A Study of Cardiovascular Autonomic Dysfunction in Type 2 Diabetes Mellitus Patients in a Tertiary Care Hospital

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ABSTRACT

Introduction: Diabetes mellitus is a major concern in India. Diabetes mellitus is a leading public health care problem in developing and developed world, with increasing incidence and long-term complications. Cardiovascular Autonomic Neuropathy (CAN) is a common but frequently overlooked complication of diabetes. So the present study was done to estimate the prevalence of cardiovascular autonomic dysfunction in type 2 diabetes mellitus patients and also the association between prolonged QTc interval and presence of cardiac autonomic neuropathy

Material and Methods: 50 patients of type 2 diabetes mellitus who fulfilled the inclusion and exclusion criteria were studied between the period January and June 2015. Various cardiovascular autonomic function tests were performed on the patients and the patients were categorized as per Ewing's criteria. QT interval was measured in ECG and corrected for cardiac cycle length. (QTc)

Results: Early CAN was seen in 14%, Severe CAN in 14%, Definite CAN in 8% patients. Atypical CAN with other combination of abnormalities was seen in 32% patients. Tests were normal in 32% patients. Sympathetic dysfunction was seen in 48% patients. Parasympathetic dysfunction was seen in 60%. Combined parasympathetic and sympathetic dysfunction was seen in 40% patients. 8% had sympathetic dysfunction alone and 20% patients had parasympathetic dysfunction alone.

Mean QTC interval of patients in this study was 411.12±36.82 msec. There was a statistically significant association between prolonged QTc interval and presence of CAN.(p <0.05).

Conclusion: Cardiovascular autonomic neuropathy is common in type 2 diabetic patients and can be recognized by simple bedside autonomic function tests. Prolonged QTc interval is an indicator for the presence of cardiovascular autonomic neuropathy in type 2 diabetic patients.

Keywords: Diabetes mellitus, cardiovascular autonomic neuropathy, QTc interval, Ewing's criteria.

INTRODUCTION

Type 2 diabetes mellitus is the most common type of diabetes in the world constituting 90% of the diabetic population. Diabetes mellitus is a leading public health care problem in developing and developed world, with increasing incidence and long-term complications. The triad of neuropathy, retinopathy and nephropathy is characteristic of chronic diabetes mellitus.

Diabetic autonomic neuropathy is among the least recognized and understood complications of diabetes[1-3], which can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic system.

Cardiac Autonomic Neuropathy (CAN) results in damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.[3] CAN results in increased incidence of silent myocardial infarction, cardiac arrest, sudden death, and inadequate response to stressful events, e.g., anesthesia and surgery. Since CAN is asymptomatic most of the time, with symptoms appearing only in the late stages, recognizing CAN in the early stages helps to delay or arrest its progression.

Thus, the present study was conducted to estimate the prevalence of cardiovascular autonomic dysfunction in type 2 diabetes mellitus patients and also the association between prolonged QTc interval and presence of cardiac autonomic neuropathy.

MATERIAL AND METHODS

A cross sectional study of 50 type 2 diabetes mellitus patients, selected according to inclusion exclusion criteria, was done in Sri Ramnarain Ruia Government General Hospital, Tirupati during the period between January 2015 and June 2015.

Inclusion criteria

1. Type 2 diabetes mellitus patients of age more than 18 years of both sexes.
2. Duration of diabetes for atleast 5 years.
3. Patients willing to give informed written consent.

Exclusion criteria

1. Anemia
2. Alcohol consumption
3. Chronic renal failure
4. Use of beta blockers
5. Serum electrolyte abnormalities
6. Asthma or chronic obstructive pulmonary disease
7. Use of drugs that prolong QTc interval
8. Non complying patients who do not consent to participate in the study.

Careful history regarding symptoms of autonomic neuropathy was obtained and a general physical examination, detailed neurological examination and tests of autonomic function were done in all patients.

Tests for assessment of cardiovascular autonomic function

The tests for the assessment of cardiovascular autonomic neuropathy were done as per standard protocols published in literature and as practiced in the AFT laboratory, AIIMS.

Tests for parasympathetic function

1. Heart rate response to deep breathing
2. Heart rate response to Valsalva Maneuver (Valsalva ratio)
3. Heart rate response to immediate standing (30: 15 ratio)

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How to cite this article: Angadi Sumaswi, Goduguchintha Lepakshi, Nagatham Padmaja. A study of cardiovascular autonomic dysfunction in type 2 diabetes mellitus patients in a tertiary care hospital. International Journal of Contemporary Medical Research 2016;3(8):2454-2457.

Test	No. of subjects (N=50)		
	Normal	Borderline	Abnormal
1) E-I difference	21 (42%)	11 (22%)	18 (36%)
2) Valsalva ratio	25 (50%)	12 (24%)	13 (26%)
3) 30:15 ratio	35 (70%)	9 (18%)	6 (12%)
4) BP response to standing	26 (52%)	15 (30%)	9 (18%)
5) BP response to sustained handgrip	26 (52%)	10 (20%)	14 (28%)

Table-1: Cardiovascular Autonomic Function Tests.

Pattern	Number (%)
Normal	16(32%)
Only sympathetic	4 (8%)
Only parasympathetic	10(20%)
Both (S+PS)	20 (40%)
Total	50(100)

Table-2: Pattern of autonomic dysfunction

Tests for sympathetic function

1. Blood pressure response to standing
2. Blood pressure response to sustained hand grip

Interpretation of test results

Test results were interpreted as per Ewing's criteria.[4]

Normal = All tests normal or 1 test borderline.

Early = One of the three heart rate tests abnormal or two borderline.

Definite = Two heart rate tests abnormal.

Severe = Two heart rate tests abnormal + one or both BP tests abnormal or both borderline

Atypical= Any other combination of abnormalities

QTC prolongation

The QT interval was measured on an ECG recorded at rest (beginning of QRS complex to the end of T wave) and corrected for cardiac cycle length (QTc) using Bazett's formula i.e. QTc =QT/√RR. A QTc interval more than 440 ms is said to be prolonged.

Other investigations done were Hb%, FBS, PPBS, HbA1c, Renal Function Tests (RFT), Serum electrolytes, Urine routine, Ophthalmic fundii examination, Chest X ray, ECG, 2D-ECHO. Before collection of data, all the subjects were briefed about the purpose of study and written informed consent was obtained. Ethical clearance was obtained from the Institutional Ethics Committee of the college.

STATISTICAL ANALYSIS

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented as Mean ± SD and results on categorical measurements were presented as proportions and percentages. Significance was assessed at 5 % level of probability. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Student's t-test was used to assess differences between continuous variables expressed as mean± SD. SPSS software (Version 17) was used for analysis.

RESULTS

The age group of diabetic patients ranged from 37- 75 years. The mean age of type 2 diabetic patients was 55.48±10.75 years. The mean age of patients with CAN was 55.85±10.22 years and that of patients without CAN was 54.69±12.11 years. 56% (28) of the study population were males and 44% (22) were females. The abnormal responses were most frequently found for heart rate response to deep breathing (36%) (table-1).

In this study, it was found that 32% (16) patients had no CAN. Positive tests of autonomic dysfunction were seen in 68% (34) patients. Only sympathetic dysfunction was seen in 8%(4) patients, only parasympathetic dysfunction in 20% (10) patients, both sympathetic and parasympathetic dysfunction in 40% (20) patients (table-2). Early CAN was seen in 14% (7), Severe CAN in 14% (7), Definite CAN in 8% (4) patients. Atypical CAN with other combination of abnormalities was seen in 32% (16) patients.

Patients with CAN had a statistically significant fall in SBP on standing than patients without CAN. They also had little rise in DBP on sustained handgrip than patients without CAN. Patients with CAN had statistically significant reduced heart rate variability (HRV) during deep breathing than patients without CAN. They also had significant difference in valsalva ratio and standing 30:15 ratio than patients without CAN (table-3).

Mean QT_C interval of patients in this study was 411.12±36.82 msec. QTc interval was significantly prolonged in patients with CAN than in patients without CAN (table-4).

DISCUSSION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[5,6] It is difficult to ascertain the exact prevalence of diabetic autonomic neuropathy, especially cardiac autonomic neuropathy since it is often asymptomatic or presents with vague symptoms. A total of 50 patients who were diagnosed to have type 2 diabetes mellitus based on ADA criteria were included in this study after considering the various inclusion and exclusion criteria.

In this study, 32% (16) patients had no CAN. Positive tests of autonomic dysfunction were seen in 68% (34) patients. Early CAN was seen in 14% (7), severe CAN in 14% (7), definite CAN in 8% (4) patients. Atypical CAN with other combination of abnormalities was seen in 32% (16) patients.

Mathur CP et al.[7] evaluated 50 diabetics for autonomic neuropathy by Ewing's criteria. Normal study was reported in 42%, early changes in 20%, definite in 30%, Severe in 4% and Atypical CAN in 4%. Pillai JN et al[8] evaluated 50 type 2 diabetes mellitus patients and found that 21 (42%) had severe autonomic neuropathy and 12 (24%) had early autonomic neuropathy by the autonomic function tests. In a study by Taha mahwi et al.[9] out of 150 cases, 106 cases had CAN. Early CAN in 35, definite CAN in 40, severe CAN in 31 patients. Agarwal et al[10] reported the prevalence of CAN in their study as 70%. Among them, early neuropathy was seen in 37%, definite neuropathy in 40%

AFT	Mean± SD	CAN		P value
		Absent	Present	
BP response to standing (fall in SBP) in mmHg	10.80±6.94	5.75±1.61	13.18±7.22	<0.001,S
BP response to sustained handgrip (rise in DBP) in mmHg	14.40±5.27	18.38±2.22	12.53±5.26	<0.001,S
HR response to deep breathing (bpm)	13.77±5.60	18.87±2.85	11.38±4.94	<0.001,S
Valsalva ratio	1.18±0.10	1.27±0.06	1.14±0.08	<0.001,S
Standing 30:15 ratio	1.07±0.08	1.12±0.10	1.05±0.06	<0.01,S

Table-3: Interpretation of Autonomic Function Tests (unpaired student's t -test)

QT_C Interval in MSEC (Mean±SD)	CAN	
	Absent	Present
411.12 ± 36.82	394.88 ± 28.91	418.76 ± 38.01
P=0.031, S		

Table-4: QT_C interval and CAN (unpaired student's t- test)

and severe autonomic dysfunction in 22.9% patients.

The abnormal responses were more frequently found for heart rate response to deep breathing (36%) which was consistent with the study done by Mathur et. al.[11] (48%). BP response to standing and standing 30:15 ratio were also found to be less sensitive in this study. The study conducted by Barthwal et al[12] had detected heart rate response to deep breathing and valsalva ratio to be the most sensitive while postural hypotension to be the least sensitive index. Domuschiev et al[13] also reported that heart rate response to deep breathing was most sensitive and was seen in 33.3% almost similar to the present study.

Tests of parasympathetic dysfunction were found to be most sensitive indicators of autonomic neuropathy. Sympathetic dysfunction was seen in 48% (24) patients. Parasympathetic dysfunction was seen in 60% (30). Combined parasympathetic and sympathetic dysfunction was seen in 40% (20) patients. 8% (4) had sympathetic dysfunction alone and 20% (10) patients had parasympathetic dysfunction alone. Study by Ramavat et al.[14] showed that 39.1% had parasympathetic neuropathy, 27% had sympathetic neuropathy, 19.2% had both parasympathetic and sympathetic neuropathy. Results in the present study are almost twice those found in this study. Only parasympathetic neuropathy was seen in 17.9% of type 2 diabetics, only sympathetic neuropathy in 6.5% of type 2 diabetic patients. The results of these categories are similar to the present study. In a study by AK Basu et al[15], 50 type 2 diabetic patients were studied. Overall prevalence of CAN was 54%. Parasympathetic neuropathy was seen in 52% cases and sympathetic neuropathy was seen in 20% cases. Study by Jyotsna et al[16] revealed that parasympathetic dysfunction was found in 44.2% and sympathetic dysfunction in 51.9% diabetics. The study was conducted in 145 type 2 diabetes mellitus patients. It was found that sympathetic dysfunction was more prevalent than parasympathetic dysfunction.

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 statement on autonomic testing portrayed Bazett's heart rate- QTc prolongation as a specific yet insensitive indicator of diabetic autonomic failure. Bellavere et al[17] in their study mentioned that diabetic cardiac autonomic neuropathy should be included among long QT syndromes.

Mean QTC interval of patients in this study was 411.12±36.82 msec. Patients who had CAN had a mean QTC interval of 418.76 ± 38.01 msec while it was 394.88 ± 28.91msec in patients who did not have CAN. This implies that QTC interval was more in patients who had CAN and this difference was statistically significant (p =0.031).

Mathur et al. in their study of 50 diabetic patients confirmed that prolonged QTc is associated with cardiac dysautonomia (p<0.01). In a study by Pillai JN et al., diabetics with autonomic neuropathy had significantly higher QTc mean and QTc max values compared to diabetics without autonomic neuropathy and controls ($P < 0.01$). In concordance with the above studies, the present study also showed significant association between cardiac dysautonomia and prolongation of QTc interval (p=0.031).

The limitation of the study is that no clinical follow-up data is available and hence the influence of autonomic neuropathy on mortality including sudden cardiac death could not be assessed.

CONCLUSION

Cardiac Autonomic Neuropathy thus is most frequently asymptomatic problem which can be identified by simple bed side tests. Early identification of Cardiac Autonomic neuropathy helps in effective prevention of cardiovascular disease related morbidity and mortality. QTc interval is a reliable indicator for the presence of Cardiac Autonomic Neuropathy.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 21-06-2016; **Published online**: 31-07-2016