of correlation

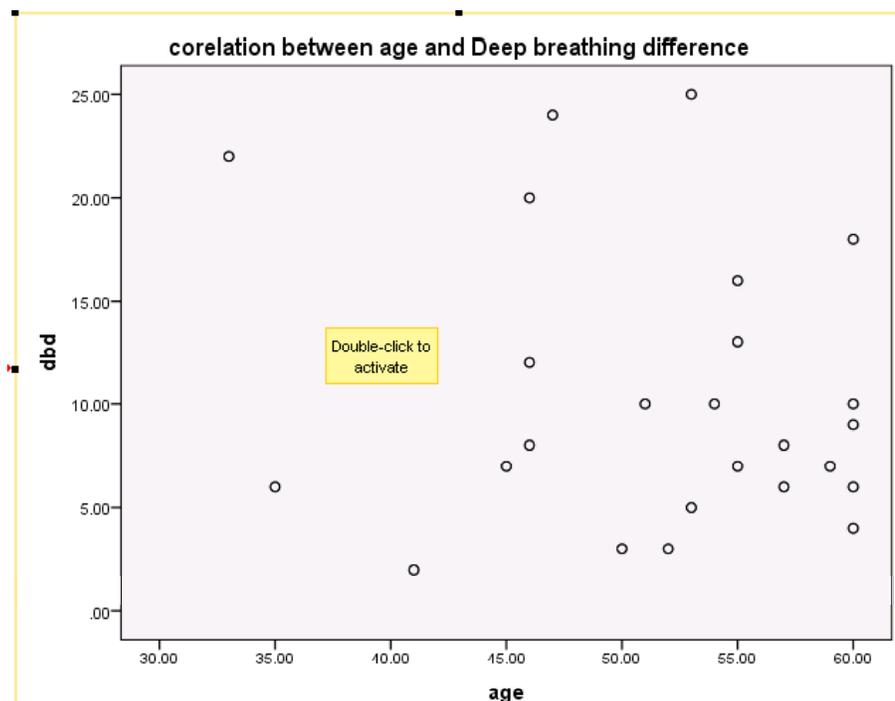


Fig. 1: Shows the scatter diagram of correlation between age of the diabetics with the parameter to assess CAN.

TABLE III : Shows the correlation of duration of diabetes with the parameters to assess cardiac autonomic neuropathy (CAN). (n=50)

Parameter	RHR (beats/min)	DBD (beats/min)	VR
Duration of diabetes(yrs)	r=0.236 p=0.099	r=-0.423 p=0.002**	r=0.034 p=0.812

*p<0.05 is considered as significant, **p<0.01 is considered as highly significant.

r=- (negative correlation): r= + (positive correlation)

RHR - Resting heart rate, DBD - Deep Breathing Difference, VR - Valasalva Ratio.

between duration of diabetes with the parameter to assess CAN.

Table IV showing the correlation between glycated hemoglobin with the parameters to assess cardiac autonomic neuropathy (CAN) there exist no correlation between Glycated hemoglobin with the RHR. There is negative correlation between Glycated hemoglobin with DBD which is statistically highly significant (p=0.04). Fig. 3 shows the scatter diagram of correlation between Glycated hemoglobin with the parameter to assess CAN. Table V shows the incidence of CAN in diabetes patients based results of tests used for assessing cardiac autonomic

TABLE IV : Shows the correlation between glycated hemoglobin with the parameters to assess cardiac autonomic neuropathy (CAN). (n=50)

Parameter	RHR (beats/min)	DBD (beats/min)	VR
Glycated hemoglobin (HbA1c values) %	r=0.000 p=0.998	r=-0.207 p=0.04*	r=-0.034 p=0.812

*p<0.05 is considered as significant, **p<0.01 is considered as highly significant.

r=- (negative correlation): r= + (positive correlation), r=00 (no correlation)

RHR - Resting heart rate, DBD - Deep Breathing Difference, VR - Valasalva Ratio

TABLE V : Showing incidence of CAN in diabetes patients based on three parameters to assess cardiac autonomic neuropathy (CAN). (n=50)

Parameter	Normal CAN	Borderline	Abnormal (with CAN)
RHR (beats/min)	Normal heart rate n=45 (90%)	-----	Resting tachycardia n=5 (10%)
R-R variation with deep breathing	DBD (>15) n=28 (56%)	DBD (10-15) n=12 (24%)	DBD (<10) n=10 (20%)
Valsalva ratio	Normal=>1.2 n=30 (60%)	Borderline (1-1.2) n=12 (24%)	Definitive CAN (<1) n=8 (16%)

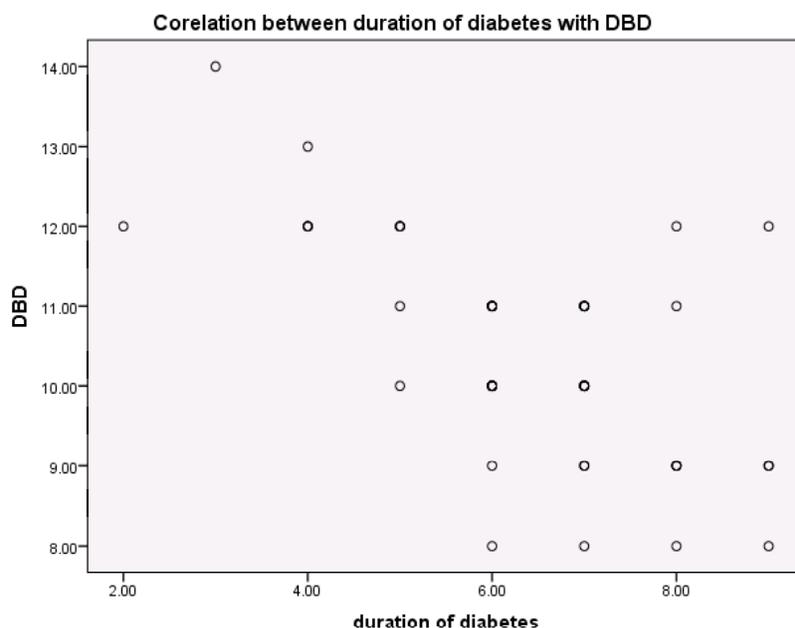


Fig. 2 : Shows the scatter diagram of correlation between duration of diabetes with the parameter to assess CAN.

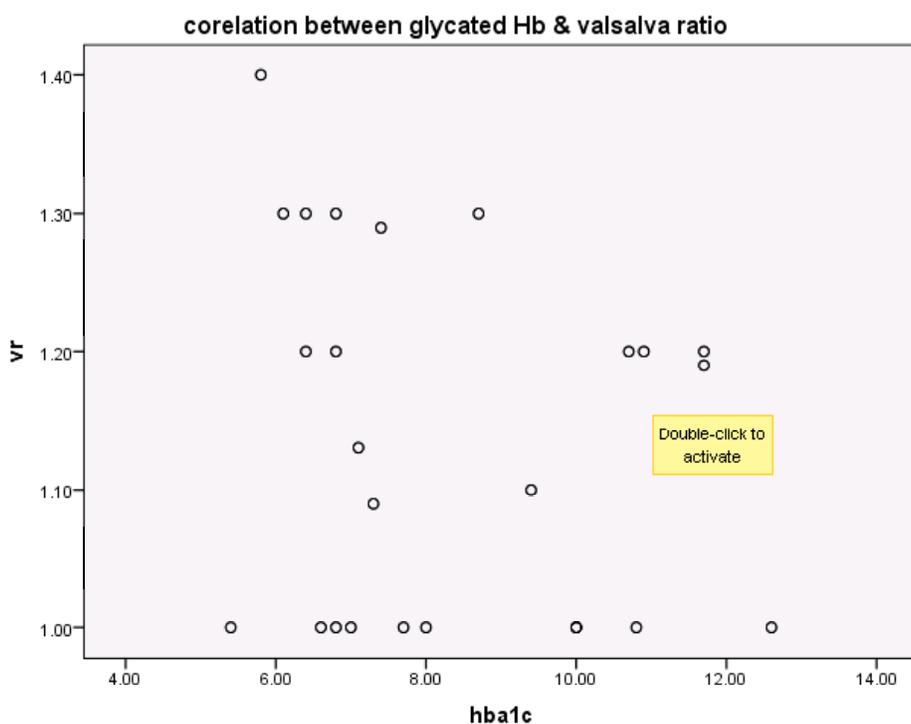


Fig. 3: Shows the scatter diagram of correlation between Glycated hemoglobin with the parameter to assess CAN.

TABLE VI: Scores of the tests used to assess CAN in diabetics. (n=50)

	<i>Normal</i>	<i>Borderline CAN</i>	<i>Definitive CAN</i>
Scoring of three parameters results to assess CAN	30 diabetics all the 3 tests normal (60%)	12 Diabetics shows any two test as abnormal with values towards borderline CAN. (24%)	8 Diabetics shows any two test as abnormal with values towards definitive CAN. (16%)

neuropathy (CAN). Table VI shows number of patients showing more than or equal to 2 test abnormal (scores of the test). among 50 diabetics, 30(60%) were normal showing results for all 3 tests as normal, 12 (24%) showing two test results abnormal with values towards borderline CAN & 8 (16%) showing two test results abnormal with values towards definitive CAN.

Discussion

In our studies among 50 diabetics, 8 (16%) were known to be having CAN, 12(24%) of them were in borderline. Table V & VI shows some form of CAN were present in 16% of the diabetics. These results are comparable with those mentioned in the literature

(19) other literature also shows increased incidence of CAN in diabetes (8, 9, 22). We also assessed the association between age, duration of diabetes and glycaemic control with the incidence of CAN. Table II shows positive correlation between age of the patient with the RHR & VR, but not statistically significant, also negative correlation between age of patient and deep breathing difference which is also not statistically significant as shown by Fig. 1. Table III shows Duration of diabetes have significant negative correlation with DBD. CAN in long-standing diabetics is caused by parasympathetic (vagal) impairment (11). Resting tachycardia is an early sign, as is loss of heart rate variation during deep breathing (12).

Table IV also showing there is a significant negative

correlation between glycemic controls with the DBD & VR. As glycated hemoglobin value increases, there occurs a reduction on both DBD and VR which indicates autonomic dysfunction. Our study goes well with another study conducted by Haji Khan Khoharo and colleagues who also showed impaired cardiac autonomic dysfunction in patients with poor glycemic control (13).

Intensive glycemic control is critical in preventing the onset and slowing the progression of CAN. The Diabetes Control and Complication Trial (DCCT) showed that intensive glycemic control reduced the prevalence of autonomic dysfunction by 53% (14). Studies shows that Higher mean A1c levels were associated with significantly higher estimated hospitalization costs and with higher rates of diabetes-related hospital utilization per 100 patient-years there by increasing the financial burden on the patients (15). Studies shown that Micro vascular complications, including nephropathy, retinopathy, and neuropathy are strongly related to hemoglobin A1c levels (HbA1c) (16).

We considered 3 tests i.e resting heart rate, heart rate variation to deep breathing and valsalva ratio. If any two of them were abnormal CAN was considered to be present. Prevalence of CAN, based on assessment of abnormal cardiovascular autonomic tests is variable (5-90%) (17).

Chanudet et al. found Valsalva ratio and abnormal R-R variation with respiration in 16% and 57% of patients respectively (18). Haji Khan Khoharo studied CAN in terms of presence of resting tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver by ECG. Definitive and borderline CAN was noted in 30% and 40% patients respectively. Intensive glycemic control is associated with a better cardiac autonomic nerve functions (19).

Pathogenesis

In diabetes, CAN is ultimately the result of complex interactions among degree of glycemic control,

disease duration, age-related neuronal attrition, and systolic and diastolic blood pressure (20). Hyperglycemia plays the key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell, which, in concert with impaired nerve perfusion, contribute to the development and progression of diabetic neuropathies. Experimental data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including: formation of advanced glycation end products, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of poly ADP ribosylation, and activation of genes involved in neuronal damage (21).

Diabetic neuropathy affects all peripheral nerves including pain fibers, motor neurons and the autonomic nervous system. It therefore can affect all organs and systems, as all are innervated. There are several distinct syndromes based upon the organ systems and members affected, but these are by no means exclusive. A patient can have sensori motor and autonomic neuropathy or any other combination.

Scope of the study: Diabetic CAN, a serious complication found in one fourth of type 1 and one third of type 2 diabetic patients, is associated with a poor prognosis. Age, duration of diabetes, poor glycemic controls were risk factor for CAN. Our study showed that longer the duration and poor glycemic control increases the incidence of CAN in diabetes.

From the above study public awareness can be done to make diabetics realize the importance of glycemic control and prevent further autonomic complications.

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