

Original Research Article

The evaluation of QTc prolongation and QT dispersion in type 2 diabetes mellitus as an indicator of cardiac autonomic neuropathy

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ABSTRACT

Background: Diabetes mellitus refers to group of metabolic disorders characterized by hyperglycemia due to an absolute or relative deficit in insulin production or action. Diabetes mellitus produces pathological changes in most organs of the body including heart, blood vessels, kidneys, nerves and eyes. Cardiovascular autonomic neuropathy (CAN) is a severely debilitating yet underdiagnosed complication of diabetes. Diabetes-associated cardiovascular autonomic neuropathy damages autonomic nerve fibers that innervate the heart and blood vessels causing abnormalities in heart rate and vascular dynamics.

Methods: Total 80 cases of diabetes mellitus were selected. Cardiac autonomic neuropathy in them was diagnosed by a series of tests recommended by Ewing et al, which include - Valsalva ratio, Deep Breath Test, Heart rate response to standing, Postural Hypotension, SHGT Increase in diastolic BP on sustained hand grip. They were divided into 2 groups A and B depending on presence or absence of cardiac autonomic neuropathy. ECG was done to calculate QTc and QTd.

Results: In group A mean QTc was 0.344 sec and in group B in patients with mild CAN mean QTc was 0.432, moderate CAN mean QTc was 0.444, and in patients of severe CAN mean QTc was 0.481. p value was 0.001 that it is highly significant. Means more was degree of CAN more was prolongation of QT and similarly more the degree of CAN more was QTd.

Conclusions: Diagnosis of cardiac autonomic neuropathy by battery of cardiac autonomic function tests is a complex procedure. The prolongation of QTc interval and more specifically QTd interval on ECG is a marker in diagnosis of cardiac autonomic neuropathy which can be easily evaluated.

Keywords: Cardiac autonomic neuropathy, Diabetes mellitus, QTc interval

INTRODUCTION

Diabetes mellitus refers to group of metabolic disorders characterized by hyperglycemia due to an absolute or relative deficit in insulin production or action. There are two broad categories of DM, designated type 1 and type 2. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorder characterized by variable degree of insulin

resistance, impaired insulin secretion, and increased glucose production.¹

The disease burden related to diabetes is high and rising in every country, fueled by the global rise in the prevalence of obesity and unhealthy lifestyles. The latest estimates show a global prevalence of 382 million people with diabetes in 2013, expected to rise to 592 million by 2035.²

The injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). Diabetic retinopathy is a common microvascular complication of diabetes. The risk of developing diabetic retinopathy of diabetes depends on both the duration and the severity of hyperglycemia. Without intervention, diabetic patients with microalbuminuria typically progress to diabetic nephropathy. As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia.³ The central pathological mechanism in macrovascular disease is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction.⁴

Cardiovascular autonomic neuropathy (CAN) is a severely debilitating yet underdiagnosed condition in patients with diabetes. CAN damages autonomic nerve fibers that innervate the heart and blood vessels, in turn causing abnormalities in heart rate and vascular dynamics. It is known to affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes.⁵

Significantly underdiagnosed, cardiovascular autonomic neuropathy exhibits multiple clinical manifestations, such as orthostasis, resting tachycardia, exercise intolerance, silent myocardial infarction, and intraoperative cardiovascular liability. It is a severely debilitating complication that often decreases survival in patients with diabetes.⁶ Diabetes-related cardiovascular autonomic neuropathy results from complex interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death.⁷

Diabetes affects autonomic nerves in a length-dependent fashion. As a result, CAN often first manifests in the vagus nerve, the body's longest parasympathetic autonomic nerve and the one responsible for almost three-quarters of parasympathetic activity; damage to the vagus nerve causes resting tachycardia and an overall decrease in parasympathetic tone. In the later stages of cardiovascular autonomic neuropathy, sympathetic denervation occurs, starting from the apex of the ventricles to the base of the heart.⁸

Various manifestations are impaired heart rate variability, Resting tachycardia, Exercise intolerance, Intraoperative and perioperative cardiovascular instability, Orthostatic hypotension, Sudden death.⁹

Prolonged QT interval has been supposed to be one of the manifestations of cardiac autonomic neuropathy which can predispose to malignant ventricular arrhythmias and to sudden death from cardiac arrest. QT Interval is the interval from the beginning of the QRS complex to the

end of the T wave. It represents the total duration of the ventricular electrical activity that is the sum of ventricular contraction and relaxation. The QT interval shortens with tachycardia and lengthens with bradycardia due to shortening and lengthening of the myocardial refractory period. QT interval cannot be viewed in absolute terms but must be corrected for the effect of the associated heart rate.

The QT interval is corrected for what it would theoretically be at a rate of 60 bpm. The corrected QT interval is known as the QTc interval. Most frequently used formula is bazette formula. The normal value for QTc is 350-430 ms. The QT dispersion which is the difference between the longest and the shortest QT interval on 12 leads ECG. QT dispersion is measured by the difference between the longest and the shortest QT intervals. QT dispersion reflects regional variation in ventricular recovery. Increased dispersion of repolarization is known to be an important factor in the development of ventricular arrhythmias.¹⁰

Cardiac autonomic neuropathy can be detected by 5 thumb rule tests as advised by Ewing, which are cumbersome for the patient. Five non-invasive autonomic function tests as recommended by Ewing are deep breath test, heart rate response to standing (30:15 ratio), valsalva ratio, diastolic blood pressure rise with sustained hand grip, and postural hypotension on standing.¹¹

The objective of this study was to calculate QTc interval prolongation and QTc dispersion in cases of Diabetes mellitus with and without cardiac autonomic neuropathy, to evaluate the significance of QTc interval prolongation and QTc dispersion in the diagnosis of cardiac autonomic neuropathy in diabetics and to correlate severity of cardiac autonomic neuropathy with QTc interval prolongation and QTc dispersion.

METHODS

The present study was conducted on 80 cases of Type 2 Diabetes Mellitus with minimum of 5-year duration taken from indoor and outdoor patients visiting SGRD Hospital, Vallah. These was divided into 2 groups of 40 patients each. Group A included those patients without diabetic cardiac autonomic neuropathy as assessed by the cardiac autonomic function tests and Group B will include those who had diabetic cardiac autonomic neuropathy

Inclusion criteria

Type 2 Diabetes mellitus with minimum 5-year duration.

Exclusion criteria

- Hypocalcemia
- Hypothermia
- Hyperkalemia

- Hypokalemia
- Acute myocardial infarction
- Cerebral injury (head injury or intracerebral haemorrhage)
- Drugs (Procainamide, Quinidine, Disopyramide, Tricyclic antidepressants, Phenothiazines, Amiodarone, Sotalol).

Following five tests was done to confirm cardiac autonomic neuropathy,

- Heart rate variability during deep breathing (normal response >15 beats/minute, borderline 11-14 beats/minute; abnormal response <10 beats/minute).
- Immediate heart rate response to standing (normal response if >1.04; borderline between 1.01 and 1.03; and abnormal if <1.00).
- Heart rate response to Valsalva manoeuvre (Normal ratio is >1.21, abnormal 1.20 or less).
- Blood pressure response during sustained hand grip (normal response >16mmHg, borderline response 10-15mmHg, abnormal response <10mmHg).
- Blood pressure response to standing (normal response <10 mmHg, borderline response 11-29mmHg, abnormal response >30mmHg).

Based on the results of the above tests, the autonomic dysfunction in Type-2 diabetes mellitus patients is categorized as none, mild, moderate and severe, 12 lead ECG was recorded on all patients of both groups, QTc interval and QTc dispersion were calculated.

QT Interval is the interval from the beginning of the QRS complex to the end of the T wave. QT interval is corrected for the effect of the associated heart rate by BAZZET formula. The QT dispersion which is the difference between the longest and the shortest QT interval on 12 leads ECG (QT dispersion = QTmax - QTmin).

RESULTS

In group A, Age of patients ranged from 30-80years with mean age of 57.75±12.25. In group B, Age of patients ranged from 30-80 years with Mean age in 58.45±10.77 (Table 1).

Table 1: Age distribution.

Age group	Group A		Group B	
	No.	%	No.	%
30-40	3	7.50	3	7.50
41-50	11	27.50	9	22.50
51-60	9	22.50	12	30.00
61-70	11	27.50	11	27.50
71-80	6	15.00	5	12.50
Total	40	100.00	40	100.00
Mean age	57.75±12.25		58.45±10.77	
p-value	0.720			

In present study In Group A, F=26 (65%) and M=14(35%) while In Group B, F=20(50%) And M=20(50%). Thus, signifies that there was no gender difference for cardiac autonomic neuropathy (Table 2).

Table 2: Sex distribution.

Sex	Group A		Group B	
	No.	%	No.	%
Female	26	65.00	20	50.00
Male	14	35.00	20	50.00
Total	40	100.00	40	100.00
p-value	0.494			

In present study, in Group A mean duration of Diabetes mellitus was 10.77±4.14 and in Group B mean duration was 12.87±4.42. The p-value was 0.031 which was significant. This signifies that as the duration of diabetes increases the risk of patient having cardiac autonomic neuropathy increases (Figure 1).

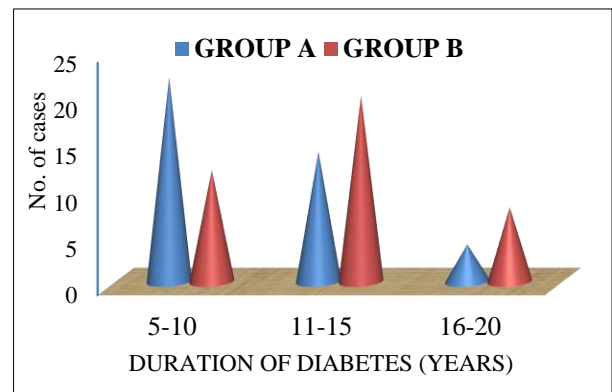


Figure 1: Duration of diabetes mellitus and cardiac autonomic neuropathy.

In group A mean HbA1c is 8.77±1.65 IN Group B patients with CAN mean HbA1c is 10.62±2.11. The p value is 0.001. So, the value of HbA1c is highly significant. As the HbA1c increases chances of patients having CAN increase (Figure 2).

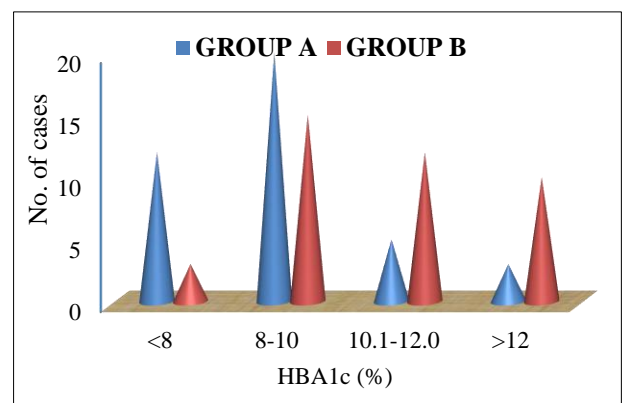


Figure 2: Correlation of HbA1c and cardiac autonomic neuropathy.

In present study In Group A 10% (4 out of 40) patients are having peripheral neuropathy and in Group B 45% (18 out of 40) patients are having peripheral neuropathy with p value of 0.001 which is highly significant means there is more chance of CAN positive patient having peripheral neuropathy (Table 3).

Table 3: Peripheral neuropathy and cardiac autonomic neuropath.

Peripheral neuropathy	Group A		Group B	
	No.	%	No.	%
Not present	37	90	22	55.00
Present	4	10	18	45.00
Total	40	100.00	40	100.00
p-value	0.001			

In present study In Group A 7.50% (3 out of 40) patients are having retinopathy and in Group B 37.50% (15 out of 40) patients are having retinopathy with p value of 0.001 which is highly significant means there is more chance of CAN positive patient having retinopathy (Table 4).

Table 4: Retinopathy and cardiac autonomic neuropathy.

Retinopathy	Group A		Group B	
	No.	%	No.	%
Not present	37	92.50	25	62.50
Present	3	7.50	15	37.50
Total	40	100.00	40	100.00
p-value	0.001			

In present study In Group A 7.50% (3 out of 40) patients are having nephropathy and in Group B 50% (20 out of 40) patients are having nephropathy with p value of 0.001 which is highly significant means there is more chance of can positive patient having nephropathy (Table 5).

Table 5: Nephropathy and cardiac autonomic neuropathy.

Nephropathy	Group A		Group B	
	No.	%	No.	%
Not present	37	92.50	20	50.00
Present	3	7.50	20	50.00
Total	40	100.00	40	100.00
p-value	0.002			

In present study VR is found in 5% of cases (2 out of 40) in group A patients and in 42.5% cases (17 out of 40) in group B patients, p-value is 0.001 means it is highly significant. Deep breath test was found in 2.5% of cases (1 out of 40) in group A patients and in 35% cases (14 out of 40) in group B patients, p-value is 0.001 means it is highly significant. Immediate Heart rate response to standing is found in 12.5% of cases (5 out of

40) in group A patients and in 37.5% cases (15 out of 40) in group B patients, p-value is 0.001 means it is significant.

Sustained hand grip was found in 17.5% of cases (7 out of 40) in group A patients and in 57.5% cases (23 out of 40) in group B patients, p-value is 0.002 means it is significant. Postural hypotension was found in 17.5% of cases (7 out of 40) in group A patients and in 85% cases (34 out of 40) in group B patients, p-value is 0.001 means it is significant (Table 6).

Table 6: Ewing’s cardiovascular autonomic function tests.

Ewing’s test	Group A	Group B
Valsalva ratio	5% (2 out of 40)	42.5% (17 out of 40)
Deep breath test	2.5% (1 out of 40)	35% (14 out of 40)
Immediate heart rate response to standing	12.5% (5 out of 40)	37.5% (15 out of 40)
Sustained hand grip test	17.5% (7 out of 40)	57.5% (23 out of 40)
Postural hypotension	17.5% (7 out of 40)	85% (34 out of 40)

In group A mean QTc is 0.344 sec and in group B in pts with Mild CAN mean QTc is 0.432, moderate can mean QTc is 0.444, and in patients of severe can mean QTc is 0.481(p value is 0.001). Means more is degree of can more is prolongation of QT (Figure 3).

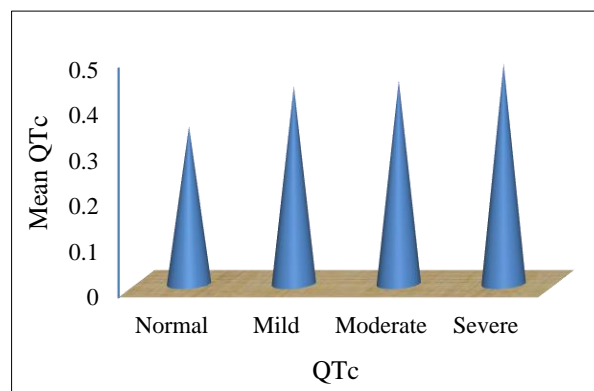


Figure 3: QTc interval and cardiac autonomic neuropathy.

Table 7: QT dispersion and cardiac autonomic neuropathy.

QTD	Mean	SD	p-value
Normal	0.043	0.059	
Mild	0.080	0.082	0.046
Moderate	0.088	0.078	0.034
Severe	0.097	0.081	0.033

In group A mean QTd is 0.043 sec and in group B in pts with Mild CAN mean QTd is 0.080, MODERATE CAN mean QTd is 0.088, and in patients of SEVERE CAN mean QTd is 0.097, p value is significant. Means more is degree of CAN more is dispersion of QT (Table 7).

DISCUSSION

Cardiac autonomic neuropathy is a common and often distressing complication of diabetes mellitus. It is found in one-third of type 2 diabetic patients. It results in postural hypotension, exercise intolerance, enhanced intraoperative instability, increased incidence of silent myocardial infarction and malignant ventricular arrhythmias.¹² Autonomic Neuropathy causes delay in ventricular depolarization and repolarization leading to prolongation of QT interval and QT dispersion in 12 lead ECG. In various studies it has been shown that cardiac autonomic neuropathy causes significant QTc interval prolongation and QTc dispersion. This study was aimed to find out the relation of corrected QT (QTc) interval and QTc dispersion with diabetic cardiac autonomic neuropathy in type 2 diabetics so that authors can identify a subset of diabetic patients who are at high risk for sudden cardiac death.¹³

The present study was conducted on 80 patients of Type 2 Diabetes Mellitus with minimum of 5-year duration. They were divided into 2 groups of 40 patients each. Group A include patients without diabetic cardiac autonomic neuropathy and Group B include those with diabetic cardiac autonomic neuropathy as assessed by the cardiac autonomic function tests. CAN in them was diagnosed by a series of tests recommended by Ewing et al (deep breath test, heart rate response to standing, valsalva ratio, diastolic blood pressure rise with sustained hand grip, and postural hypotension on standing). Then all the patients are divided according to the scoring system. A score of 0-2 was assigned to each test. The sum of scores obtained from each test was used to classify them into cardiac autonomic neuropathy involvement grades. Score of 0-1 was given as no CAN, score of 2 as mild, 3-4 as moderate and 5 and more as severe CAN.

In group A, age of patients ranged from 30-80 years with mean age of 57.75 ± 12.25 . Majority of the patients belonged to 4th to 6th decades of life. In group B, Age of patients ranged from 30-80 years with mean age in 58.45 ± 10.7 , with majority of patients between 51-60 years of age. It was comparable to the study conducted by Pillai et al, with mean age in the group A was 52.2 ± 7.2 years and that in group B was 55.2 ± 8.2 years.^{13,14} While in the study conducted by Khoharo et al, the mean age was 47 ± 13 years.¹⁵ In group A, 26 (65%) were females and 14 (35%) were males while in group B, 20 (50%) were females and 20 (50%) were males. In study conducted by Khoharo et al, total of 186 patients with type 2 diabetes were studied, comprising 98 (52.68%) males and 88 (47.31%) females. In present study, in group A mean

duration of Diabetes mellitus was 10.77 ± 4.14 and in group B mean duration was 12.87 ± 4.42 , p-value was 0.031 which was significant. This signifies that as the duration of diabetes increases the risk of patient having cardiac autonomic neuropathy increases. In study conducted by Pillai et al, mean duration after diagnosis of diabetes was 10.9 ± 4.1 years in the autonomic neuropathy group and 8.1 ± 3 in the no autonomic neuropathy group ($p < 0.05$, statistically significant). In group A mean HbA1C was 8.77 ± 1.65 and in group B mean HbA1c was 10.62 ± 2.1 . The p value was 0.001 which was statistically significant thus as the level of HbA1c increases risk of patients having cardiac autonomic neuropathy increases. In Study conducted by Takebayashi et al, in group A mean HbA1C was 5.1 ± 0.7 and in group B patients mean HbA1C was 9.2 ± 2.2 .¹⁶

In Group A 7.50% (3 out of 40) patients were having retinopathy and in Group B 37.50% (15 out of 40) patients were having retinopathy with p value of 0.001 which was highly significant means there is more chance of retinopathy in patients having cardiac autonomic neuropathy. In study conducted by Ewing et al, he found retinopathy in 45% (32 out of 73) of diabetic patients.¹⁷ In this study, in group A 7.50% (3 out of 40) patients were having nephropathy and in Group B 50% (20 out of 40) patients were having nephropathy with p value of 0.001 which is highly significant means more chance of nephropathy in patients having cardiac autonomic neuropathy.

In study conducted by Ewing et al, he found nephropathy in 36% (26 out of 73) of diabetic patients. In this study, in group A 10% (4 out of 40) patients were having peripheral neuropathy and in group B 45% (18 out of 40) patients were having peripheral neuropathy with p value of 0.001 which was highly significant means more chance of peripheral neuropathy in patients having cardiac autonomic neuropathy. In study conducted by Ewing et al, he found nephropathy in 51% (37 out of 73) of diabetic patients. In present study VR was found in 5% of cases (2 out of 40) in group A patients and in 42.5% cases (17 out of 40) in group B patients, p -value was 0.001 means it was highly significant. Ewing et al, found abnormal valsalva ratio in 62% cases of diabetics studied by them. Barthwal et al, found abnormal valsalva ratio in 22.3% of cases.¹⁸ In present study deep breath test was found in 2.5% of cases (1 out of 40) in group A patients and in 35% cases (14 out of 40) in group B patients. p-value is 0.001 means it was highly significant. Barthwal et al, found abnormal deep breath test in 38.3% of cases.

In present study Immediate Heart rate response to standing was found in 12.5% of cases (5 out of 40) in group A patients and in 37.5% cases (15 out of 40) in group B patients, p-value was 0.001 which means it was highly significant. Barthwal et al, found abnormal Immediate Heart rate response to standing in 17% of cases. In present study, Sustained hand grip was found in 17.5% of cases (7 out of 40) in group A patients and in

57.5% cases (23 out of 40) in group B patients, p-value is 0.002 means it was significant. Ewing et al, found abnormal S.H.G test in 45% of cases. Barthwal et al, found abnormal S.H.G test in 14.9% of cases. Mathur et al, found abnormal S.H.G test in 8% of cases. Postural hypotension was found in 17.5% of cases (7 out of 40) in group A patients and in 85% cases (34 out of 40) in group B patients, p-value was 0.001 means it was significant.¹⁹

In study conducted by Ewing et al, postural hypotension was found in 69% of cases. In this study, in group A mean QTc was 0.344 sec and in group B in patients with mild CAN mean QTc was 0.432, moderate CAN mean QTc was 0.444, and in patients of severe CAN mean QTc was 0.481 (p value is 0.001). Means more is degree of cardiac autonomic neuropathy more is prolongation of QT. Neki et al, found mean QTc to be 0.402 ± 0.028 seconds in mild degree CAN, 0.416 ± 0.032 seconds in moderate degree CAN, 0.428 ± 0.032 seconds in severe CAN.²⁰ In group A mean QTd was 0.043 sec and in group B in patients with mild CAN mean QTd was 0.080, moderate CAN mean QTd was 0.088, and in patients of severe CAN mean QTd was 0.097, p value was significant. Means more is degree of CAN more was dispersion of QT. Malik et al, found mean QTd value in mild, moderate and severe cases of cardiac autonomic neuropathy as 0.085-0.095 seconds, 0.09-0.10 seconds and 0.095- 0.15 seconds respectively.²¹ QTd prolongation is more significant indicator of cardiac autonomic neuropathy in diabetes patients.

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