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CORRELATION OF CORRECTED QT INTERVAL WITH CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Prolonged corrected QT (QTc) interval is an early marker of cardiac autonomic neuropathy (CAN), predisposing patients to arrhythmias, silent myocardial infarction, and sudden cardiac death. Early identification is crucial for preventing complications.

Materials and Methods: A cross-sectional study was conducted among 100 patients with type 2 diabetes mellitus. Fasting blood sugar (FBS), postprandial blood sugar (PPBS), and HbA1c were measured. Resting electrocardiography was performed, and QTc was calculated using Bazett's formula. Cardiac autonomic function was assessed using Ewing's battery of tests.

Results: The mean age was 50.54 ± 6.50 years with a slight female predominance (52%). QTc prolongation was observed in 66% of patients. Mean QTc was significantly higher in patients with HbA1c >6.5% (451.31 ± 33.87 ms) compared to those with HbA1c <6.5% (377.50 ± 37.72 ms). QTc showed a significant positive correlation with HbA1c ($r = 0.39$, $p = 0.004$) and duration of diabetes ($r = 0.34$, $p = 0.001$). Prevalence of definite CAN increased significantly with longer duration of diabetes ($p < 0.001$).

Conclusion: QTc prolongation is significantly associated with cardiac autonomic neuropathy in T2DM patients. QTc measurement can serve as a simple, non-invasive screening tool for early detection of CAN.

Keywords: Type 2 Diabetes Mellitus; QTc Interval; Cardiac Autonomic Neuropathy; Electrocardiography; HbA1c.

INTRODUCTION

Diabetes mellitus is a major global health problem, with an estimated 415 million individuals affected worldwide, of whom nearly 193 million remain undiagnosed. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of cases and is a leading cause of both microvascular and macrovascular complications, contributing significantly to morbidity, mortality, and healthcare burden.[1]

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Persistent hyperglycemia leads to long-term damage affecting multiple organ systems, including the cardiovascular and nervous systems[2]. Cardiac autonomic neuropathy (CAN) is one of the most serious yet underdiagnosed complications of diabetes, with prevalence increasing with longer duration of disease and poor glycemic control.[3]

CAN results from damage to autonomic nerve fibers innervating the heart and blood vessels, leading to abnormalities in heart rate regulation and vascular tone. It is strongly associated with increased risk of arrhythmias, silent myocardial ischemia, and sudden cardiac death.[4]

Electrocardiography (ECG) is a simple, non-invasive tool used to assess cardiac electrical activity. Among ECG parameters, the QT interval represents the duration of ventricular depolarization and repolarization. The corrected QT interval (QTc), adjusted for heart rate, is widely used in clinical practice to evaluate myocardial repolarization abnormalities.

The association between QTc prolongation and cardiac autonomic neuropathy was first described in 1980, establishing QTc as a potential marker for early detection of autonomic dysfunction[5]. Several studies

have demonstrated that QT interval prolongation is more common in diabetic patients with autonomic neuropathy and correlates with its severity.[6]

QTc prolongation has also been identified as a predictor of malignant ventricular arrhythmias and sudden cardiac death in diabetic patients.[7] The QT interval is influenced by multiple factors, including autonomic nervous system activity and glycemic status. Both hypoglycemia and hyperglycemia have been shown to prolong the QT interval, highlighting the role of metabolic control in cardiac electrophysiology.[8]

Recent studies suggest that prolonged QTc interval is an independent predictor of cardiovascular and all-cause mortality in patients with T2DM[9]. Despite its clinical importance, cardiac autonomic neuropathy often remains asymptomatic in early stages and may go undetected until advanced complications occur.

Bedside autonomic function tests, such as those described by Ewing and Clarke, provide a simple and non-invasive approach to assess autonomic dysfunction[10]. However, these tests are not always routinely performed in clinical practice.

Given the simplicity, accessibility, and cost-effectiveness of ECG, QTc interval measurement may serve as a valuable screening tool for early identification of cardiac autonomic neuropathy in patients with T2DM.

Prolonged QTc interval serves as an early indicator of cardiac autonomic dysfunction, which may lead to serious complications such as arrhythmias, silent myocardial infarction, and sudden cardiac death. Early identification may facilitate timely intervention and reduce morbidity and mortality.

Objectives

1. To evaluate the relationship between QTc interval and cardiac autonomic neuropathy in patients with type 2 diabetes mellitus
2. To assess the association between QTc interval and duration of diabetes

MATERIALS AND METHODS

Study Design and Setting;

This cross-sectional observational study was conducted at Narayana Medical College, Nellore, India, over a period of 18 months.

Study Population;

A total of 100 patients with type 2 diabetes mellitus (T2DM) attending the Medicine and Cardiology outpatient departments (OPD) and inpatients were included in the study. Participants were enrolled after obtaining written informed consent following a detailed explanation of the study protocol.

Inclusion Criteria;

- Patients diagnosed with type 2 diabetes mellitus
- Newly diagnosed as well as patients already on treatment

Exclusion Criteria

- Age >60 years
- Known ischemic heart disease
- Congenital heart disease
- Hypertension
- Chronic obstructive pulmonary disease
- Parkinsonism
- Uremia

Diagnostic Criteria for Diabetes Mellitus

Diagnosis of diabetes mellitus was based on the criteria laid down by the American Diabetes Association;

- Fasting plasma glucose ≥126 mg/dL, or
- 2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test, or
- Random plasma glucose ≥200 mg/dL with symptoms of hyperglycemia, or
- HbA1c ≥6.5%

Data Collection and Laboratory Investigations

All participants underwent detailed clinical examination and laboratory investigations.

Biochemical Analysis

- Fasting blood glucose (FBS): 2 mL venous blood collected in sodium fluoride vacutainer after at least 8 hours of fasting
- Postprandial blood glucose (PPBS): 2 mL venous blood collected 2 hours after a meal
- Samples were centrifuged at 3000 rpm for 5 minutes
- Blood glucose estimation was performed using the glucose oxidase–peroxidase method
- HbA1c: 2 mL venous blood collected in EDTA vacutainer and estimated using high-performance liquid chromatography (HPLC)

Additional Investigations

- Complete blood picture
- Complete urine examination
- Renal function tests
- Serum electrolytes
- Fasting lipid profile
- 12-lead resting electrocardiogram (ECG)

Electrocardiographic Assessment;

A standard resting 12-lead ECG was recorded in all participants under standardized conditions. Lead V2 was used for QT interval measurement.

The QT interval was measured from the onset of the QRS complex to the end of the T wave. The corrected QT interval (QTc) was calculated using Bazett's formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Normal QTc values were considered as:

- <440 ms in males
- <470 ms in females

QTc prolongation was defined as values exceeding these thresholds.

Autonomic Function Tests

Cardiac autonomic function was assessed using bedside tests described by Ewing DJ and Clarke BF. Participants were instructed to avoid caffeine on the day of testing, and recordings were performed 5–8 hours after meals. Blood pressure was measured

using a sphygmomanometer, and heart rate variability was assessed using ECG monitoring.
The following tests were performed:

- Heart rate response to deep breathing
- Valsalva maneuver
- Immediate heart rate response to standing (30:15 ratio)
- Blood pressure response to standing
- Blood pressure response to sustained handgrip

For deep breathing test, participants were instructed to breathe at a rate of six cycles per minute (5 seconds inspiration and 5 seconds expiration). Continuous ECG recording was obtained for one minute, and the difference between maximum and minimum heart rate was calculated.
Outcome Measures;

- QTc interval duration
- Presence and severity of cardiac autonomic neuropathy
- Correlation of QTc with glycemic parameters and duration of diabetes

Statistical Analysis
Data were analyzed using Microsoft Excel 2013. Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables.

- Student's t-test was used for comparison between groups
- Correlation analysis was performed to assess relationships between variables
- A p-value <0.05 was considered statistically significant at a 95% confidence interval

RESULTS

Table 1 shows the distribution of CAN scores across duration of diabetes. The prevalence of definite CAN increased significantly with longer duration of diabetes. Patients with duration >120 months had the highest proportion of definite CAN (58%), compared to 8% in those with duration <60 months ($p < 0.001$).

Table 1: Distribution of CAN Score by Duration of Diabetes

CAN Score	<60 months (n=34)	60–120 months (n=33)	>120 months (n=33)
0–1 (Normal)	24 (72%)	16 (48%)	9 (26%)
2–4 (Borderline)	7 (20%)	9 (28%)	5 (16%)
≥5 (Definite CAN)	3 (8%)	8 (24%)	19 (58%)

Out of 100 patients, 96% had HbA1c >6.5%, indicating poor glycemic control.
Patients with HbA1c >6.5% had significantly higher QTc intervals compared to those with HbA1c <6.5%.

Table 2: HbA1c Distribution

HbA1c	Frequency	Percentage
<6.5%	4	4%
>6.5%	96	96%

Table 3: QT and QTc Interval by HbA1c

HbA1c	QT (ms)	QTc (ms)
<6.5%	400	377.50 ± 37.72
>6.5%	476	451.31 ± 33.87

Electrocardiographic Parameters
The mean QTc interval in the study population was 456.96 ± 33.5 ms.

Table 4: ECG Parameters

Parameter	Min	Max	Mean	95% CI	Median	SD	SEM
RR interval (sec)	0.52	1.12	0.71	0.60–0.70	0.74	0.15	0.02
QT (ms)	320	480	383.2	371.2–395.1	360	42.06	5.94
QTc (ms)	380	504	456.96	447.4–466.4	467	33.5	4.74

Prevalence of QTc Prolongation
QTc prolongation (>440 ms) was observed in 66% of patients.

Table 5: QTc Prolongation

QTc Status	Frequency	Percentage
Present	66	66%
Absent	34	34%

Correlation Analysis
A significant positive correlation was observed between QTc interval and HbA1c ($r = 0.39$, $p = 0.004$). Similarly, QTc showed a significant correlation with duration of diabetes ($r = 0.34$, $p = 0.001$).

Table 6: Correlation of QTc with HbA1c

Variable	r value	p value
QTc vs HbA1c	0.39	0.004*

Table 7: Correlation of QTc with Duration of Diabetes

Variable	r value	p value
QTc vs Duration of DM	0.34	0.001*

Association between QTc and HbA1c

Mean HbA1c was significantly higher in patients with prolonged QTc compared to those without prolongation.

Table 8: Association between QTc and HbA1c

QTc Status	HbA1c (Mean ± SD)
Present	11.00 ± 2.89
Absent	9.08 ± 1.50

QT and QTc with Duration of Diabetes

QT and QTc intervals increased with longer duration of diabetes. The association was statistically significant.

Table 9: QT Interval by Duration of Diabetes

Duration	QT (ms)
<60 months	381.05 ± 35.70
60–120 months	360.00 ± 26.66
120–180 months	420.00 ± 84.85

ANOVA: F = 3.73, p = 0.03

Table 10: QTc Interval by Duration of Diabetes

Duration	QTc (ms)
<60 months	450.57 ± 35.38
60–120 months	452.20 ± 25.34
120–180 months	485.50 ± 26.16

ANOVA: p = 0.04

Association between CAN and QTc Prolongation

A significant association was observed between QTc prolongation and severity of cardiac autonomic neuropathy (p = 0.001). Patients with prolonged QTc had a higher prevalence of definite CAN.

Table 11: Association between QTc and CAN

QTc (ms)	Definite CAN	Borderline CAN	No CAN
≤440 ms	6 (20%)	15 (69%)	38 (80%)
>440 ms	24 (80%)	7 (31%)	10 (20%)

DISCUSSION

Type 2 diabetes mellitus (T2DM) is associated with a high risk of cardiovascular morbidity and mortality, largely due to accelerated atherosclerosis and autonomic dysfunction. Asian populations, particularly Asian Indians, demonstrate higher insulin resistance compared to Caucasians, even after adjusting for age, gender, and body mass index, contributing to increased cardiovascular risk.[11] The Framingham Heart Study identified diabetes as an independent risk factor for cardiovascular disease, associated with dyslipidemia, hypertension, and obesity, all of which promote atherosclerosis.[12]

Cardiac autonomic neuropathy (CAN) is a serious yet underdiagnosed complication of diabetes, resulting from damage to autonomic nerve fibers supplying the heart and blood vessels. This leads to abnormalities in heart rate variability and vascular tone, contributing to silent myocardial ischemia and sudden cardiac death[13]. The absence of classical anginal symptoms in diabetic patients is attributed to autonomic dysfunction, resulting in delayed diagnosis and poor prognosis of coronary artery disease (CAD).[14]

Silent myocardial infarction and sudden cardiac death are well-recognized consequences of diabetic autonomic neuropathy. Early detection of CAN is therefore essential to prevent progression and reduce mortality. However, CAN often remains asymptomatic in its early stages and may coexist with other neuropathies, making diagnosis challenging.[15]

The association between prolonged corrected QT (QTc) interval and cardiac autonomic neuropathy was first described in 1980, providing a simple and objective method for early detection of autonomic dysfunction[16]. Despite this, there remains limited data on the utility of QTc interval as a screening marker for CAN, particularly in the Indian population.

In the present study, the mean age of participants was 50.54 ± 6.50 years, with a slight female predominance (52%). A majority of patients had poor glycemic control, with 96% having HbA1c >6.5%. The prevalence of definite CAN increased significantly with duration of diabetes, from 8% in

patients with duration <60 months to 58% in those with duration >120 months ($p < 0.001$). These findings are consistent with previous studies demonstrating that CAN prevalence increases with disease duration and poor glycemic control.[17]

The mean QTc interval observed in this study was 456.96 ± 33.5 ms, and QTc prolongation (>440 ms) was present in 66% of patients. This is comparable to earlier reports showing a high prevalence of QTc prolongation among diabetic patients with autonomic dysfunction.[18]

A statistically significant positive correlation was observed between QTc interval and HbA1c ($r = 0.39$, $p = 0.004$), indicating that poor glycemic control contributes to prolonged ventricular repolarization. This finding is supported by studies demonstrating that both chronic hyperglycemia and glycemic variability influence cardiac electrophysiology and QT interval duration.[19]

Similarly, QTc interval showed a significant positive correlation with duration of diabetes ($r = 0.34$, $p = 0.001$), suggesting progressive autonomic dysfunction with longer disease duration. Chronic hyperglycemia leads to cumulative damage to autonomic nerve fibers, resulting in worsening CAN over time.[20]

In the present study, both QT and QTc intervals showed significant association with duration of diabetes. Patients with duration >120 months had the highest QTc values (485.50 ± 26.16 ms), indicating progressive impairment of cardiac autonomic function.

A strong association was also observed between QTc prolongation and severity of CAN. Among patients with QTc >440 ms, 80% had definite CAN compared to only 20% among those with QTc ≤440 ms ($p = 0.001$). This supports the hypothesis that QTc prolongation reflects underlying autonomic imbalance involving both sympathetic and parasympathetic dysfunction.[21]

Previous studies have established that QTc prolongation is an independent predictor of ventricular arrhythmias and cardiovascular mortality in diabetic patients.[22] It has also been shown to predict all-cause mortality. Although there is some variability in defining the upper limit of normal QTc, values >440 ms are generally considered clinically significant.

The findings of this study emphasize the role of QTc interval as a simple, non-invasive, and cost-effective screening tool for early detection of cardiac autonomic neuropathy. Given the widespread availability of ECG, QTc measurement can be easily incorporated into routine clinical evaluation of patients with T2DM.

Furthermore, diabetic patients are at increased risk of undiagnosed coronary artery disease due to absence of typical symptoms. Evidence suggests that cardiovascular risk in diabetic patients without prior myocardial infarction is comparable to that of non-diabetic individuals with previous myocardial infarction[23]. This highlights the importance of early detection of subclinical cardiovascular disease in diabetes.

CONCLUSION

Cardiac autonomic neuropathy (CAN) is a common complication among patients with type 2 diabetes mellitus in our study population, and its prevalence increases with the duration of diabetes and poor glycemic control. A significant association was observed between QTc interval prolongation and the presence as well as severity of CAN.

QTc interval, derived from a standard electrocardiogram, serves as a simple, non-invasive, and cost-effective tool for the early detection of cardiac autonomic dysfunction. Given its reasonable sensitivity and specificity, QTc measurement can be incorporated into routine clinical evaluation of diabetic patients for early identification of CAN.

Early screening and optimal glycemic control are essential to delay the onset and progression of autonomic neuropathy, thereby reducing the risk of serious cardiovascular complications such as arrhythmias, silent myocardial infarction, and sudden cardiac death.

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