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Original Research Article

Alteration of cardiovascular autonomic activity in type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycaemia due to absolute or relative insulin deficiency. Cardiovascular autonomic neuropathy (CAN) invokes potentially life-threatening outcomes especially in poorly controlled diabetic patients. This study was to evaluate the prevalence of CAN in diabetic patients and its relationship with QTc interval.
Methods: This observational study of two year duration was included total 123 patients of more than 30 (thirty) years and up to 60 (sixty) years of age who were presented with diabetic mellitus (DM) those were evaluated for CAN using four distinct clinical tests-Resting heart rate (RHR), test for orthostatic hypotension (OH), hand gripping test (HGT) and QTc interval on ECG. Data were analyzed with statistical package for social sciences (SPSS), version 23.
Results: The mean age of all 103 studied patients was 48.94±8.69 years; Mostly patients belong to 50-60 years of age and the majority was males (69.0%). Out of 103 72.8% patients were reported with CAN (51 males and 24 females) and without CAN were 27.2.0% (20 males and 8 females), 36% of patients of Definite Parasympathetic neuropathy, 25% Normal and 20% of Sympathetic neuropathic patients. HbA1c level increases the danger of CAN also. QTc interval is a reliable indicator for the presence of CAN.
Conclusions: Duration of diabetes is directly proportional to the prevalence of CAN. Various cardiac autonomic function tests detect CAN.

Keywords: Cardiac autonomic neuropathy, Diabetic mellitus, Hand gripping test, Orthostatic Hypotension, QTc interval, Resting heart rate

INTRODUCTION

Diabetes mellitus (DM- type 2) is the most common type of diabetes in the world constituting 90 percentage of the diabetic population. In India also it has become a significant concern. According to the WHO, the gist of diabetes mellitus in India is 31.7 million and projected number for 2030 is 79.44 million.[1]

CAN results in destruction to the autonomic nerve fibers (ANF) that innervate the heart and blood vessels (BV), resulting in irregularity in heart rate control and vascular dynamics.[2] The generality of autonomic-nervous system (ANS) dysfunction in diabetes is not precisely known; however, tests of autonomic function have shown impairment in nearly 20-30% of diabetic patients.[3]

Available studies have underlined a variety of factors to be related with CAN and indicate that its prevalence increases with age of the diabetic patients, diabetes duration, and bad glycemic control.[2] Age of the patient, diabetes duration, smoking, and obesity are independent

risk element for minimized heart rate variability (HRV) in type-2 diabetes.[4] A different study concluded that uncommon HbA1c levels, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycemia were risk components for developing CAD in type 1 diabetes.[5]

CAN is still widely under-diagnosed, likely because require for training and expertise in the performance of cardiovascular autonomic tests.[6] In specific, information on the commonness of CAN in patients who recently diagnosed type 2 diabetes is scarce and not simple to interpret because both the various diagnostic approaches regarding the numbers and many type of tests performed and the differences in the diagnostic cutoff points.[7-10] The widespread presence of CAN at diagnosis of diabetes is still uncertain.[11]

Authors undertook the present study to assess the prevalence of autonomic dysfunction (AD) in type-2 diabetic patients and to correlate its control and duration to the degree of AD.

METHODS

This prospective cross-sectional study was done at department of Medicine at CSS Hospital, Subharti Medical College, Meerut. A total 123 patients of more than 30 (thirty) years of age and up to 60 (sixty) years of age who were presented with diabetic mellitus (DM) were studied during the study period from 2016 to 2018 were enrolled. The research procedure followed was in accordance with and after approval of ethical standards of Subharti Medical college, Meerut, ethics committee (Human).

Inclusion criteria

- Patients >30 years of age up to 60 years and had type 2 DM that diagnosed as per American diabetes association 2013 guidelines were included.

Exclusion criteria

- Alcoholic liver disease patients, congestive cardiac failure, chronic renal failure, hereditary neuropathies, leprosy(as per history and skin changes), patients on drugs known to produce autonomic abnormalities, e.g. antihypertensive, tranquilizers, antidepressants, diuretics, calcium channel blockers and those were not consenting to participate in this study were excluded from the study.

There were 123 type 2 DM patients were enrolled in this study, 11 patients were refused, and 9 were not fit in the inclusion criteria. Finally, 103 patients were taken. Detailed history and physical examinations were done that recorded on predesigned proforma that was prepared in English and local language (Annexure 1) which was used during an interview from each patient. Patient's personal history, physical examination findings like name, age, sex, demographic profile, height, weight, BMI, blood pressure, history of present illness, blood sugar level, diabetic mellitus duration, hypertension, past history, family history, blood and laboratory measurement (HbA1c), urine R/M, renal function test, liver function test and electrocardiogram were recorded.

Authors used non-probability purposive sampling method for this study. All patients were wholly explained about the discrete maneuvers like a hand grip, standing, and squeeze of the ball. The recruited cases were tested for

Resting heart rate (RHR)

An RHR of>100 beats per minute considered abnormal.[12]

Orthostatic hypotension (OH)

Blood pressure (BP) was 1st measured (by the aneroid sphygmomanometer) in the supine position and then the patient was ordered to stand up. BP was measured again after 2minutes of standing. A fall in systolic BP with more than 20mmHg and or in diastolic BP with more than 10mmHg was considered abnormal.[12]

Hand gripping test (HRT)

The BP of the patient was initially measured in the supine position, the patient was ordered to squeeze a small ball in his/her hand for about 5minutes while lying on bed and then his/her BP was measured again. An increase in diastolic BP <15mmHg was considered abnormal.[12]

ECG recording

QT interval length and QT dispersion: In a standard ECG (Schiller AT1, Cardiovit, Switzerland), noted in a prone position, respiratory rate (RR) and QT intervals were recorded by two independent observers, who were blinded to patients' details, using a ruler and magnifying glass. QT interval was studied from the beginning of QRS complex to the end of the T-wave in the intersection with the isoelectric line.[13] QT corrected for the length of the previous cycle (QTc) was acquired using Bazett's formulae.[14,15]

QTc = QT/HRR (sec)

For each patient, the readings of QTc and QTd represent mean values of the readings of two different observers. ECG findings were performed on the same day as daily glycemia profile.[14]

Blood glucose levels of diabetes mellitus were confirmed by classification and diagnosis criteria lay by WHO (1999).[16] All these tests were conducted using random kit from USA.[16] CAN was assessed according to Ewing's protocol.[17]

Data were analyzed with statistical package for social sciences (SPSS), version 23 (SPSS Inc., Chicago, IL). chi-square test or paired sample t-test used for assessment of the prevalence of AD in type-2 DM patients and duration of DM to the degree of AD Correlation between variables was tested by spearman correlation coefficient. The level P<0.05 was considered as the cutoff value or significance.

RESULTS

Demographic profile

The mean age of all 103 studied patients was 48.94±8.69 years; the majorities were in 51-60 years of age group (49; 47.5%) (Figure 1) and mostly patients were male (68.9%) in this study (Figure 2).

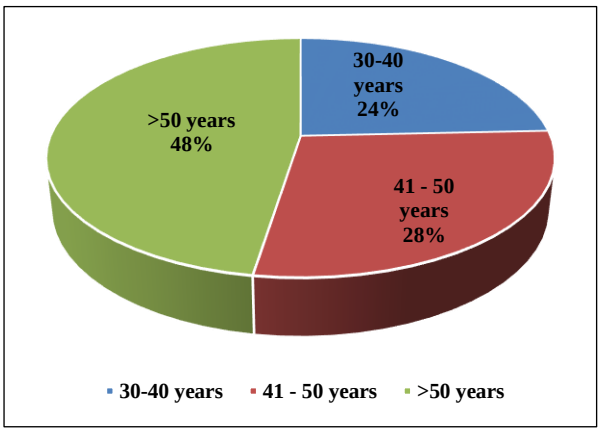

Figure 1: Age distribution.

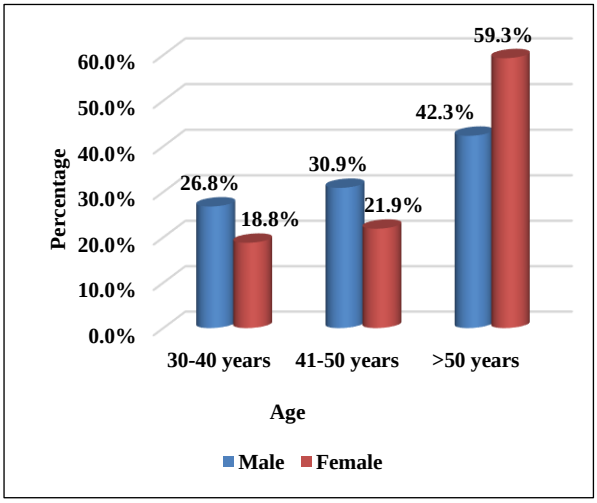

Figure 2: Gender distribution.

Prevalence of AD in type- 2 DM patients

There 39.8% patients have had diabetics since last 11-15 years followed by 30% patients from 6-10 years and the least 10.7% were had less than or equal to 5 years diabetic duration (Table 1).

Table 1: Demographic profile details of patients.

Age group (years)	Number of patients (n=103) (%)	Male (n=71) (%)	Female (n=32) (%)
30-40	25 (24.3)	19 (26.8)	6 (18.8)
41-50	28 (28.2)	21 (30.9)	7 (21.9)
51-60	49 (47.5)	30 (42.3)	19 (59.3)

HbA1c (%) level was 7-10 of 62.1.0% patients followed by 30.2% of patients who had more than 10%. Out of 103 72.8% patients (n=75) were reported with CAN (51 males and 24 females) and without CAN were 27.2.0% (20 males and 8 females) (Figure 2).

Correlation control and duration of type-2 diabetes mellitus to the degree of AD

On the basis of the pattern of AD the majority 35.9% of patients were in definite parasympathetic neuropathy followed by normal and sympathetic neuropathy in 24.3% and 20.4% patients respectively (Table 2).

Table 2: Distribution of type 2 DM cases (%) in abnormal parasympathetic and sympathetic CV reflexes.

Pattern of AD	No. of cases (n=103)	(%)
Normal	25	24.3
Early parasympathetic neuropathy	20	19.4
Definite parasympathetic neuropathy	37	35.9
Sympathetic neuropathy	21	20.4

On the basis of CAN and the abnormal responses were more common for heart rate response to standing (30:15 ratio) (48.0%) come after by Valsalva ratio (45.0%) and HRV during intense breathing (43.0%) patients and all the tests parameters were found to-be statistically-significant (p<0.05) among with CAN present and without CAN group values (Table 3).

QTc interval and CAN and the association was found to be statistically-significant (p<0.05) among CAN and normal patients' values (Table 4).

The correlation between HbA1c and different parameters of CAN and HRV during intense breathing was found to be statistically-significant is the most sensitive parasympathetic cardiac autonomic function test which detects CAN (Table 5).

Table 3: Interpretation of autonomic function tests.

Test	Over all Mean±SD	CAN		p-value
		Absent	Present	
Valsalva ratio	1.15±0.07	1.23±0.01	1.12±0.06	<0.001
HRV during deep breathing	13.07±2.71	15.56±0.71	12.24±2.61	<0.001
HR in response to standing (30:15 ratio	0.97±0.14	1.02±0.02	0.95±0.15	0.023
BP response to sustained hand grip	12.36±3.72	13.64±3.57	11.93±3.69	0.46
Orthostatic hypotension	15.86±9.71	18.08±9.85	15.1±4.1	0.035

Unpaired student's t test

Table 4: QTc interval and CAN.

QTC interval (Mean±SD)	CAN	
	Absent	Present
430.91±10.93	423.12±10.97	430.07±10.86

p-value = 0.007 (unpaired student's t test)

Table 5: Relation between HbA1c and different parameters of CAN.

CAN parameters	Spearman's correlation	p-value
Valsalva ratio	-0.022	0.829
HRV during deep breathing	-0.097	0.039
HR in response to standing (30:15 ratio)	0.005	0.964
BP response to sustained hand grip	0.238	0.017
Orthostatic hypotension	-0.001	0.991

DISCUSSION

Our analysis disclosed that a total of 72.8% patients with type-2 DM had CAN. It further disclosed that there were non-significant differences between incidences of CAN between both sexes, but the difference in incidence between different age-groups was significant. In another descriptive study which was done at Hyderabad, Pakistan, researchers reported the incidence of the definitive and borderline CAN in patients with type-2 DM to be 30% and 40% respectively, which was very alike to our findings. The researchers remarked that in-depth glycemic control is affiliated with superior cardiac autonomic nerve functions.[12]

CAN is a significant complication of DM that is strongly similar with about five-fold increased risk of cardiovascular mortality. Authors have used the cross-sectional design similarly Arif ZA et al, study and Prakash B et al, also did same observational study that carried out in a tertiary care center.[12,16] This study was best suitable study-type for knowing the prevalence of disease onto a population within limited period of time and it required fewer resources than other type of case control or cohort study. CAN is by far one of the most studied forms among the different forms of diabetic autonomic neuropathies.[18,19] Screening for CAN was performed in T2DM patients at diagnosis in particular those at greater risk for CAN due to a history of bad glycemic control (HbA1c>7%), or the presence of one crucial CVD risk factor, or other chronic complications of DM (level B). CAN measurement can be used for cardiovascular risk stratification and as a marker for enlarged risk of intraoperative cardiovascular lability.[20]

Ewing's tests/time-domain practice are suitable for diagnosis of CAN. However, Ewing's tests are simpler and can be more easily implemented during routine clinical use, Arif ZA et al study, and Prakash B et al, used Ewing's method to diagnosed CAN in studied patients similar to present study.[12,16,17]

The mean age of studied patients in this study was 48.76±8.41 years with the larger part of patients in the age group 51-60 years (47.5%), and also mostly patients were male (68.9%). Our results were comparable to the studies performed Sumaswi A et al, reported mean age as 55.48±10.75 years, similarly, Arif ZA et al, Basu AK et al, and Pathak A et al.[12,21-23] The discussion on demographic details depicts that the problem of CAN mainly occurs in 5th and 6th decades of life and majority of patients were males which is also reported by several comparable studies done in past as mentioned above.

In this study, prevalence of CAN was found to be 75.0% that was comparable to other studies performed by Sumaswi A et al, Basu AK et al, Kumar N et al, HassanZF et al, which shows that CAN increase with the patients of diabetes especially in prolonged diabetes.[21,22,24,25] Basu AK et al, reported comparably

less prevalence this is because their sample size was comparatively small.[22] A recent study in Jaipur done by Mehta S et al, revealed prevalence of CAN among 58% cases.[26] In a study by Mahwi TO et al, out of 150 cases, 106 (70.7%) cases had CAN.[27]

In the present study early, parasympathetic neuropathy was observed in 19.4%, definite parasympathetic neuropathy (35.9%) and sympathetic neuropathy (20.4%). Basu AK et al, reported the comparable result by observing Parasympathetic neuropathy in 52.0% and Sympathetic neuropathy in 20.0%.[22] Arif ZA et al, also reported parasympathetic neuropathy in 52.0% and sympathetic neuropathy in 20.0%.[12] Another study by Ramavat MR et al, reported the prevalence of sympathetic among 28.9% and parasympathetic CAN among 44% patients respectively.[28] Kumar N et al, 67 patients (71%) reported one/more tests positive for parasympathetic dysfunction and 44 patients (47%) reported one/more tests positive for sympathetic dysfunction.[24] Pathak A et al, reported parasympathetic neuropathy in 52% of cases, and sympathetic neuropathy in 26% of cases.[23] Prevalence of parasympathetic neuropathy and sympathetic neuropathy shows the parasympathetic neuropathy was more prevalent in both presents as well as previous studies.

In present study, the QTc interval found to be 430.91±10.93 and 423.12±10.97 in patients without CAN and 430.07±10.86 in patients with CAN and the association was found to be statistically-significant ($p<0.05$). Sumaswi A et al, Mathur C et al, and Pillai JN et al, reported similar results and significant association between CAN and non-CAN patients in their studies.[21,29,30] Diabetics accompanied autonomic neuropathy had significantly higher QTc mean and QTc max values contrasted to diabetics without autonomic neuropathy and controls ($P<0.01$). This implies that QTC interval was more in patients who had CAN and this difference was statistically-significant ($p<0.05$). In Khoharo HK et al, study, QTc be seen a statistically-significant correlation with known diabetes duration and heart rate variability with respiration ($p<0.05$).[31] Several studies have evaluated the correlation between prolongation of the QTc interval with the hypothesis that sympathetic dysfunction may prolong the interval. A 1992 consensus report on autonomic testing portrayed Bazett's heart rate- QTc prolongation as a particular yet insensitive index of diabetic autonomic failure. Bellavere F et al, in their study mentioned that diabetic cardiac autonomic neuropathy should be included among long QT syndromes.[32]

In this study heart rate response to intense/deep breathing had the foremost correlation with HbA1c ($r = -0.097$) come after by Valsalva ratio (-0.022) and the BP response to sustained handgrip was badly correlated to HbA1c ($r = 0.238$). Kumar N et al, reported that heart rate response to deep/intense breathing had the best correlation with HbA1c ($r = -0.656$) come after by Valsalva ratio ($r = -0.505$), SBP fall on standing was badly correlated to HbA1c ($r = 0.374$) which was comparable to the present study.[24] Memon A reported a negative correlation of HRV, 30-15th ratio, valsalva ratio, BP response to the sustained handgrip, systolic, and diastolic BP with a statistically significant difference.[33] The BP response to standing is found positively correlated with glycemic control. These findings are close to Nayak UB et al, and Noronha JL et al, but contrary to reported by Toyry JP et al.[34-36] This implies that heart rate response to intense breathing is the most sensitive parasympathetic cardiac autonomic function test which detects CAN, followed by Valsalva maneuver and heart rate response to standing and heart rate response to.

Strength

Authors opt cross-sectional studies which are comparatively inexpensive and easy to assess exposures or outcome. Useful for public health planning like diabetics and it can measure association among CAN.

Limitations of this study were small sample size, results cannot be enforced to the general population, the study has not done a clinical follow-up of patients to know the further outcome. Data is available and hence the influence of autonomic neuropathy on mortality including sudden cardiac death could not be assessed.

CONCLUSION

The prevalence/generality of CAN is 72.8%. Various cardiac autonomic function tests detect cardiac autonomic neuropathy. Symptoms of autonomic neuropathy are not as sensitive as the autonomic function tests to detect cardiac neuropathy. Therefore, evaluation of autonomic cardiovascular reflexes provides a satisfactory method for the evaluation of CAN.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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