



A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

CONTEXT: Cardiac Autonomic Neuropathy (CAN) is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to its diagnosis. Currently, Cardiovascular autonomic reflex tests (CART) are the gold standard for diagnosing CAN in persons with DM. It include four tests: (i) heart rate variation to deep breathing (ii) heart rate variation to Valsalva, (iii) heart rate response to standing (30:15), and (iv) orthostatic hypotension. But these tests are cumbersome and not easy to perform in every patient. Therefore, there is a need of simple, non-invasive bed side test to detect early autonomic involvement in diabetes.

AIM OF THE STUDY : To determine QTc maximum, QTc mean, QTc minimum, QTc dispersion in Type 2 diabetic patients. Comparison of QTc maximum, QTc minimum, QTc dispersion, QTc mean in both study group and control group. To study the significance of QTd as an indicator of CAN in Type 2 Diabetes mellitus.

SETTINGS AND DESIGN: Analytical Case Control Study.

MATERIALS AND METHODS: The study was conducted among patients from General Medicine wards of Government Rajaji Hospital, Madurai during the period of February 2016 to July 2016. The study included 100 cases of diabetes and 100 age and sex matched controls. Subjects believed to fulfill all eligibility criteria, and none of the exclusion criteria were included in the study.

STATISTICAL ANALYSIS: One way ANOVA, Pearson correlation and Chi square test.

RESULTS: The average age for study group was 55 years. Among the 100 patients studied 55 were males and 45 females. Among the cases studied 62 had CAN. Of these 62, 44 had Grade 2 (severe) CAN, 18 had Grade 1 (early) CAN. Mean heart rate was found to be high in diabetic patients compared to controls. Among the cases the heart rate was higher in those with severe CAN. QT mean, QT minimum, QT maximum, QT dispersion was significantly more in patients with CAN than those without CAN and controls. Among those with CAN these were found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN.

CONCLUSIONS: Diabetics with CAN had significantly higher QTc mean, QTc maximum, QTc minimum, QTc dispersion values compared to diabetics without CAN and controls.

KEYWORDS : CARDIAC AUTONOMIC NEUROPATHY, QT DISPERSION, TYPE 2 DIABETES MELLITUS.

Introduction:

Diabetes Mellitus is a group of metabolic diseases characterised by chronic hyperglycemia associated with abnormal metabolism of proteins, fats and carbohydrates due to absolute or relative insulin deficiency¹³. Cardiac Autonomic Neuropathy (CAN) is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to its diagnosis. Currently, Cardiovascular autonomic reflex tests (CART) are the gold standard for diagnosing CAN in persons with DM. It include four tests: (i) heart rate variation to deep breathing (ii) heart rate variation to Valsalva, (iii) heart rate response to standing (30:15), and (iv) orthostatic hypotension (OH)²⁰. Maneuvers used in the first three tests induce changes in heart rate variability that primarily assess the parasympathetic ANS. In contrast, Orthostatic hypotension or the variation in systolic BP in supine and standing positions evaluates the function of the sympathetic ANS. But these tests are cumbersome and not easy to perform in every patient. Therefore, there is a need of simple, non-invasive bed side test to detect early autonomic involvement in diabetes.

In 1980 an association of prolonged QT interval with CAN was established. This opened the possibility of rapid objective method to detect cardiac dysautonomia. So keeping in mind the possible role of QTc & QTd on morbidity & mortality in a patient with diabetic CAN, the present study was done to study the relationship of prolonged QTc & QTd with CAN in Type 2 diabetes.

MATERIALS AND METHODS:

Study Population: The study was conducted among patients from General Medicine wards of Government Rajaji Hospital, Madurai during the period of February 2016 to July 2016. The aim of the study was to find out the significance of QTd as an indicator of CAN in Type 2 Diabetes mellitus. The study included 100 cases of diabetes and 100 age and sex matched controls.

Inclusion Criteria:

Onset of diabetes after 30 years and Duration more than or equal to 5 years

Exclusion Criteria:

- i. History of hypertension
- ii. History of electrocardiography (ECG) evidence of coronary artery disease
- iii. Stroke/transient ischemic attack (TIA)
- iv. Electrolyte imbalance like hypokalemia or hypocalcemia
- v. History of heart failure
- vi. History of renal dysfunction
- vii. History of hypothyroidism
- viii. Patients on drugs affecting autonomic tone or QT interval

Ethical Committee Approval: Obtained.

Study Protocol:

A previously designed proforma was used to collect the demographic and clinical details of the patients. History regarding symptoms of autonomic neuropathy like orthostatic hypotension, palpitations, exercise intolerance, bladder symptoms, diarrhoea, constipation, heat intolerance, sweating, anhidrosis, dry skin, erectile dysfunction and female sexual dysfunction was asked for.

History regarding duration of diabetes and past history of hypertension, stroke, Chronic kidney disease, cardiac disease, history of pregnancy or lactation, history of any chronic drug intake, family history of diabetes mellitus, hypertension, Coronary artery disease were recorded.

Clinical examination of height, weight, blood pressure, heart rate, pulse rate, was done for all patients. Body mass index was found. ECG was recorded for all patients.

Lab investigations like complete hemogram, Renal function tests, Liver function tests, urine routine examination, FBS, PPBS, lipid profile were done.

A battery of five autonomic function tests are done in all cases to assess CAN. The tests conducted were:

Postural fall in systolic blood pressure (BP) Increase in diastolic pressure during hand grip Heart rate response to Valsalva manoeuvre Deep breathing test Heart rate response to standing A 12 lead ECG is taken after 10 minutes rest in all patients at 50 mm/second speed. RR interval, heart rate, QTc interval, QTc maximum, QTc minimum and QTc dispersion are calculated from the ECG.

Comparisons of heart rate, QTc mean, QTc max, QTc min, QTc dispersion are made in various groups and controls and significance assessed by Students t test. Relation between age, sex, and autonomic neuropathy are assessed by Pearson correlation test.

STATISTICAL ANALYSIS:

The information collected regarding all selected cases were recorded in master chart. Data analysis was done with the help of computer using Statistical Package for Social Sciences (SPSS) software developed by IBM Corporation. Using this software percentage, mean, standard deviation and p value were calculated through Pearson correlation and Student t test and p value of < 0.05 was taken as significant.

RESULTS:

Most of the patients belonged to the age group 50-60 years, followed by 40-50 years. The average age for study group was 54 years Among the 100 cases studied 62 had CAN. Of these 62, 44 had Grade 2 (severe) CAN, 18 had Grade 1 (early) CAN. In the control group 3 had Grade 1 CAN, which can be attributed to their age.

Among the Type 2 Diabetes Mellitus patients and controls QTc mean was found to be significantly high in diabetic patients with Grade 2 CAN. There was no significant difference in QTC mean values between diabetics without CAN and healthy controls.

Among the Type 2 Diabetes Mellitus patients and controls QT dispersion was found to be significantly high in diabetic patients with Grade 2 CAN. QTd was found to be high in diabetics with Grade 1 CAN compared to controls Group QT dispersion (ms) Grade 2 CAN 54.09 Grade 1 CAN 37.11 Grade 0 CAN 33.11 Control gp 26.48 Among 81 patients with Type 2 Diabetes Mellitus with duration of diabetes 5-10 years, 35 patients had no features of CAN. 18 patients had Grade 1 CAN, 28 patients had Grade 2 CAN. Among the study group 16 patients had duration of diabetes 10-15 years. Of these patients, 3 had no features of CAN, 13 had Grade 2 CAN. Among 3 patients with disease duration more than 15 years, 3 had Grade 2 CAN. The incidence of CAN and its severity found to be higher with longer duration of the disease with a correlation coefficient of 0.520.

Among 76 patients with PPBS <250mg/dl, 20 had Grade 2 CAN, 18 had Grade 1 CAN and 38 had no features of CAN. Of 6 patients with PPBS between 250-300 mg/dl, all of them had Grade 2 CAN. Out of 18 patients with PPBS > 300 mg/dl all of them had Grade 2 CAN. On analysing the data, Pearson correlation coefficient is found to be 0.717, which indicates high correlation.

Among those with autonomic neuropathy mean resting heart rate was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN (p<0.01). There was no significant difference in mean heart rate among diabetic patients without autonomic neuropathy and healthy controls (p=0.110).

The QTc minimum of Type 2 diabetic patients was compared with healthy controls. It was found that QTc minimum was significantly more in study group than control group (p<0.01). Within the study group QTc minimum was found to be significantly more in patients with CAN than in patients without CAN (p<0.01). Unlike QT maximum, QT minimum did not show statistically significant difference between patients with Grade 2 CAN and those with Grade 1 CAN (p=0.275). There was no significant difference in QTc minimum among diabetic patients without CAN and healthy controls (p=0.929).

The QT dispersion of Type 2 diabetic patients was compared with healthy controls. It was found that QT dispersion was significantly more in study group than control group (p<0.01). Within the study group QT dispersion was found to be significantly more in patients with CAN than in patients without CAN (p<0.01). Among those with CAN QT dispersion was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN (p<0.01). Unlike other parameters QTd showed significant difference between diabetics without autonomic neuropathy and healthy controls (0.024).

CAN in T2DM patients and controls

CAN GRADE	CASES			CONTROLS		
	Males	Females	Total	Males	Females	Total
Grade0	27	11	38	52	44	96
Grade1	8	10	18	2	1	3
Grade2	20	24	44	1	0	1

QT dispersion in study and control groups

Group	QT dispersion (ms)
Grade 2 CAN	54.09
Grade 1 CAN	37.11
Grade 0 CAN	33.11
Control gp	26.48

DISCUSSION:

The present study findings are consistent with and correlate those of prior studies documenting that ECG can be used as a bedside tool to assess the presence of CAN in Type 2 diabetes mellitus patients.

In this study QTc mean and QTc maximum, QTc minimum and QTc dispersion values were measured in the severe and early autonomic neuropathy group and compared with no autonomic neuropathy group and controls. QTc mean in the four groups were 425.64 msec, 402.22 msec, 390.32 and 387.57 msec, respectively. The difference between autonomic neuropathy and no autonomic neuropathy group was statistically significant. But there was no statistically significant difference in QTc mean value among diabetics without autonomic neuropathy and controls.

Similarly, QTc maximum values were 452.91 msec, 420.89 msec, 406.74 msec and 400.80 msec, respectively in the four groups. Difference between the groups were statistically significant except that there was no statistically significant difference in QTc maximum value among diabetics without autonomic neuropathy and controls. QTc maximum in the severe autonomic neuropathy group (452.91 msec) was significantly more than that in early neuropathy group (420.89 msec). In our study, 79% of severe autonomic neuropathy patients ie 35 patients out of 44 with severe CAN had QTc maximum more than 440 msec. In the previous study by Germandy G et al., QTc intervals in definite CAN was 456 msec, and in early 435 msec, and without CAN-413 msec. QTc minimum values were 398.36 msec, 383.56 msec, 373.89 msec and 374.58 msec, respectively in the four groups. Difference between the groups were statistically significant except that there was no statistically significant difference in QTc minimum value among diabetics without autonomic neuropathy and controls. Unlike other parameters QTc minimum did not show significant difference between patients with Grade 2 (398.36 msec) and Grade 1 CAN (383.56 msec).

Diabetic patients with CAN showed an increase in QTc dispersion in our study that correlates with cardiac adrenergic dysinnervation. Increased QT dispersion was demonstrated in diabetic patients during episodes of hypoglycemia. In our study, QTc dispersion in the case group with severe diabetic autonomic neuropathy was 54.09 msec, compared to 37.11 msec in diabetics with early autonomic neuropathy; 33.11 msec in diabetics without autonomic neuropathy; and 26.48 in healthy controls. The difference was statistically very significant. In contrast to other parameters QTc dispersion was found to be significantly more in diabetics without autonomic neuropathy than healthy controls making it an even more sensitive parameter. Normal QT dispersion is <50 msec. 47% of the severe autonomic neuropathy group ie 21 out of 44 patients with severe autonomic neuropathy had QTc dispersion of more than 50 msec. Since all other factors which may cause prolongation of QTc were ruled out in this study group, the prolonged QTc intervals in our group can be considered to be due to autonomic dysfunction.

In addition, in the early stages of autonomic neuropathy, when the patient is asymptomatic and diagnosis of autonomic neuropathy can be made out only by doing cumbersome autonomic function tests, our study showed that QT dispersion, QT minimum, QT maximum and QT mean helped in the identification of such patients. The present study showed that QT dispersion, QT minimum, QT maximum and QT mean was significantly more in diabetics with early diabetic neuropathy and controls.

Diagnosing patients with early autonomic neuropathy is very important, since aggressive management by lifestyle modification and

strict glycemic control helps in delaying the progression of CAN in such patients. QT dispersion was found to be a even more sensitive indicator, as it was found to be higher in diabetic patients without CAN compared to healthy controls.

CONCLUSION:

Diabetics with CAN had significantly higher QTc mean, QTc maximum ,QTc minimum values compared to diabetics without CAN and controls.

QTc dispersion was significantly more among patients with CAN compared to those without CAN and controls.

QTc mean, QTc maximum ,QTc dispersion values were significantly more among patients with severe CAN compared to early CAN.

QTc minimum values were not significantly different among patients with Severe vs. Early CAN.

QTc dispersion values were significantly different among patients without CAN and controls

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