

Study of QTc Dispersion in Electrocardiogram in Patients of Type-2 Diabetes Mellitus

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Abstract

Introduction: QTc dispersion is a measure of the spatial dispersion of ventricular recovery time. Recent studies have found an association between cardiac autonomic neuropathy (CAN) and prolonged QT interval, which leads to increased mortality due to ventricular arrhythmias, silent ischemia, and cardiac arrest. In our study, we compared the QTc dispersion in electrocardiogram (ECG) in type-2 diabetes mellitus (DM) patients with that of the age- and sex-matched non-diabetics controls and studied the correlation between QTc dispersion and CAN in type-2 DM.

Materials and Methods: In a hospital based case-control study, QTc dispersion was compared between the 120 type-2 DM patients (as cases), and 60 non-diabetic healthy age- and sex-matched subjects (as controls). CAN assessment was made using the standard Ewing and Clarke tests. QT interval was calculated manually in all the 12 leads of the ECG and corrected (QTc) using Bazett's formula. The dispersion in the QTc interval (QTc max - QTc min) among the 12 leads in the ECG was calculated for each subject.

Observations: Out of the 120 diabetic cases, 69 (57.5%) had evidence of CAN. Diabetics with CAN were having a significantly longer duration of diabetes and raised HbA_{1c} as compared to diabetics without CAN and controls. Mean QTc dispersion (in msec) and mean QTc dispersion % among the diabetics with CAN (46.2 ± 17.6; 12.05%) were significantly higher as compared to the diabetics without CAN (25.3 ± 10.0; 6.45%, $P < 0.01$) and to the controls (23.36 ± 13.2; 6.37%, $P < 0.01$), respectively.

Conclusions: QTc dispersion was significantly higher among the diabetic with CAN group as compared with the diabetics without CAN group indicating the association of increased dispersion in QT interval with cardiac dysautonomia. Thus, QTc dispersion can be a helpful indicator of CAN and sudden cardiac mortality among the diabetic individuals.

Key words: Cardiac autonomic dysfunction, Diabetes mellitus, Mortality, QTc dispersion

INTRODUCTION

Diabetes is one of the largest global health emergencies of the 21st century. India is home to the second largest number of adults living with diabetes worldwide after China. There were 69.1 million cases of diabetes in India in 2015.¹⁻³ Type-2 diabetes is the predominant form of diabetes worldwide accounting for 90% of the total diabetes cases globally.⁴

Diabetes is associated with many life-threatening complications. Autonomic neuropathy is one of the most important complications of diabetes mellitus (DM) and can affect any organ system. Cardiovascular system denervation is one of its earliest manifestations, leading to cardiac autonomic neuropathy (CAN). CAN is one of the most commonly overlooked complication of diabetes which has a causative association with silent myocardial ischemia, ventricular arrhythmias and sudden cardiac death.⁵

Several studies have reported an association of prolonged QT interval with CAN.⁶ QT interval is a measurement of myocardial depolarization and repolarization, which may be influenced by kinetics of myocardial cells and central autonomic neural tone.⁷ QT dispersion is defined as the difference between the longest (QT_{max}) and the shortest (QT_{min}) QT intervals within a 12-lead surface

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electrocardiogram (ECG). The association between an abnormal QT interval and sudden cardiac death is well known.⁷ It has been hypothesized that irregular and regional cardiac autonomic denervation in DM leads to increased QT dispersion.⁷ In various studies conducted so far, an unconfirmed relationship between increased QT dispersion and autonomic system involvement in diabetes is suggested, which opened the possibility of a rapid objective method to detect cardiac dysautonomia and use QTc dispersion as an indices of autonomic dysfunction in diabetes. These tests can be used as a surrogate for the diagnosis of autonomic neuropathy of any system because it is rare to find involvement of any other division of the ANS in the absence of cardiovascular autonomic dysfunction.

MATERIALS AND METHODS

The study was conducted over a period of 1½ year at NSCB Medical College, Jabalpur on 180 subjects - 120 type-2 DM patients fulfilling inclusion criteria (as cases) and 60 age- and sex-matched healthy individuals (as controls).

Inclusion Criteria

Patients are having type-2 DM willing to be a part of the study.

Exclusion Criteria

Patient not willing to be a part of the study; patients with history of ischemic heart disease, hypertension, chronic obstructive pulmonary disease, valvular heart disease, cardiac arrhythmia patients, cardiomyopathy, and thyroid dysfunction; patients taking any drug known to affect cardiac repolarization such as antiarrhythmic, antihypertensive drugs, tricyclic antidepressant, theophylline, lithium carbonate, and erythromycin; patients with type-1 DM; patients with electrolyte imbalance.

Study Design

Hospital based observational study

Diabetic patients visiting the diabetic/medicine OPD fulfilling all the inclusion criteria and willing to be a part of the study were selected, and complete medical history, clinical examination, and investigations were performed. CAN was assessed by a battery of cardiac autonomic reflex tests proposed by Ewing and Clarke⁸ We evaluated cases of type-2 DM disease for QTc dispersion in their ECGs and CAN signs and symptoms, and compared it with the age- and sex-matched non-diabetic controls. QTc dispersion was calculated manually by the help of a 12-lead surface ECG.

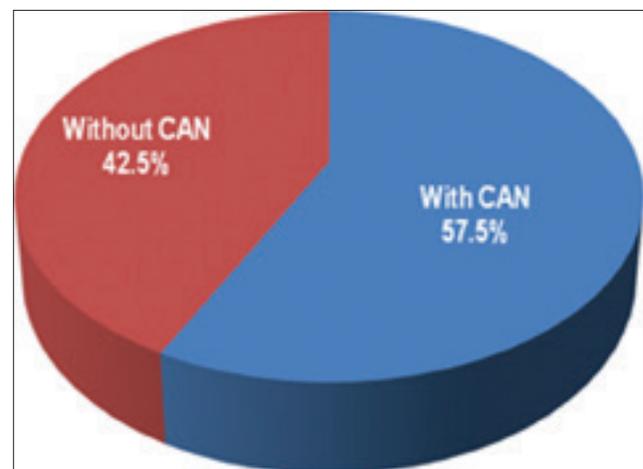
The data were analyzed using SPSS 20. Appropriate univariate and bivariate statistical analysis were performed using the Student's *t*-test for the continuous variable (age) and two-tailed Fisher exact test or Chi-square (χ^2) test for categorical variables.

To measure the linear dependence between two random variables Pearson's correlation coefficient was used. All means were expressed as mean \pm standard deviation, and all proportions were expressed in percentages. The critical levels of significance of the results were considered at 0.05 levels, i.e., $P < 0.05$ was considered significant. Analysis of variance was also applied for comparison of three observations of QTc parameters and multiple comparisons between each group were performed using Bonferroni *post-hoc* test.

All the subjects were informed about the study protocol and written informed consent was obtained. The study was approved by the Ethics Committee of Madhya Pradesh Medical Science University.

RESULTS (GRAPH 1)

- The mean age of the diabetic cases in our study was found to be 53.61 ± 8.75 years, and that of controls is 47.0 ± 16.32 years.
- The mean body mass index among the diabetic cases with CAN was 25.98 ± 2.56 kg/m² and that of diabetic cases without CAN was 25.66 ± 2.26 kg/m² and among controls was 24.44 ± 2.89 kg/m². The waist hip ratio of the cases was 1.15 ± 0.36 and that of the controls was 0.97 ± 0.25 .
- Out of the 120 diabetic cases, majority 69 (57.5%) were males, and 51 (42.5%) were females. Among the 60 controls, majority 38 (63.3%) were males, and 22 (36.6%) were females.
- Among the 120 diabetic cases, two subgroups are formed on the basis of presence and absence of CAN, with 69 (57.5%) were found to have CAN, and 51 (42.5%) were not having CAN features.
- Among the 69 diabetic cases with CAN, majority 47 (68.11%) were having diabetic retinopathy with



Graph 1: Occurrence of cardiac autonomic neuropathy in diabetic patients

37 (53.6%) were having non-proliferative diabetic retinopathy and 10 (14.5%) were having a proliferative type, and 22 (31.9%) were normal. Among the 51 diabetic cases without CAN, majority 36 (70.6%) were normal ($\chi^2 = 18.108; P < 0.001$ [highly significant]).

- Among the 69 diabetic cases with CAN, majority 40 (57.97%) were having diabetic nephropathy, with 23 (33.33%) were having microalbuminuria diabetic nephropathy and 17 (42.5%) were having macroalbuminuria, and 29 (42.02%) were normal. Among the 51 diabetic cases without CAN, majority 36 (70.58%) were normal ($\chi^2 = 8.173; P < 0.05$).
- The association of CAN with retinopathy and CAN with nephropathy both were found to be significant ($P < 0.05$).
- The mean QTc dispersion among the diabetics with CAN was significantly increased as compared with that of the diabetics without CAN group and the controls group, respectively (i.e., 46.20 ± 17.66 vs. 25.37 ± 10.01 ms; $P < 0.01$ and vs. 23.36 ± 13.15 , $P < 0.01$, respectively).
- Furthermore, the mean QTc maximum and the QTc dispersion percentage among the diabetics with CAN was significantly increased as compared with that of the diabetics without CAN group and the controls group, respectively.
- The mean QTc dispersion among the diabetics with proteinuria present group was found to be significant compared to the control group (29.78 ± 12.94 vs. 23.36 ± 13.15 ; $P < 0.05$).
- The mean QTc dispersion among the diabetics with retinopathy was significantly increased as compared to the control group (i.e., 38.67 ± 15.95 vs. 23.36 ± 13.15 ms; $P < 0.01$) and also between the diabetics without retinopathy group and the control group (35.93 ± 20.17 vs. 23.36 ± 13.15 ms, $P < 0.01$).
- Thus, QTc dispersion is found to be significantly elevated among the diabetics as compared to the controls and also found to be significantly associated with CAN (Table 1).

the presence of CAN increase significantly ($P < 0.001$) among the diabetics.

- On comparing the mean values of QTc parameters with the glycemic control in diabetes, dividing diabetic cases into two groups, first (Group 1) with HbA1C more than or equals to 6.5 and second (Group 2) with HbA1C more than 6.5. It was found that the mean QTc maximum, QTc minimum, mean QTc dispersion, and mean QTc dispersion percentage (%), all were significantly raised when Groups 1 and 2 were individually compared with the non-diabetic control group. Among the Groups 1 and 2, no significant difference was found, though increasing trends of QTc parameters with HbA1C was observed. Our findings are consistent with Psallas *et al.*,⁹ study, where HbA1C among the type-2 diabetics was $7.7 + 1.6$ and among the controls $5.6 + 0.6$ ($P < 0.05$), but no significant difference between the diabetics with CAN group and diabetics without CAN group.
- In our study, on comparing the QT interval (corrected) among the three groups - diabetics with CAN (Group 1), diabetics without CAN (Group 2), and control (Group 3), the mean QTc maximum, mean QTc minimum, mean QTc dispersion, and mean QTc Dispersion %, all were found to be significantly raised between Groups 1 and 3. Also between the Groups 2 and 3, values of mean QTc maximum and QTc minimum were found to be significant, but QTc dispersion though showed an increasing trend but was not statistically significant. And comparing between the Groups 1 and 2, the values of mean QTc dispersion and mean QTc dispersion percentage (%) was found to be significantly raised while mean QTc maximum and QTc minimum were showing an increasing trend but were not statistically significant, our results were consistent with another study.¹⁰ A study conducted by Chugh *et al.*,⁷ found that mean QTc maximum, mean QTc dispersion and dispersion % were highly significant between the diabetics with CAN and control groups and diabetics with CAN and diabetics without CAN groups, but not significant between diabetics without CAN and control groups. Thus, findings consistent with our study results.
- The principal finding of our study is that QT dispersion is significantly greater in patients with

DISCUSSION

- On correlating the duration of diabetes and presence of CAN, we found that longer the duration of diabetes,

Table 1: Comparison of mean QTc parameters with diabetics neuropathy

Study group	Mean QTc max	Mean QTc min	Mean QTc D	Mean QTc D percent
With CAN (n=69)	429.01**#±41.34	383.02*#±40.05	46.20***\$±17.66	12.05***\$±5.03
Without CAN (n=51)	418.72*±35.37	393.37**±33.07	25.37±10.01	6.45±2.57
Control (n=60)	390.20±40.30	367.43±38.12	23.36±13.15	6.37±3.75

* $P < 0.05$ (significant) versus control group. ** $P < 0.01$ (significant) versus control group, # $P > 0.05$ (non-significant) versus control group, # $P > 0.05$ (non-significant) versus without CAN group, \$\$ $P < 0.01$ (significant) versus without CAN group, CAN: Cardiac autonomic neuropathy

DM and autonomic dysfunction than in normal control subjects, and there was a trend for greater QT dispersion in diabetic patients with than without autonomic dysfunction.

CONCLUSION

- Cardiac autonomic dysfunction is a prevalent and serious microvascular complication for individuals with diabetes. Development and severity of CAN represents a continuous progression of disease, hence, its severity is directly related to duration and degree of hyperglycemia in DM.
- In our study, a significantly increased QTc interval and QTc dispersion among the diabetic cases as compared to the normal healthy controls suggests the higher risk for ventricular arrhythmias and sudden cardiac death among the diabetic's individuals. Since QT interval represents the ventricular repolarization, thus increased QT dispersion indicates toward the inhomogeneity of the myocardium, indicating toward the ventricular instability.
- QTc dispersion was also found to be significant among the diabetics with CAN as compared with the diabetics without CAN, indicating that QTc dispersion can be used as an easy, bedside indicator for the assessment of cardiac autonomic dysfunction and also as a prognostic marker for assessment of risk for ventricular arrhythmias, silent ischemia, and cardiac arrest among the diabetics.
- These findings suggest that diabetic patients with autonomic dysfunction have increased dispersion of ventricular refractoriness, which may be one of the factors contributing to the increased incidence of sudden death observed in these patients.¹¹ These observations also lend further support to the previous studies¹² demonstrating that many subsets of patients with increased QT dispersion are at increased risk for sudden death.
- Correlation of prolonged QTc interval with poor glycemic control has suggested that poor glycemic control among the diabetic individuals leads to the early manifestation of autonomic dysfunction. Also

in individuals with long-standing diabetes, QTc parameters were found to be prolonged suggesting the natural history of the disease and its progression to involve various other organs of the body with time.

- Early detection and early prevention of CAN is very essential in preventing diabetic individuals from increased risk of sudden cardiac mortalities. Thus, QTc dispersion can be used in future as an early indicator of the presence as well as severity assessment of the cardiac autonomic dysfunction, though further studies are required for the confirmation and authentication of the findings obtained during our study.

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