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A Study of Cardiac Autonomic Neuropathy and Its Correlation with QTc Dispersion in Type-2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration between all authors. Authors M. Mahesh and MAS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors M. Mahesh, MAS and PKK managed the analyses of the study. Authors MAS and M. Madhumitha managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the presence of cardiac autonomic neuropathy in Type-2 Diabetes and to correlate autonomic dysfunction with QTc dispersion.
Study Design: This was a hospital based cross-sectional study carried out in the department of Medicine JSS Hospital Mysore, India between March 2012 and March 2013.
Methodology: We included 50 Diabetes patients (Cases) and 50 Non Diabetes healthy adults (Controls) of both genders. Five standard cardiovascular response tests were carried out (Valsalva ratio, expiration-inspiration ratio, immediate heart rate response to standing, fall of systolic blood pressure on standing and sustained hand grip test) to determine the severity of cardiac autonomic neuropathy. QTc dispersion was determined by subtracting heart rate-corrected minimum QTc interval (QTc min) from maximum QT interval (QTc max) from standard electrocardiogram.
Results: 17 patients (34%) had evidence of cardiac autonomic neuropathy. Of this 8 (16%) had borderline and 9(18%) had abnormal CAN. In the control group only 1(2%) had CAN. (P value of 0.000) Mean QTc in cases was 41.60+/-18.11) and in controls was 20.80(+/-4.88) QTc dispersion

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was 32.7(+/-13.0) in those without CAN and 48.75(+/-9.71) in borderline CAN and 67.77(+/-9.71_in abnormal CAN group. (P =0.000).

Conclusion: Prolonged QTc a feature of autonomic dysfunction due to diabetes. QTc dispersion correlates significantly with presence of cardiac autonomic neuropathy and may be a simple and useful measure for detection of cardiac autonomic neuropathy.

Keywords: Diabetes Mellitus; cardiovascular neuropathy; QTc, QTdispersion dysautonomia.

1. INTRODUCTION

Diabetes mellitus is ranked seventh among major causes of death, and rated third when all its fatal complications are taken into account [1] Autonomic neuropathy is one of the important complications of diabetes mellitus and can affect any organ. One of its earliest manifestations is denervation of cardiovascular system. Cardiac Autonomic Neuropathy (CAN) is of importance because of its causative association with silent myocardial ischemia, arrhythmias and sudden cardiac death [2]. Detection of CAN involves usage of a battery of tests such as heart rate response to Valsalva manoeuver, BP response to standing and handgrip. However these are cumbersome to perform. Therefore, there was a need of simple, non-invasive bed side test to detect autonomic involvement in diabetes. Several reports have shown association of prolonged QT interval with CAN [3] QT interval is a measurement of myocardial depolarization and repolarization, influenced by central autonomic neural tone and kinetics of myocardial cells [4]. The range of the inter-lead durations in the QT interval duration is termed QT dispersion (QTd).

It has been hypothesised that irregular and regional cardiac autonomic denervation in diabeties mellitus leads to increased QT dispersion. The association between an abnormal QT interval and sudden cardiac death is well known [5] Kumhar MR et al. [5] opined that severity of cardiac autonomic neuropathy strongly correlated with QTc dispersion Various studies conducted so far suggested an unconfirmed relationships between prolonged QT dispersion and autonomic system involvement in diabetes. While some investigators have reported that diabetics with CAN have QTc prolongation, others have reported shortening [6] QT dispersion has been found have significant clinical determinants and is stated by some authors to be an important predictor of mortality in diabetes [7,8]. This study was therefore taken up to evaluate CAN in Type-2 diabetes and its correlation with QT dispersion.

2. MATERIALS AND METHODS

This was a hospital based cross-sectional study carried out at JSS Hospital, a tertiary care teaching hospital attached to JSS Medical College at Mysore City, South India. 50 patients of both genders aged more than 30 years diagnosed to have Type 2 DM were taken up. 50 Non-Diabetic healthy adults aged more than 30 years of both genders were recruited as controls Excluded were diabetic patients with Ischemic Heart Disease, HIV, diabetics with electrolyte imbalance, diabetics who were on drugs known to interfere with autonomic function tests, diabetics who had hypoglycemia in the preceding 24 hours, diabetics with anemia and also pregnant diabetics. Cardiac Autonomic Function (CAN) was tested by Ewing's Battery of bedside maneuvers as follows [9].

Calculation of QTc dispersion A 12-lead resting ECG was recorded at a paper speed of 25 mm/sec, containing a minimum of four beats per lead. QT interval was measured from first deflection of QRS complex to the point of T wave offset. To adjust QT for heart rate, we calculated QTc according to Bazett's formula: $QTc=QT/\sqrt{RI}$ RI, where RR is the RR interval in seconds [10]. The QTc dispersion was determined as the difference between the maximum and minimum value of QTc interval. QTc dispersion =QTc max-QTc min

2.1 Heart Rate Variation with Valsalva Maneuver

The patient was asked to blow through mercury manometer up to 40 mm Hg and to maintain mercury column at that level for 15 seconds Continuous ECG was recorded during the procedure and fifteen seconds after the release of pressure. The ratio of longest R-R interval after the manoeuvre to shortest interval during manoeuvre was measured the result was expressed as Valsalva ratio. A ratio of 1.21 or greater was taken as normal.1.11 to 1.20 as borderline and 1.10 or less as abnormal.

Table 1. Autonomic function tests and scoring

Sl No	Tests	Normal	Borderline	Abnormal
1	Valsalva ratio	>1.21	1.11-1.20	<1.10
2	HR to deep breathing	>15	11-14	<10
3	HR to standing	>1.04	1.01-1.03	<1.00
4	BP response to standing	<10 (mm.Hg)	11-29 (mm. Hg)	>30 (mm Hg)
5	BP response to hand grip	>16 (mm. Hg)	11-15 (mm. Hg)	<10 (mm Hg)

An individual patient can get a score from 0 to 10. For grading of cardiovascular autonomic function, results were classified as normal, borderline, and abnormal (scored 0, 1 and 2 respectively). An overall score ≤3 was considered as no CAN, >3 and <8 was considered as borderline CAN and score ≥8 was considered definitive CAN

2.2 Heart Rate Response to Deep Breathing

The subject was instructed to take breaths deeply and evenly at six breaths per minute, taking five seconds for inspiration and five seconds for expiration. The longest and shortest R-R intervals during expiration and inspiration were measured. The difference between maximum and minimum heart rate was calculated. A difference of more than 15 beats per minute was taken as normal result. A difference of 11-15 beats per minute was taken as borderline and a difference of less than 10 beats per minute was taken as abnormal.

2.3 Heart Rate Response to Standing

The subject being in supine position the ECG was taken and the subject was instructed to move quickly from supine to upright posture and ECG was taken in upright posture. The ratio of longest R-R interval to shortest R-R interval after the patient moved quickly from supine to upright posture was calculated. The ratio of 1.04 or greater was taken as normal.1.01 to 1.03 as borderline and 1 or less as abnormal result.

2.4 Blood Pressure Response to Standing

This test was performed by measuring the blood pressure while subject was lying quietly and later by making the patient to stand up and recording the blood pressure after 3 minutes. A difference in systolic BP less than 10 mm of Hg was taken as normal. A fall of 11 to 29 mm of Hg was taken as borderline result and a fall of more than 30 mm of Hg as abnormal.

2.5 Blood Pressure Response to Sustained Hand Grip

Two sphygmo-manometers were used. The cuff of one was inflated at 10 mm of Hg and the patient was asked to compress the cuff to the maximum extent with the hand and to maintain pressure on the cuff at 30% of maximum effort for 3 minutes. The blood pressure was recorded with the second apparatus at the beginning and end of 3 minutes. A rise of diastolic pressure of more than 16 mm of Hg was taken a normal. A value of 11 to 15 mm was taken as borderline result and reading of less than 10 mm of Hg was taken as abnormal result.

Scores were given for each test as follows normal (0), borderline (1), and abnormal (2) An overall score obtained by addition of all individual scores was computed. ≤3 was considered as normal(no CAN), >3 and <8 was considered as borderline CAN and score ≥8 was considered as abnormal(CAN Present) [Table 1 above].

All the tests were carried out by a single investigator using the same instruments to ensure quality control and to eliminate inter-observer bias.

2.6 Statistical Methods

Descriptives procedure was used to display univariate summary statistics for several variables in a single table and to calculate standardized values (z scores). The frequencies procedure for describing the types of variables and the crosstabs procedure as a measure of association for two-way tables were employed. The Independent-Samples T test procedure was used to compare means. The Chi-Square Test procedure tabulated variables into categories and computed a chi-square statistic. All the statistical calculations were done through SPSS 16.0 (2007) for windows.

3. RESULTS AND DISCUSSION

Total number of subjects was 100 and the total number of cases was 50. Total number of controls was 50. In both cases and controls there were 30 males and 20 females. Mean age of the cases was 55.08 (±4.1) years. Mean age of the controls was 55.04 (±4.8) years. Largest number of cases was in age group of 51- 60 years. In the study group 17 patients (34%) had CAN. Of this

8(16%) had borderline CAN and 9(18%) patients had abnormal CAN. In the control group only 1(2%) patient had CAN. The 'p' value was significant (0.000).The results of individual tests are depicted in Tables 2 and 3.

The comparison of QTc dispersion between cases and controls showed that Mean QTc dispersion in cases was 41.60(±18.11) and in controls was 20.80(±4.88). P=0.000. There was significant difference in QTc dispersion values between total number of cases and controls. On comparision of QTc dispersion with age between cases and controls the following were noted. Cases between the ages of 31-40 had mean QTc dispersion of 35.00±19.14, while controls in this age group had mean QTc dispersion of 17.50±5.00. This was a significant difference. P=0.000 Cases between the ages of 41- 50 had mean QTc dispersion of 30.00±10.54, while controls had mean QTc dispersion of 25±8.49. This was not stastically significant. Cases between age of 51- 60 had mean QTc dispersion of 46.25±18.60, while controls had mean QTc dispersion of 20.00±2.94. P=0.000. This was a significant difference. Cases above the age group of 60 years had mean QTc dispersion of 44±18.90, while controls had mean QTc dispersion of 20.00±00. P=0.000. This was a significant difference the comparision of CAN with QTc dispersion in cases and controls revealed that QTc dispersion was 32.7±13.0 msec in those without CAN. whereas in patients with CAN who were in borderline group QTc dispersion was 48.75±9.71. In patients who were in the abnormal group of CAN QTC dispersion was 67.77±9.71. The difference between the group was statistically significant with 'p' value of 0.000. [Table 4].

3.1 Discussion

Diabetic autonomic neuropathy is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life. The incidence of cardiac autonomic neuropathy in this study was 34%. The overall prevalence of cardiac autonomic neuropathy in diabetics is not precisely known [11]. Prevalence of CAN, based on assessment of abnormal cardiovascular autonomic tests, is variable (5-90%) [12]. JM Pappachan et al. [13] found that the prevalence of CAN was 60%. D. Ziegler et al. [14] concluded that the overall prevalence of CAN was 46.6%.

QT interval is the interval in the ECG from the beginning of the QRS complex to the end of the T wave. The QTc (corrected QT interval) is the QT interval estimated at a rate of 60/minute. QTc > 440 ms (0.44s) is considered as prolonged. QT dispersion is the difference between the maximum and minimum QT interval on the 12 lead ECG (QTd = QT max - QT min). QTd > 80 ms (0.08s) is usually considered as prolonged.

QTc dispersion represents the spatial dispersion of repolarization and it is used as an indication of electrical instability and as a marker of arrhythmogenic risk. Several studies have found a significantly greater QTc dispersion in diabetics when compared with controls [15-17].

Table 2. Cardiac autonomic neuropathy tests and their results in cases

Test	Number of patients		
	Normal values	Borderline values	Abnormal values
Heart rate response to standing	34(68%)	8(16%)	8(16%)
Heart rate response to deep breathing	19(38%)	18(36%)	13(26%)
Valsalva ratio	29(58%)	16(32%)	5(10%)
Postural drop in systolic BP	30(60%)	20(40%)	0
Diastolic rise in BP following hand grip	27(54%)	10(20%)	13(26%)

Table 3. Cardiac autonomic neuropathy tests and their results in controls

Test	Normal	Number of subjects	
		Borderline	Abnormal
Heart rate response to standing	47(94%)	3(6%)	-
Heart rate response to deep breathing	38(76%)	10(20%)	2(4%)
Valsalva ratio	37(74%)	13(26%)	-
Postural drop in systolic BP	49(98%)	1(2%)	-
Diastolic rise in BP following hand grip	50(100%)	-	

Table 4. Comparision of CAN with Qtc dispersion in cases

	No	QTc dispersion	
		Mean	Std deviation
Normal	33	32.7273	13.05582
Abnormal	9	67.7778	9.71825

P=0.000

In this study, The QTc dispersion was significantly higher in diabetic patients when compared with controls. Familoni et al. [18] studied the relationship between QT intervals and cardiac autonomic neuropathy in Nigerian patients with Type 2 Diabetes Mellitus and found that the QT interval (QTc, QTd,) were significantly longer in patients than controls. Others also have found a significantly higher QTc dispersion in diabetic patients when compared with controls [18,19], Cardoso Claudia et al. [20] opined that Diabetics had increased QT dispersion compared to controls. The results of the present study are in agreement with those of above studies which found significant differences in QTc dispersion between diabetics and controls.

In the present study, it was observed that as the CAN score increased QTc dispersion also increased. In contrast, the present study is at variance with the study by Psallas M et al. They studied QT dispersion: and its association with microalbuminuria in diabetes and concluded that no significant differences were found in QT dispersion between patients with and without CAN. The present study has found that CAN is positively correlated with the QTc dispersion, thereby implying that there is a need for earlier and regular evaluation of autonomic nervous system in Type 2 DM to prevent further cardiac complications. The present study showed that as the duration of DM increased there was increase in incidence of CAN but this was not statistically significant.

Diabetics with prolonged QTc dispersion are at higher risk for arrhythmias due to imbalance between the sympathetic and parasympathetic limbs of autonomic nervous system. Diabetic patient develop vagal denervation frequently and early in the disease and therefore may loose the protective influence on adrenergically mediated arrhythmias. The precise mechanism of QTc prolongation is unknown but it has been hypothesised that sympathetic imbalance is responsible as parasympathetic have little influence on QTc modulations.

QTc dispersion prolongation may arise from imbalance in sympathetic innervations of the diabetic myocardium, and this may increase the risk of ventricular arrhythmias. QTc dispersion prolongation may also a be marker for sudden death in diabetic CAN.

This study is not without limitations. A larger sample would certainly have increased the statistical power. Nevertheless this study has clearly demonstrated a prolonged and more heterogeneous repolarization in diabetes patients This could explain greater vulnerability of these patients to cardiac arrhythmias. Therefore, the assessment of CAN may be important in risk stratification of diabetic patients. This needs confirmation in future larger prospective studies.

4. CONCLUSION

Cardiovascular autonomic neuropathy is a common complication of diabetes mellitus. Prolonged QTc dispersion is common in patients with autonomic dysfunction due to diabetes. QTc dispersion correlates significantly with presence of CAN. QTc dispersion can be used as a parameter to assess cardiac autonomic neuropathy.

CONSENT

The patients and subjects have given their informed consent for the study. All authors declare that 'written informed consent was obtained from the subjects (or other approved parties) for publication of the study results.

ETHICAL APPROVAL

The study was presented before the Institutional ethical committee of JSS Medical College and was thereby granted due approval for carrying out the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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