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**Original research article**

# Research on the role of the corrected QT interval in the diagnosis of cardiovascular autonomic neuropathy in type 2 diabetic mellitus

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**Abstract**

**Background:** India is sometimes called the "diabetic capital of the world" due to the country's alarmingly rising rate of diabetes mellitus. Worldwide, Type 2 Diabetes has become a serious health issue.

**Material and Methods:** From the pool of Type 2 Diabetics receiving care at NRIIMS's General Medicine Department in Visakhapatnam, 100 patients met the study's inclusion and exclusion criteria. From October 2021 to December 2022, a full year of data was collected for this investigation.

**Results:** This study's findings add to the growing body of evidence showing that cardiac autonomic dysfunction is widespread among diabetic patients. Multiple investigations, some of which were carried out in India, have found findings that are consistent with one another. Using validated but basic measures of cardiovascular autonomic function, this study showed severe anomalies in autonomic function.

**Conclusion:** The study found the following results, our hospital's research group found a high prevalence of cardiovascular autonomic neuropathy among type 2 diabetes. As diabetes progresses, so does the risk of developing CAN.

**Keywords:** Diabetes mellitus, autonomic neuropathy, cardiovascular, interval, and diagnosis

## Introduction

Diabetes mellitus (DM) is becoming increasingly common in India, earning the country the nickname "diabetic capital of the world." One of the world's leading health concerns is type 2 diabetes [1]. According to the World Health Organization, there were 31.7 million people with diabetes in India in 2000, and that figure is expected to rise to 79.4 million by 2030 [2].

Secondary route physiological abnormalities in numerous organ systems caused by metabolic dysregulation in people with DM are associated with high morbidity and place a significant burden on the healthcare system if they are not treated promptly and effectively. One of the most common problems that increases mortality in these people is cardiovascular disease. Atherosclerotic coronary artery disease (CAD), diabetic cardiomyopathy (DCM), and cardiac autonomic neuropathy (CAN) [3] are the three main cardiovascular consequences of DM.

While many people with diabetes experience autonomic dysfunction, clinical autonomic neuropathy is quite uncommon. Silent myocardial infarction and unexpected death among diabetics are caused by CAN. Therefore, it is important to recognize asymptomatic cardiac dysautonomia early to assist slow or stop its progression. DAN's significance has not been fully acknowledged [4], despite its correlation with an elevated risk of cardiovascular mortality and its association with various symptoms and impairments.

These days, diagnosing dysautonomia typically involves testing autonomic functions. There is no need for expensive machinery or intrusive procedures for these examinations. The only things you'll need are a sphygmomanometer, a heart rate monitor, and an electrocardiogram machine. A basic non-invasive electrocardiogram (ECG) and blood pressure monitor are useful for identifying asymptomatic cardiac autonomic neuropathy. Postural hypotension and inadequate cardio vascular reflex tests are independently associated with an increased risk of death in patients with type 2 diabetes.Glycemic control in type 1 diabetes and hypertension, dyslipidemia, obesity, and poor glycemic control in type 2 diabetes are well-established risk factors for CAN. CAN is a potential progression promoter of diabetic nephropathy [5], as well as a risk marker of mortality and cardiovascular morbidity.

In 1980, researchers noticed for the first time that a longer QTc interval was linked to cardiac autonomic neuropathy, opening the door to the potential of a fast, objective method for detecting the condition. Further research showed that patients with diabetes mellitus who had a longer QTc interval also had cardiac dysautonomia [6]. The goals of this study are to (1) determine the prevalence of cardiovascular autonomic neuropathy in relation to diabetes duration in our hospital and (2) evaluate the diagnostic

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value of the corrected QT interval. The purpose of this research was to determine how common Cardiovascular Autonomic Neuropathy is among our hospital's Type 2 Diabetes patients. Examining how long someone has had diabetes in connection to their level of Cardiovascular Autonomic Neuropathy. Researching how Cardiac Autonomic Neuropathy affects the QTc interval.

**Materials and Methods**

From the population of Type 2 Diabetics admitted to the NRIIMS, Visakhapatnam, General Medicine department, a total of 100 patients who met the inclusion and exclusion criteria were included in the study. Based on how long they'd had diabetes, the patients were divided into three categories. In the Medical ward, a patient's autonomic neuropathy was evaluated using an electrocardiogram (ECG) monitor, a pulse oximeter, and a sphygmomanometer. Using the data we had, we compared each group to the others. From October 2021 until December 2022, this study was done.

**Study design**

This cross-sectional study aims to determine the prevalence of cardiovascular autonomic neuropathy in people with Type 2 diabetes and examine any associations between the presence of this condition and the duration of the disease. The purpose of this study was to look at the correlation between cardiac autonomic dysfunction and the corrected QT interval. Patients were told to avoid consuming anything with caffeine on the day of their tests. Generally speaking, recordings are made anywhere from five to eight hours after a meal. Standard sphygmomanometers were used to manually record blood pressure. A regular HRM, pulse oximeter, and a continuous ECG recording were used to derive the HRV. The QTc interval was determined from a baseline ECG recorded using a conventional ECG machine. In their 6th edition of their book, Ewing and Clarke outlined the bedside tests used to evaluate the autonomic nervous system. All patients were given the five exams detailed below.

A mercury sphygmomanometer was attached to a 20 ml syringe, and the patient was instructed to sit quietly while maintaining a blood pressure of 40 mm Hg for 10 seconds by blowing into the syringe's empty barrel. The ratio between the highest possible heart rate during blowing and the lowest possible heart rate when in compensatory bradycardia after stopping is determined.

Alternatively, one can determine the ratio by comparing the R-R interval of the 30th beat after standing to that of the 15th beat. The subject's supine blood pressure was measured using a sphygmomanometer. After a minute of standing, blood pressure was taken once more. The difference between the systolic pressure while lying down and while standing up was used to calculate the postural drop in blood pressure. The average systolic blood pressure was determined after three measurements were taken.

Prior to the procedure, the patient's blood pressure was taken thrice. The handgrip was made possible by a modified sphygmomanometer. The doctor instructed the patient to squeeze the rubber balloon with all his or her might. During this period of peak voluntary effort, a mercury manometer reading was collected. The patient was then instructed to hold a contraction of 30% of their maximum voluntary strength for up to five minutes. Throughout the course of the handgrip, blood pressure was monitored every minute. The outcome was reported as a percentage, calculated by subtracting the patient's highest diastolic blood pressure reading from their average diastolic blood pressure reading before beginning the handgrip exercise three times. This questionnaire complemented the bedside tests well since cardiac autonomic neuropathy is frequently accompanied by other signs of autonomic neuropathy.

**Inclusion Criteria:** Type 2 diabetics already on treatment and newly diagnosed T2DM patients.

**Exclusion Criteria**

- Age above 60 years
- Documented ischaemic heart disease
- Documented valvular or congenital heart disease
- Hypertension
- COPD
- Uraemia
- Parkinsonism

**Statistical Analysis**

Statistical analysis was carried out for 100 patients. Interpretation of the results and QTc interval were analyzed. One way Analysis of Variance (ANOVA) was performed for comparison of means of more than two groups. The significance of difference between the proportions was indicated by the Chi-square statistic. The significance of difference in mean between the groups was calculated by student T-test. Variables were considered to be significant. Intervariate analysis was done by using Pearson’s R- value correlation.

**Results**

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The study group consists of 100 patients with Type 2 diabetes. The following tables list the information about the age variation and gender distribution of the study group. The patients were divided into 3 groups depending on duration of diabetes were taken.

**Table 1:** Age variation among study groups

| Duration of DM | N | Mean Age | SD |
|---|---|---|---|
| < 5 yrs | 33 | 50.27 | 2.63 |
| 5-10 yrs | 33 | 51.94 | 2.11 |
| >10 yrs | 34 | 54.91 | 1.99 |

There is significant difference in the age between all the 3 groups. Between 1st and 2nd group, value of p=0.001 between 2nd and 3rd group.

**Table 2:** Gender distribution among study groups

| Duration of DM | | <5 yrs. | | 5-10 yrs. | | >10 yrs. | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| Gender | Male | 18 | 54 | 19 | 58 | 19 | 56 |
| | Female | 15 | 46 | 14 | 42 | 15 | 44 |
| Total | | 33 | 100 | 33 | 100 | 34 | 100 |

Among 100 patients, 56 patients were men and remaining 44 were women. There is no significant difference in duration of diabetes mellitus and the sex of the person. Mean age of patients in the groups A, B and C were 50.27, 51.94 and 54.91 respectively. This shows there is significant variation in age among the three groups. As the duration of DM2 increases, naturally the mean age of the patients also increases. Hence it is significant.

**Cardiovascular autonomic dysfunction study group**

In the study population, the prevalence of definite CAN was 8%, 24% and 58% in group A, B and C respectively. The prevalence of definite CAN increases with increase in duration of diabetes.

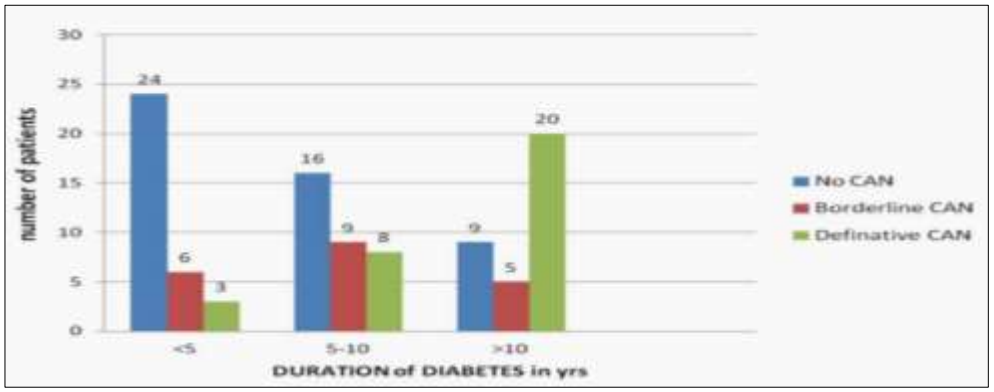


**Fig 1:** Frequency distribution of patients on the basis of CAN score

**Table 3:** Mean QTc in three study groups

| Duration of DM | | n | MEAN | SD |
|---|---|---|---|---|
| **< 5 yrs** | | 33 | 410.03 | 52.92 |
| **5-10 yrs** | | 33 | 425.61 | 42.71 |
| **>10 yrs** | | 34 | 462.62 | 55.32 |

These observations tell us as the as the duration of diabetes type 2 increases QTc goes on becoming prolonged.

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**Table 4:** QTc result with diagnosis

| Screening test Results QTc | Interpretation | | Total |
|---|---|---|---|
| | Definitive CAN + ve | CAN -ve | |
| >440 | 25 | 11 | 44 |
| < 440 | 6 | 38 | 36 |
| Total | 31 | 49 | 80 |

The QTc values are correlated with the interpretation obtained from the Cardiac autonomic function tests. From the table the Sensitivity the True positives is calculated as 80% and the Specificity the True negatives is calculated as 78.08%.

**Correlation between cardiac autonomic neuropathy**

From the table, QTc interval prolongation occurs with development of CAN. Prolongation of QTc interval is well correlated with Cardiac Autonomic Neuropathy.

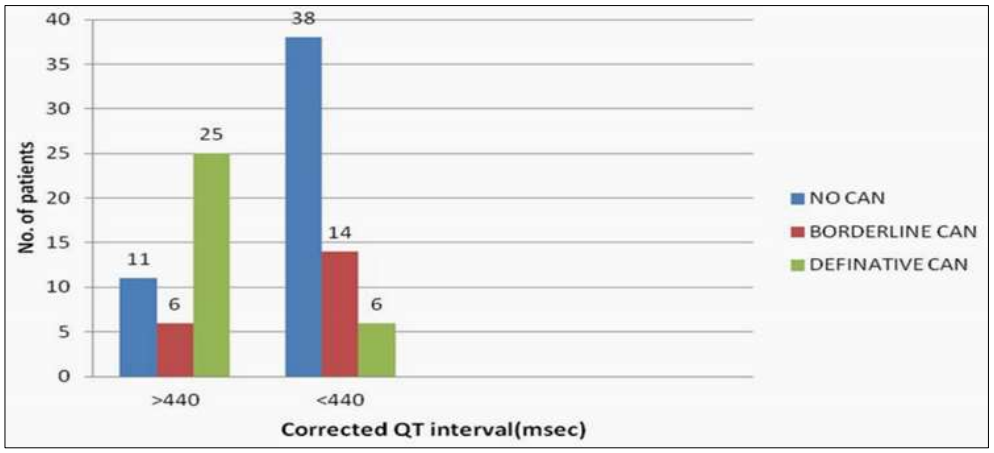


**Fig 2:** Correlation between cardiac autonomic neuropathy and QTc interval

**Percentage of symptomatic and asymptomatic**

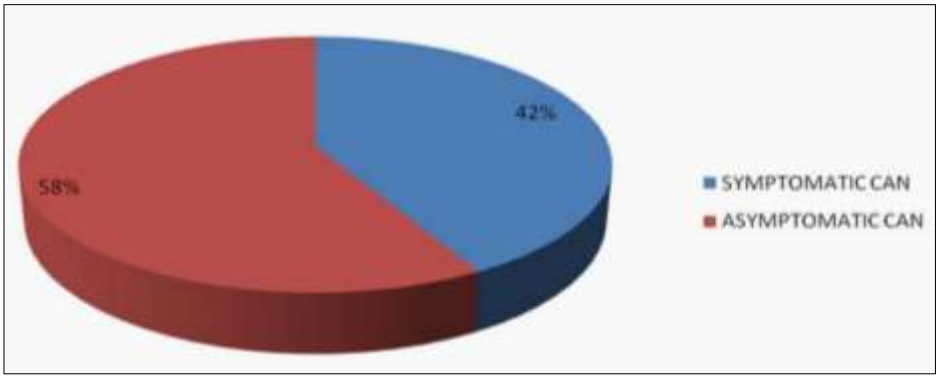


**Fig 3:** Percentage of symptomatic and asymptomatic CAN+ve patients

**Discussion**

This study's findings add to the growing body of evidence showing that cardiac autonomic dysfunction is widespread among diabetic patients. Previous investigations in India and elsewhere have found similar outcomes [7, 8]. Using validated but basic measures of cardiovascular autonomic function, this study showed severe anomalies in autonomic function. The sensitivity of autonomic function tests was researched and published by Vinik et al. on a cohort of 3516 patients with type 1 and type 2 diabetes. HRV during deep breathing tests and Valsalva was found to have a sensitivity of 98% and 93%, respectively [9-12].

With a sensitivity of 96.77% and a specificity of 93.54%, respectively, presented values show that aberrant heart rate variability during deep breathing is present in 30 of 31 patients with definite CAN. Early autonomic neuropathy4 is characterized by abnormal heart rate variability (HRV) during deep breathing. The risk of silent myocardial ischemia and mortality4 is highly correlated with lower levels of cardiovascular autonomic function, as evaluated by HRV, according to a meta-analysis of published data. The incidence of CAN was investigated by Mohan et al. [12] in 336 patients with type 2 diabetes mellitus

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in southern India. The prevalence of CAN increased as diabetes lasted longer. The prevalence of autonomic dysfunction was 28.2% in children aged 0-5 years. Our research found that 28 percent of children aged 0-5 experienced autonomic dysfunction; of these, 8 percent were diagnosed with definite CAN and 20 percent showed signs of borderline or early CAN.

Autonomic neuropathy in type 2 diabetes was investigated by Toyry J P et al, [9]. After 5 and 10 years of follow-up, 133 newly diagnosed T2DM patients and 144 healthy controls (62 men) were re-examined. Long-term diabetes was associated with a higher incidence of cardiovascular autonomic neuropathy. Pappachan J M et al, [3] used the five autonomic function tests outlined in Ewing's technique to determine the prevalence of CAN among 100 people with type 1 and type 2 diabetes mellitus in south India. Similar to the results of this study (51%), the prevalence of CAN was 60%.

Similar to our findings, Vinik et al. discovered that parasympathetic damage occurs before sympathetic damage in diabetic cardiovascular autonomic neuropathy. Thus, prior to blood pressure tests, abnormalities appear on autonomic tests assessing the parasympathetic system, such as the Heart Rate Variability (HRV) to deep breath, Valsalva maneuver. Our research shows that anomalies in HRV are common among those with borderline CAN, although hypertension is uncommon. The significance of HRV testing as a screening tool for early autonomic impairment in diabetes is underlined once more by these findings. Autonomic dysfunction symptoms were evident in only 13 of the 31 individuals (42.22%) with confirmed CAN. Nearly 58% of patients with confirmed CAN did not exhibit any symptoms. This exemplifies why even in asymptomatic diabetics, screening for autonomic dysfunction is crucial. Silent myocardial infarction and sudden death are common in patients with significant cardiac autonomic dysfunction [13].

In addition, among the 49 individuals who did not have CAN, 9 (19.1%) showed signs of autonomic dysfunction. Autonomic neuropathy manifests itself clinically years after diabetes has been present. Although autonomic dysfunction-like symptoms are widespread, they are not always attributable to autonomic neuropathy [4]. According to research by Chen H S et al. [17], patients with abnormal CVR tests had a worse 8-year survival rate (63.6% in men and 76.4% in females) compared to those with normal CVR tests (80.9% and 93.3%, respectively). Patients with Type 2 diabetes and abnormal CVR testing may have an elevated risk of death, and those with postural hypotension and an abnormal CVR have an even higher risk of death. In people with Type 2 diabetes mellitus, abnormal CVR testing may be a major predictor of mortality. However, type 2 diabetes patients can develop subclinical autonomic dysfunction within a year of diagnosis, and type 1 diabetic patients can develop it within two years of diagnosis [4].

Massin et al. [14] showed that the beginning of puberty is a crucial time for the onset of CAN, and they recommended that all type 1 diabetes patients start screening for CAN at this point. To establish a baseline, Vinik et al. [4] suggested measuring HRV at the time of type 2 diabetes diagnosis and within 5 years after type 1 diabetes diagnosis (unless an individual has symptoms suggestive of autonomic dysfunction earlier). By providing early detection, regular HRV testing encourages prompt diagnostic and treatment measures. There were patients with borderline or early autonomic dysfunction, and this information can motivate both the patient and the doctor to work on better metabolic control and to employ medications like ACE inhibitors and ß-blockers, which have been shown to be useful for patients with CAN. Twenty (20%) of the 100 patients tested were diagnosed with borderline dysfunction; this number increased to 28% in the 5-10 year group and 32% in the longer duration group. The process of managing patients and ultimately changing outcomes begins much before the identification of these high-risk individuals. Once a problem has been recognized, it has to be managed properly. When individuals at high risk or those shown to be in early stages are not treated until extensive symptomatology is apparent, nothing has been done, therefore preventative actions are necessary. Researchers have found that maintaining blood sugar levels at or near normal levels is the best method to halt the course of CAN and delay its onset. Tight glycemic management, including reeducation of the patient about the need for regular monitoring and hypoglycemia, is thus crucial for those with autonomic dysfunction. End organ prevention, including ACE inhibitors and aspirin use, and pharmaceutical and non-pharmacological therapies to enhance blood pressure and lipid control, may be accelerated if autonomic dysfunction in diabetic patients is detected early. Patients with diabetes who are found to have autonomic nerve dysfunction can also benefit from better nutrition and less alcohol and tobacco use [4-6].

When CAN is diagnosed early, treatment with alpha-lipoic acid and vitamin E, two antioxidants that appear to reduce or prevent the course of neuropathies in some studies [13], can begin sooner. Out of 31 individuals with confirmed CAN, the ECG shows a prolonged corrected QT interval in 25 (80% sensitivity, 78% specificity).A statistically significant link was found between CAN and QTc prolongation in this research. QT prolongation in the electrocardiogram (ECG) has been studied for its potential in the diagnosis of CAN in diabetic patients by Pappachan J M et al, [14-16]. QTc prolongation was found to have a sensitivity of 77% and a specificity of 62.5% in detecting CAN in patients with type 1 diabetes, and a sensitivity of 75% and a specificity of 75% in patients with type 2 diabetes. They determined that the QTc interval in ECG is a reliable diagnostic tool for CAN. Our research found a similar relationship between sensitivity and specificity for QTc (80% and 78%, respectively).

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To better understand the correlation between CAN and QTc interval, C P Mathur et al. [17] compared 50 diabetic patients to 20 healthy controls. Among the 19 diabetics with CAN, 15 had QTc prolongation (78.94%). QTc prolongation was not found in either CAN-free diabetics or healthy controls. A sensitivity of 82.6% and a specificity of 100% were measured. Our findings are consistent with this sensitivity value, but there is no correlation with the specificity value.

**Conclusion**

The findings of this investigation are as follows: The research group from our hospital has a significant prevalence of type 2 diabetics with cardiovascular autonomic neuropathy. As the duration of diabetes lengthens, so will the prevalence of CAN. After ten years, autonomic dysfunction affects almost 50% of type 2 diabetes patients. QTc prolongation is significantly associated with autonomic dysfunction of the cardiovascular system. Heart autonomic neuropathy can be diagnosed with some degree of sensitivity using the ECG QTc interval.

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**Conflict of interest:** None

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