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Original Research Paper

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UTILITY OF THE CORRECTED QT INTERVAL PROLONGATION IN THE DIAGNOSIS OF THE CARDIAC AUTONOMIC NEUROPATHY IN THE TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Insulin resistance and abnormal insulin secretion are central to the development of Type 2 Diabetes Mellitus (T2DM). Diabetic Autonomic Neuropathy (DAN) is detrimental and currently a usual complication of Diabetes Mellitus (DM). Despite of its ability to cause sudden painless cardiac arrest and death in patients due to the cardiac autonomic instability, it is presumably underrated and untreated. The Cardiac Autonomic Neuropathy (CAN) is usually detected at a subclinical stage by means of several Cardiovascular Autonomic Reflex Tests (CART). An association between the Cardiac Autonomic Neuropathy (CAN) and the Corrected QT (QTc) interval prolongation & the use of the Corrected QT (QTc) interval prolongation as a relatively easier diagnostic tool was demonstrated in many studies. This study reinforces the aforementioned statement. **Aim:** To study the utility of the Corrected QT (QTc) interval in the diagnosis of the Cardiac Autonomic Neuropathy (CAN) in the Type 2 Diabetes Mellitus (T2DM) patients. **Objectives:** To assess the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients. To calculate the Corrected QT (QTc) interval in Type 2 Diabetes Mellitus (T2DM) patients. To correlate the Cardiac Autonomic Neuropathy (CAN) with the Corrected QT (QTc) interval prolongation in Type 2 Diabetes Mellitus (T2DM) patients. **Design and setting:** It was a prospective observational study conducted among the 100 Type 2 Diabetes Mellitus (T2DM) patients attending Rajah Muthiah Medical College and Hospital. **Methods:** The Cardiac Autonomic Neuropathy (CAN) among the 100 Type 2 Diabetes Mellitus (T2DM) patients was assessed by the Eving's five autonomic function tests. The Corrected QT (QTc) interval was calculated by Bazett's formula. The correlation between the Cardiac Autonomic Neuropathy (CAN) score and the Corrected QT (QTc) interval prolongation was analyzed. **Results:** In the study population, 68 had Cardiac Autonomic Neuropathy (CAN) and 48 had Corrected QT (QTc) interval prolongation. The sensitivity, specificity and positive predictive value of the Corrected QT (QTc) interval prolongation for the diagnosis of the Cardiac Autonomic Neuropathy (CAN) in the Type 2 Diabetes Mellitus (T2DM) patients were 66.2%, 90.6% and 93.8% respectively. Higher Cardiac Autonomic Neuropathy (CAN) scores correlated with longer Corrected QT (QTc) interval (p value of <0.05). **Conclusions:** The Corrected QT (QTc) interval prolongation in the Electro Cardio Graph (ECG) can be used to diagnose the Cardiac Autonomic Neuropathy (CAN) in the Type 2 Diabetes Mellitus (T2DM) patients with reasonable sensitivity, specificity and positive predictive value.

KEYWORDS : Type 2 Diabetes Mellitus, Diabetic Autonomic Neuropathy, Cardiac Autonomic Neuropathy, Cardiovascular Autonomic Reflex Tests, Corrected QT interval prolongation.

INTRODUCTION

Diabetes Mellitus (DM) is a group of common metabolic disorder which damages nearly all organ systems in the human body. It is estimated that the prevalence of Diabetes Mellitus (DM) in India is likely to go up to 57.2 million by the year 2025.[1]

The Cardio Vascular Diseases (CVD) are one among the most common complications of Diabetes Mellitus (DM) that increases the mortality in these patients. The Cardio Vascular Diseases (CVD) due to Diabetes Mellitus (DM) are classified into three groups namely Cardiac Autonomic Neuropathy (CAN), atherosclerotic Coronary Artery Disease (CAD) and diabetic cardiomyopathy.

The Cardiac Autonomic Neuropathy (CAN) is one among the common forms of Diabetic Autonomic Neuropathy (DAN) and causes abnormalities in the control of heart rate as well as the peripheral and central vascular dynamics, the clinical presentations of which includes orthostatic hypotension, intraoperative cardiovascular lability, exercise intolerance and painless myocardial ischemia contributing to morbidity, reduced quality of life and mortality among Diabetes Mellitus (DM) patients.[2]

The incidence of painless myocardial ischemia in diabetics seems to be very high and the Cardiac Autonomic Neuropathy (CAN) is the most probable reason for the absence of pain.[3] The risk of sudden cardiac death is high in patients with the Cardiac Autonomic Neuropathy (CAN).[4,5]

The Cardiac Autonomic Neuropathy (CAN) is one of the complications that develops slowly over the years. The prevalence of the Cardiac Autonomic Neuropathy (CAN) is reported to be high.[6,12,13] Several non-invasive tests like cardiac autonomic function tests by Eving's methodology,[7] analyses of spontaneous beat-to-beat blood pressure and heart rate variabilities,[8] downward tilting baroreflex sensitivity test,[9] a new indicator test based on the measurement of sweat production after exposure to dermal foot perspiration,[10] and time domain heart rate variability and heart rate turbulence parameters assessed on 24 hours digital Holter recordings,[11] are used for the diagnosis of the Cardiac Autonomic Neuropathy (CAN) Although these tests are sensitive and reproducible but they are laborious and time consuming, hence they are not the practical screening methods for the large number of patients with Diabetes Mellitus (DM).

In the Electro Cardio Graph (ECG), the Corrected QT (QTc) interval prolongation is found to be a specific indicator of the Cardiac Autonomic Neuropathy (CAN) in most studies,[5,12,17] but its reported sensitivity varied in different studies.[12,17-19] Moreover, the Corrected QT (QTc) interval prolongation has shown to predict the sudden cardiac death in Diabetes Mellitus (DM) patients.[4,20-25]

Patients and methods:

The study was done between March 2021 and February 2022. It was a prospective observational study among the 100 Type 2 Diabetes Mellitus (T2DM) patients attending Rajah Muthiah Medical College and Hospital, Chidambaram, Tamil Nadu, India.

Inclusion criteria:

The Type 2 Diabetes Mellitus (T2DM) patients more than 30 years of age, diagnosed according to the World Health Organization (WHO) criteria, already on treatment. Type 2 Diabetes Mellitus (T2DM) for the duration of more than or equal to 5 years. Both males and females were included in the study group.

Exclusion criteria:

History of hypertension, heart failure, valvular or congenital heart disease, renal dysfunction, thyroid disorders, acute stroke and history or Electro Cardio Graphic (ECG) evidence of Coronary Artery Disease (CAD). Electrolyte imbalance like hypokalemia or hypocalcaemia. Patients on drugs like beta blocker, digoxin and calcium channel blockers were excluded from this study.

Study procedure

The patients were interviewed and examined clinically in detail. The baseline biochemical and hematological investigations were done for all the Type 2 Diabetes Mellitus (T2DM) patients. The following Eving's five autonomic function tests[7] for detecting the Cardiac Autonomic Neuropathy (CAN) were performed in the enrolled patients: (1) The heart rate at rest (Heart rate of more than 100 beats/min at rest was taken as abnormal); (2) The blood pressure for orthostatic or postural hypotension (Initially the blood pressure was recorded in the supine posture and repeated just after 2 min of standing, a fall in the Systolic Blood Pressure (SBP) of more than 20 mm Hg and/ or Diastolic Blood Pressure of more than 10 mm Hg were taken as abnormal); (3) The response of heart rate to the valsalva maneuver (The Electro Cardio Graph (ECG) was continuously recorded during the procedure and the ratio of the longest RR interval during the release phase to the shortest RR interval during the straining phase was calculated and a value of less than 1.2 was taken as abnormal); (4) The response of heart rate to deep breathing (The Electro Cardio Graph (ECG) was continuously monitored while the patient was taking breath at a regular rate of 6 to 12 breaths/min and a difference in the heart rate of less than 15 beats/min between expiration and inspiration was taken as abnormal); and (5) The response of Diastolic Blood Pressure (DBP) to an isometric exercise (the patient was asked to squeeze a small ball in his/her left hand for about 5 min and an increase in the Diastolic Blood Pressure (DBP) of less than 15 mm Hg was taken as abnormal). The results of each of the above five tests for the diagnosis of the Cardiac Autonomic Neuropathy (CAN) were classified into the three separate groups based on the severity of the abnormality detected and each of them was given a definite point as described by Bellavere et al[14] (table 1).

Table 1: The Eving's five autonomic function tests

Autonomic function tests	Points
1. Blood pressure response to standing	
Fall of Systolic Blood Pressure >30 mmHg	1
Fall of Systolic Blood Pressure 20 – 30 mmHg	½
Fall of Systolic Blood Pressure < 20 mmHg	0
2. Blood pressure response to sustained hand grip	
Rise in Diastolic Blood Pressure < 10 mmHg	1
Rise in Diastolic Blood Pressure 10 – 15 mmHg	½
Rise in Diastolic Blood Pressure > 15 mmHg	0
3. Heart rate response to valsalva manoeuvre	
Value < 1.10	1
Value 1.10 – 1.2	½
Value > 1.2	0
4. Heart rate response to deep breathing	
< 10 beats per minute	1
10 – 15 beats per minute	½
> 15 beats per minute	0
5. Resting heart rate	
> 110 beats per min	1
100 – 110 beats per min	½
< 100 beats per min	0

Cardiac Autonomic Neuropathy (CAN) score determination

The total points from each of the aforementioned five tests were added and the Cardiac Autonomic Neuropathy (CAN) score[7,14] was segregated as follows: CAN score 0 (total points 0), CAN score 1 (points 0.5–1.5), CAN score 2 (points 2–3), and CAN score 3 (points ≥3.5). CAN was considered abnormal, borderline or normal if the CAN scores were ≥2, 1 or 0 respectively.[7]

Other tests performed

A 12 lead surface Electro Cardio Graph (ECG) (including the rhythm strip) was taken for the enrolled patients. The QT interval was calculated from the Electro Cardio Graph (ECG) of each participants and the value obtained was corrected for the heart rate to get the Corrected QT (QTc) interval in each of the 12 leads using the Bazett's formula. The maximum value of the Corrected QT (QTc) interval (QTc max) that is more than 440 ms was considered abnormal or prolonged. Other tests like complete blood count, renal function tests, serum electrolytes, glycosylated hemoglobin, thyroid function tests and echocardiography were also performed in the participants.

Estimation of the heart rate at rest
↓
Blood pressure response to standing
↓
Electro Cardio Graph (ECG) tracing for the determination of the Corrected QT (QTc) interval
↓
Assessing the response of heart rate to the valsalva maneuver
↓
Assessing the variability of heart rate to deep breathing
↓
Assessing the response of Diastolic Blood Pressure (DBP) to sustained handgrip

Flow chart 1: Algorithm for cardiac autonomic neuropathy

Data analysis

The collected data were analyzed with IBM.SPSS statistics software 23 version. For analysis of frequency of data in descriptive statistics continuous variables were analyzed using mean and standard deviation and categorical variables were analyzed as percentage. For the Multivariate analysis Oneway ANOVA with Tukey's Post - Hoc test was used. The Receiver Operator Characteristic (ROC) curve analysis was utilized to determine the sensitivity, specificity, positive predictive value and negative predictive value on comparison of the Corrected QT (QTc) interval with the Cardiac Autonomic Neuropathy (CAN) score. Chi-square test was used to find association among categorical variables. In all statistical tools the p value of less than 0.05 is considered as significant level.

RESULTS

Of the patients who attended Rajah Muthiah Medical College and Hospital during the study period, 100 patients who fulfilled the inclusion criteria were studied and their data were analyzed. The male:female ratio was 58:42. The abnormalities detected in the tests for the Cardiac Autonomic Neuropathy (CAN) are shown in the figure 1.

Out of 100 participants, 25 patients had a CAN score of ≥ 2, indicating abnormal CAN score; 43 had a CAN score of 1 (borderline CAN score) and 32 had a CAN score of 0 (normal CAN score).

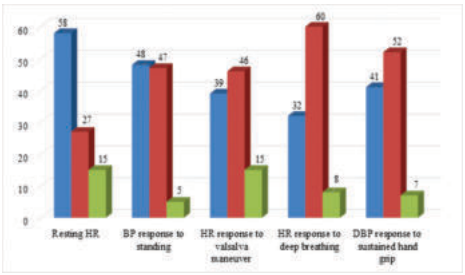

Figure 1: Results of the Cardiac Autonomic Neuropathy (CAN) tests

HR – Heart Rate; BP – Blood Pressure; DBP – Diastolic Blood Pressure Blue – Point 0; Brown – Point ½; Green – Point 1

Among the study group of 100 Type 2 Diabetes Mellitus (T2DM) patients, 48 had prolongation in the Corrected QT (QTc) interval (more than 440 milliseconds).

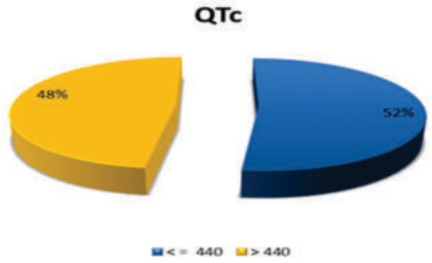

Figure 2: The Corrected QT (QTc) interval prolongation prevalence

QTc interval and CAN severity

The relationship between the Cardiac Autonomic Neuropathy (CAN) score and the Corrected QT (QTc) interval is depicted as follows

Table 2: QTc & CAN score cross tabulation

Qtc interval		CAN		Total
		Present	Absent	
Qtc	> 440	45	3	48
	≤ 440	23	29	52
Total		68	32	100

Out of 45 patients with the Cardiac Autonomic Neuropathy (CAN) and the Corrected QT (QTc) interval prolongation, 21 had an abnormal and 24 had borderline Cardiac Autonomic Neuropathy (CAN) score.

Table 3: Chi-Square tests

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.159[a]	2	.000
Likelihood Ratio	37.546	2	.000
Linear-by-Linear Association	32.023	1	.000
N of Valid Cases	100		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 12.00.

The Corrected QT (QTc) interval and the Cardiac Autonomic Neuropathy (CAN) score cross tabulation and comparison was done which showed statistical significance. Pearson Chi-Square value was 33.150 and likelihood ratio of 37.546 with p value of <0.05.

Table 4: Diagnostic utility of the Corrected QT (QTc) interval for the detection of the Cardiac Autonomic Neuropathy (CAN) among Type 2 Diabetes Mellitus (T2DM) patients

Prolonged QTc interval for detecting CAN	Type 2 Diabetes Mellitus % (95% CI)
Sensitivity	66.2
Specificity	90.6
Positive predictive value	93.8
Negative predictive value	55.8
Accuracy	74.0

The Corrected QT (QTc) interval prolongation had 66.2% sensitivity and 90.6% specificity in diagnosing the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients with a 93.8% positive predictive value, 55.8% negative predictive value and an accuracy of 74%.

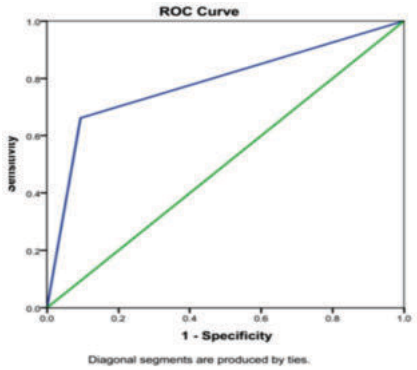

Figure 3: ROC (Receiver Operating Characteristic) curve for determining the diagnostic utility of the Corrected QT (QTc) interval prolongation in Type 2 Diabetes Mellitus (T2DM) patients.

From the above curve, area under curve was 0.754 with 95% Confidence Interval (CI) of 0.691 to 0.877. Thus the Corrected QT (QTc) interval prolongation is fair in diagnosing the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients.

DISCUSSION

The high prevalence of the Cardiac Autonomic Neuropathy (CAN) (68%) among the patients with Type 2 Diabetes Mellitus (T2DM) in our study was similar to the previous observations by Mehta et al (57.5%),[6] Tentolouris et al (62%),[12] and Thi et al (67.6%).[13] Various previous studies demonstrated that cardiac dysfunction is common in Type 2 Diabetes Mellitus (T2DM) patients and shows an increase in prevalence as the duration of Diabetes Mellitus increases.[26]

In our study, among 100 diabetics 42 females and 58 males were included after considering the exclusion and the inclusion criteria. Among 100 patients, 21 had duration of 5 - 10 years, 53 had duration of 10 - 15 years and 26 had duration of more than 15 years. Out of 100 participants, 34 had symptoms of Cardiac Autonomic Neuropathy (CAN) and rest 66 were asymptomatic.

In this study population 25 had an abnormal, 43 had borderline and 32 had normal Cardiac Autonomic Neuropathy (CAN) scores.

Out of 100 patients, 4.8%, 18.9% and 53.8% with 5 – 10 years, 10 - 15 years and >15 years of diabetes respectively showed an abnormal Cardiac Autonomic Neuropathy (CAN) score. Chi square tests showed that there is a significant relation between the duration of Type 2 Diabetes Mellitus (T2DM) and the Cardiac Autonomic Neuropathy (CAN) scores. Among 100 patients, mean Corrected QT (QTc) interval in patients with 5 – 10 years of diabetes was 428.29 (min-408, max-452), 10 - 15 years was 438.75 (min- 400, max-483) and >15 years was

454.27 (min-432, max-500). There was a statistically significant relation between the Corrected QT (QTc) interval and the duration of Diabetes Mellitus (DM). Post Hoc tests done for multiple comparisons between the duration of Diabetes Mellitus (DM) and the Corrected QT (QTc) interval as dependent variable also showed statistical significance with p value <0.05.

Mohan et al[26] from India studied the Cardiac Autonomic Neuropathy (CAN) in 336 patients which showed an increase in the prevalence of the Cardiac Autonomic Neuropathy (CAN) as the duration of Diabetes Mellitus (DM) increases. Pappachan J M et al[27] studies evaluated the usefulness of the Corrected QT (QTc) interval prolongation in the Electro Cardio Graph (ECG) to diagnose the Cardiac Autonomic Neuropathy (CAN) in patients with Diabetes Mellitus (DM). Sensitivity and specificity of the Corrected QT (QTc) interval prolongation in diagnosing the Cardiac Autonomic Neuropathy (CAN) were 76.5% and 75% in Type 2 Diabetes Mellitus (T2DM) patients. The study concluded that the Corrected QT (QTc) interval prolongation can be used to diagnose the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients with reasonable sensitivity and specificity.

In our study, the Corrected QT (QTc) interval prolongation had 66.2% sensitivity and 90.6% specificity in diagnosing the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients with a 93.8% positive predictive value, 55.8% negative predictive value and an accuracy of 74%. Thus, the Corrected QT (QTc) interval prolongation can be used as a relatively easier diagnostic tool.

This study has few important limitations. The sample sizes were relatively small. The patients with hypertension and nephropathy were excluded from the study because of their likelihood of having baseline Electro Cardio Graphic (ECG) abnormalities and also because these diseases interfere with the autonomic function tests. Diabetic patients with these diseases might have a greater risk for the Cardiac Autonomic Neuropathy (CAN).[13, 15, 16] Only about one third of the patients attending our hospital (Rajah Muthiah Medical College and Hospital) satisfied the inclusion criteria; hence the actual prevalence of the Cardiac Autonomic Neuropathy (CAN) among the total population of diabetics might have been greater.

CONCLUSIONS

The Cardiac Autonomic Neuropathy (CAN) is a common complication of Type 2 Diabetes Mellitus (T2DM). The Corrected QT (QTc) interval prolongation in the Electro Cardio Graph (ECG) has reasonable sensitivity, specificity and positive predictive value for the diagnosis of the Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus (T2DM) patients. The severity of the Cardiac Autonomic Neuropathy (CAN) has a correlation with the degree of the Corrected QT (QTc) interval prolongation. The Corrected QT (QTc) interval prolongation being a high risk factor for the major vascular events in the Type 2 Diabetes Mellitus (T2DM) patients, it should be assessed periodically by the 12 lead Electro Cardio Graph (ECG) in Type 2 Diabetes Mellitus (T2DM) patients.

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