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Cardiovascular Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus Amongst Rural Patients from Central Rural India: A Prospective Hospital Based Study

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Abstract
Background: *Cardiac autonomic neuropathy (CAN) is a frequent chronic complication of diabetes mellitus with potentially life-threatening outcomes. There is very little information available on epidemiology of cardiac autonomic neuropathy (CAN) in diabetic population from rural India. Many studies have concluded that abnormal HbA1c levels, hypertension, distal symmetrical polyneuropathy, retinopathy and exposure to hyperglycemia are risk factors for developing CAN in diabetes.*
Aim: *To assess the frequency of cardiovascular autonomic neuropathy (CAN) in patients with poorly controlled type 2 diabetes mellitus in rural population of India.*
Methods: *We studied CAN in 500 poorly controlled type2 diabetic patients of age group above 30 years and HbA1c above 6.5% from Dec 2008 to Dec 2016 at tertiary care rural hospital of UP University of Medical Sciences, Saifai, Etawah(UP), India. All the patients in the study were evaluated for CAN using four different clinical tests- Resting heart rate, test for orthostatic hypotension, hand gripping test and QTc interval on ECG. Patients were labeled as CAN +ve if any two or more than two of the above listed tests were found positive/abnormal.*
Results: *Our study included 500 diabetic patients .Out of these diabetic patients, 300 (60%) were male and 200(40%) female. Out of 500 diabetic patients, 220(44%) were CAN positive and 280(56%) CAN negative. Out of 220 CAN positive diabetics, 140(46.7%) were male and 80(40.3%) were female showing no significant difference between male and female. However there was significant difference in prevalence of CAN in different age groups eg out of 220 CAN positive diabetics, 54(24.6%) were in age group of 31 to 40 years,76(34.6%) in age group of 41 to 50 years,86(39%) in age group of 51 to 60 years and 4(1.8%) in age group of above 60 years.*
Conclusion: *The study concluded that CAN is common in poorly controlled diabetics in rural Indian population Clinician must try to identify CAN by simple tests in poorly controlled diabetic patients at earliest possible to prevent its further complication and long term morbidity and mortality*
Keywords: *Diabetes mellitus, Autonomic neuropathy, Heart rate variability, Cardiovascular reflex tests.*

Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency. Cardiac autonomic neuropathy (CAN), a type of gene-realized symmetric polyneuropathy, is the most examined and clinically significant diabetic autonomic neuropathy[(1)]. The autonomic nervous system has two major components, the parasympathetic and the sympathetic nervous systems. These may operate independently of each other or interact cooperat-ively to control heart rate, cardiac output, myocardial contractility, cardiac electrophysiology and the constriction & dilatation of blood vessels[(2)]. CAN is caused by damage to the autonomic nerve fibers that innervate the heart and blood vessels and leads to abnormalities in cardiovascular dynamics [(2,3,4)]. The earliest finding of CAN, even at the subclinical stage, is a decrease in heart rate variability (HRV) [(3,4,5)]. CAN is caused by the impairment of the autonomic nerve fibers regulating heart rate, cardiac output, myocardial contractility, cardiac electrophysiology and blood vessel constriction and dilatation. It causes a wide range of cardiac disorders including resting tachycardia, arrhythmias, intraoperative cardiovascular instab-ility, asymptomatic myocardial ischemia and infarction. Cardiovascular autonomic neuropathy (CAN) is one of the serious complications of diabetes [(6,7,8)]. Resting tachycardia and fixed heart rate are characteristic late findings in diabetic patients with vagal impairment due to CAN [(8,9,10)]. Therefore, diabetic patients who are likely to have CAN should be tested for cardiac stress test before undertaking an exercise program[(5,7,9)]. The autonomic dysfunction impairs exercise tolerance, reduces response to heart rate and blood pressure as well as blunts the increased cardiac output in response to exercise [(6)]. Diabetic patients also run a 2–3 folds higher risk of cardiovascular morbidity and mortality during surgery. There is an associa-tion between CAN and intraoperative hypothermia and orthostatic hypotension, although the fall in blood pressure may also be asymptomatic[(7)]. The mechanisms by which CAN causes increased mortality remains obscure and it is often difficult to determine the independent effects of CAN on intraoperative mortality because of the coexisting cardiovascular disease (CVD). Two prospective studies have studied the relationship between CAN and major intraoperative cardiovascular events. One potential cause of higher mortality during surgery in such patients could be severe but asymptomatic ischemia which can induce lethal arrhythmia [(7,8)]. Patients with severe autonomic dysfunction also have a higher risk of BP instability. Most of studies recommend yearly screening for autonomic neuropathy in type 2 diabetes mellitus from the time of diagnosis [(9,10,11,12,13)]

Materials and Methods

This study included five hundred (500) type 2 diabetes patients who attended medical wards and/or OPDs at UP University of Medical Sciences, Saifai, Etawah, UP, India. All the patients from either sex who met the following inclusion criteria were considered for inclusion in this study.

1. Age: above 30 years
2. HbA1C: > 6.5%

Patients meeting the following exclusion criteria were excluded from the study:

Patients with hypotension, Congestive cardiac failure, Ischemic heart Disease, Hyperthyroidism, Chronic renal failure, Patients on medications such as Vasodilators, Diuretics, Anti-arrhythmic, Beta-blockers, Alpha-agonist or Alpha-blockers.

An informed consent for inclusion in this study was obtained from all the patients. We used non-probability purposive sampling technique for this study. All patients were fully explained about the different maneuvers like hand grip, standing and squeezing of ball. The recruited patients were tested for resting heart rate. A resting heart rate of more than 100 beats per minute was considered abnormal. Orthostatic hypotension – Blood pressure was first measured (using the aneroid sphygmomanometer) in supine position and then the patient was instructed to stand up. Blood pressure was again measured after 3 min of standing. A fall in systolic blood pressure of >20 mmHg and/or in diastolic

blood pressure >10 mmHg was considered abnormal.

Hand gripping test – The blood pressure of the patient was first measured in supine position. The patient was instructed to squeeze a small ball in his/her hand for about 5 min while lying in the bed and then his/her blood pressure was measured (using the aneroid sphygmomanometer) again. An increase in diastolic blood pressure <15 mmHg was considered abnormal.

ECG recording - QTc interval >440 ms or prolonged was considered abnormal.

If the findings on any two or more of the above tests in a patient were abnormal, the patient was diagnosed as positive for CAN.

Data was entered and analyzed by SPSS version 22. The frequencies and percentages were calculated for qualitative variables such as gender and age group and chi-square test was used to compare the proportions. Mean ± SD was calculated for numerical variables like age in years, pulse rate (lying/supine, standing), blood pressure (lying/supine, standing and after hand griping), QTc interval, random blood sugar level (RBS) and HbA1c. All the data was analyzed for a 94% confidence interval. A p-value ≤0.05 was considered as statistically significant.

Results

A total of 500 type 2 diabetic patients fulfilling the inclusion criteria were included in this study. The mean age of these patients was 55.6 ± 7.6 years. Out of 500 patients, 180 (36%) were between 26 and 40 years, 200 (40%) between 41 and 50 years, 100 (20%) between 51 and 60 years and 20(4%) above 60 years. Table1 below shows sex and age-wise distribution of the study population

Table-1 Distribution of age (n=500)

Gender	N	%
Male	300	60
Female	200	40
Age group (Years)	N	%
31-40	180	36
41-50	200	40
51-60	100	20
>60	20	04
Mean + SD 55.5+7.5		

There were 300 (60%) male and 200 (40%) female patients in the study group with an average weight of 70 + 10 kg and mean HbA1c level of 8.5 ± 4.1%. The mean blood pressure in the studied patients was found to be 135.3 ± 26.4 mmHg and the mean random blood sugar level was 160 ± 60 mg/dl. A total of 220 (44%) patients were found to have cardiovascular autonomic neuropathy (CAN) based on the diagnostic protocol described above. The mean QTc interval was 480 ± 20 (m sec) as given in Table 2 below

Table-2 Distribution of diabetic patients (n=500)
Random blood sugar (mg/dl):160 + 60
QTc (m sec): 480 + 20

Gender	CAN positive	CAN negative
Male	140(46.7%)	160(53.3%)
Female	80(40%)	120(60%)

p value > 0.20

There was no statistically significant difference in incidence of CAN among patients belonging to two genders (p > 0.20). However, a statistically significant difference in incidence of CAN was observed when comparing occurrence of CAN in different age groups (p < 0.04), as given in Table 3 below

Table-3

Distribution of age by CAN				
Age-years(%)	31-40	41-50	51-60	>60
DM with CAN	54(24.6%)	76(34.6%)	86(39%)	4(1.8%)
DM without CAN	163(58.21%)	71(25.36%)	42(15%)	4(1.43%)

Discussion

Our analysis revealed that a total of 220 (44%) patients with type 2 diabetes mellitus had cardiovascular autonomic neuropathy (CAN). It further revealed that there were no significant differences between incidences of CAN between two sexes, but the difference in incidence between different age groups was significant.

In another descriptive study from Hyderabad, Pakistan, researchers found the incidence of definitive and borderline CAN in patients with type 2 diabetes mellitus to be 43% and 45% respectively, which was very similar to our findings. The researchers observed that intensive glycemic control is associated with a better cardiac autonomic nerve

functions. Mean age of the patient in their study was 55.5 ± 7.5years with male to female ratio of 3:2, a finding again very similar to ours. Mean duration of diabetes at the time of diagnosis was 15 ± 3.5 years and mean HbA1c level was 10.5 ± 3.5% dl indicating very bad glycemic control in the studied population. The researchers concluded that variability of heart rate with respiration was significantly related to duration but not to the control of diabetes ($p < 0.05$). QTc showed a statistically significant correlation with the known duration of diabetes and heart rate variability with respiration ($p < 0.05$) [12,13,14]

In another cross sectional study to determine the prevalence and risk factors for cardiac autonomic neuropathy (CAN) among 100 patients with type 1 and type 2 diabetes mellitus, using five autonomic function tests by Eving's methodology, researchers found the incidence of CAN to be 60%. Univariate analysis showed a significant association between CAN and higher age (odds ratio (OR) 15.70), prolongation of QTc (OR 5.50), duration of disease over 10 years (OR 2) and peripheral neuropathy (< 0.001) in patients with type 1 diabetes. Significant risks factors for CAN among patients with type 2 diabetes included coexistent peripheral neuropathy (OR 14), prolonged QTc (OR 9.75), higher age (OR 7.2) and disease duration over 10 years (OR 1.92) in univariate analysis, but none of these factors showed independent risk in multivariate analysis. The Disease duration over 10 years resulted in QTc prolongation in a significant numbers of cases with type 1 and type 2 diabetes [14,15,16]. In our study, we found a strong correlation between occurrence of CAN and widening of QTc interval and age at diagnosis. However, we found no significant correlation between gender and incidence of CAN.

Other researchers have studies to detect other useful indicators for diagnosing CAN. Another study described the usefulness of heart rate variability (HRV) and complexity analyses from short term ECG recordings as a screening tool for CAN. A total of 17 sets of ECG recordings taken from diabetic subjects with and without CAN performed in resting supine position were evaluated. The study demonstrated the potential utility of SampEn (a complexity based estimator) of HRV in identifying asymptomatic CAN16.17.18 Another study evaluated the impact of parental type 2 diabetes on the autonomic nervous system of non-diabetic offspring. The study attempted to determine if the evaluated non-diabetic subjects with parents having type 2 diabetes had autonomic neuropathy and if autonomic neuropathy in these subjects was associated with changes in 24-h ambulatory blood pressure (AMBP) and urinary albumin excretion rate (UAER). The study examined 223 non-diabetic offspring of type 2 diabetic subjects and a control group of 258 offspring of non-diabetic subjects. The prevalence of autonomic neuropathy in the non-diabetic offspring with parental type 2 diabetes (6.7%) was significantly higher compared with the control group (1.6%). Autonomic neuropathy in such subjects was also found to be associated with a higher fasting insulin level, higher UAER, higher 24-h mean AMBP and reduced diurnal blood pressure variation after adjustment for age, sex, and BMI. In conclusion, parental type 2 diabetes was found to be associated with alterations in the autonomic nervous system in non-diabetic subjects [17,19,20]

A study from India attempted to determine the prevalence of CAN in type 2 diabetes mellitus and to correlate CAN with retinopathy, microalbuminuria and glycated haemoglobin levels. The results of this study revealed that 54% of studied patients had CAN. Furthermore, the researchers found that 52% patients had parasympathetic neuropathy, 20% had sympathetic neuropathy and 28% had two abnormal cardiovascular reflexes. The researchers also observed microalbuminuria and retinopathy in 36% and 10% of these patients respectively [18,20,21]. The percentage of CAN in our study was comparatively lesser than the above study. This difference in results may be due to operational definitions and further classification of CAN into different groups. Autonomic neuropathy is a serious complication of diabetes mellitus.

Another study found the prevalence of CAN among diabetic patients to be 51.9%. The prevalence of

sympathetic and parasympathetic CAN was 28.9% and 44% respectively. These researchers also noted a significant difference in the incidence of CAN between type 1 and type 2 diabetic patients [19,21]

The postural drop in blood pressure caused by autonomic neuropathy in diabetes mellitus is regarded as a risk factor for cardiovascular disease. A study was conducted in a tertiary care hospital of India to assess the prevalence of orthostatic hypotension in diabetic patients and to find its correlation with hypertension in patients with diabetes mellitus. Two hundred indoor diabetic patients were assessed; of which 26% were found to have orthostatic hypotension [20,21]

Conclusions

The cardiac autonomic neuropathy is common in poorly controlled diabetic patients in rural India. The clinician should identify CAN at earliest possible by doing simple tests to prevent complications of CAN and long term morbidity and mortality. This study also demands for larger scale rural population based studies in future.

Conflicts of interest: None
Source of Funding: None
Ethical Issue: None

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