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A STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE-2 DIABETES MELLITUS THROUGH BESIDE TEST (EWINGS BATTERY) AND USE OF QTc INTERVAL IN ITS PREDICTION.

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Abstract

Background: Cardiac autonomic neuropathy (CAN) is a common but underdiagnosed complication of Type 2 Diabetes Mellitus (T2DM), associated with increased cardiovascular morbidity and mortality. Early detection using simple clinical and electrocardiographic markers is essential for timely intervention. ***Objective:*** To determine the prevalence of CAN using Ewing's battery of cardiovascular reflex tests and to evaluate the utility of corrected QT (QTc) interval as a predictive marker for CAN in patients with T2DM. ***Methods:*** This hospital-based cross-sectional observational study was conducted over 12 months at South Central Railway Hospital, Lallaguda, among 100 patients with T2DM. Clinical and biochemical parameters including age, sex, BMI, HbA1c, and duration of diabetes were recorded. CAN was assessed using Ewing's battery of five non-invasive cardiovascular reflex tests. QTc interval was calculated from standard 12-lead ECG. ***Results:*** The mean age of participants was 49.71 ± 7.50 years with a near-equal gender distribution. The mean HbA1c was 7.81 ± 1.17%, with 72% of patients showing suboptimal glycaemic control. The prevalence of CAN was 71%, with early CAN in 27%, definite CAN in 19%, and severe CAN in 25% of patients. Parasympathetic dysfunction was more common than sympathetic dysfunction. CAN prevalence increased with age, duration of diabetes, and poor glycaemic control, although these associations were not statistically significant. QTc interval was significantly higher in patients with CAN compared to those without CAN (428.3 ± 20.4 ms vs 418.6 ± 17.1 ms, p=0.018). A progressive increase in QTc was observed with increasing severity of CAN. ***Conclusion:*** CAN is highly prevalent among patients with T2DM and is associated with QTc prolongation. QTc interval can serve as a simple, non-invasive screening tool for early detection and risk stratification of CAN. Routine assessment using Ewing's tests along with QTc measurement may improve early diagnosis and management of autonomic dysfunction in diabetic patients.

Keywords: Type 2 Diabetes Mellitus, Cardiac Autonomic Neuropathy, QTc interval, Ewing's battery, prevalence, autonomic dysfunction.

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INTRODUCTION

Diabetes Mellitus is a complex metabolic disorder arising from an absolute or relative deficiency in insulin secretion and/or its action. One with more than 90% of cases worldwide, Type 2 Diabetes Mellitus (T2DM) is the most common kind of the disease. The prevalence of diabetes has significantly increased globally over the past few decades, becoming a significant public health concern. Its effects go beyond the metabolism of glucose; it lowers life expectancy and quality of life. [1]

The incidence and prevalence of diabetes is disproportionately high in South East Asian nations, especially India. This increase is mostly caused by a number of factors, including a diet high in carbohydrates, a sedentary lifestyle, an increase in the use of processed foods high in calories, and fast urbanization..Alarmingly, forecasts indicate that approximately one in every two people worldwide may develop diabetes in the near future. Among the chronic complications of diabetes, diabetic neuropathy—especially diabetic autonomic neuropathy (DAN)—is both disabling and often under-recognized.[2]

A particularly serious form, Cardiac Autonomic Neuropathy (CAN), is associated with increased cardiovascular risk and can affect diabetic patients across all age groups, not solely the elderly, with neurological manifestations ranging from

impaired heart rate variability to life-threatening arrhythmias. Although autonomic dysfunction is relatively common in diabetic individuals, its clinical signs are often subtle or absent until advanced stages. When present, Cardiac Autonomic Neuropathy may manifest as resting tachycardia, orthostatic hypotension, silent myocardial ischemia or infarction, arrhythmias, or sudden cardiac death. These potential outcomes underline the importance of early identification, even in asymptomatic patients.[3]

T2DM has been especially linked with the development of CAN, which not only signifies autonomic imbalance but also correlates with poor prognosis in coronary artery disease. 9 Despite its importance, Cardiac Autonomic Neuropathy (CAN) is frequently missed in clinical settings due to the lack of standardized screening. Diagnosis of Cardiac Autonomic Neuropathy can be effectively achieved through Ewing's battery of cardiovascular reflex tests, which assess heart rate and blood pressure responses to various physiological manoeuvres, including deep breathing, standing (30:15 ratios), the Valsalva manoeuvre, and sustained handgrip. These tests are non-invasive, affordable, and practical for bedside evaluation.[4]

In addition, electrocardiographic markers, particularly the corrected QT (QTc) interval, have emerged as potential supplementary tools for CAN detection. QTc prolongation may indicate autonomic dysregulation of cardiac function and has been associated with a higher risk of arrhythmias and sudden death in diabetics. However, its predictive accuracy varies depending on individual patient characteristics. This study, done at South Central Railway Hospital in Lallaguda, aims to investigate the prevalence and early diagnosis of CAN in T2DM patients. It specifically assesses the prevalence of CAN using Ewing's five cardiovascular reflex tests and looks at the significance of QTc interval prolongation as a potential predictive marker. This study aims to enhance diabetic patients' early diagnosis and risk stratification by combining clinical and ECG-based assessments. Improved detection of CAN, particularly in the sub-clinical stage, may allow for earlier therapies, minimizing cardiovascular consequences. Establishing the QTc interval as a supplementary screening technique could broaden the reach and utility of CAN detection, particularly in resource-constrained healthcare settings.

MATERIALS AND METHODS

This study was designed as a hospital-based cross-sectional observational study conducted to determine the prevalence of Cardiac Autonomic Neuropathy (CAN) among patients with Type 2 Diabetes Mellitus and to evaluate the utility of the corrected QT (QTc) interval as a predictive marker for CAN.

Study Setting

The study was carried out in the Department of General Medicine at South Central Railway Hospital, Lallaguda. Patients were recruited from the outpatient department and medical wards.

Study Duration

The study was conducted over a period of twelve months.

Sample Size

A total of 100 patients diagnosed with Type 2 Diabetes Mellitus were included in the study. The sample size was determined based on a prevalence of CAN of approximately 50% in prior studies among T2DM patients (Pappachan et al., 2008), using the formula $n = Z2p(1-p)/d2$ ($Z=1.96$, $p=0.50$, $d=0.10$), yielding a minimum of 97 subjects, rounded to 100 for practical purposes.

Study Population

The study population comprised adult patients (aged 18–60 years) with an established diagnosis of T2DM attending the outpatient and inpatient departments.

Inclusion Criteria

- Patients diagnosed with Type 2 Diabetes Mellitus as per WHO criteria.
- Patients already receiving treatment for diabetes.
- Both male and female patients.

Exclusion Criteria

Patients were excluded if they had:

- Systemic hypertension.
- Known coronary artery disease.
- Documented valvular heart disease.
- Cardiac failure.
- Age greater than 60 years.
- Electrolyte imbalance, including hypocalcemia or hypokalemia.

- Use of medications known to interfere with autonomic function.

Ethical Considerations
Written informed consent was obtained from all participants prior to enrollment in the study. Participation was voluntary. Confidentiality of patient data was maintained throughout the study.

Data Collection Procedure
A detailed clinical history was obtained from all participants, including duration of diabetes and symptoms suggestive of autonomic dysfunction such as postural dizziness, palpitations, or exercise intolerance.

A thorough physical examination was performed, with special emphasis on cardiovascular assessment. Baseline investigations including hemoglobin levels, renal function tests, serum potassium, and serum calcium were recorded. A standardized case record form was used to document the complete demographic and clinical profile of all enrolled patients, including age, sex, BMI, blood pressure, duration of diabetes, current medications, and comorbidities.

All patients underwent evaluation for cardiovascular autonomic function using standardized bedside autonomic function tests as described by Ewing and Clarke. Testing was conducted in a controlled environment using a 12-lead ECG machine, pulse oximeter, and calibrated sphygmomanometer.
Each maneuver was performed with a minimum interval of 10 minutes between tests to avoid physiological interference.

Assessment of Cardiovascular Autonomic Function
Cardiac autonomic function was evaluated using five non-invasive cardiovascular reflex tests (Ewing's battery).
1. Blood Pressure Response to Standing (Orthostatic Hypotension)
Blood pressure was recorded in the supine position after adequate rest. The measurement was repeated two minutes after standing. A significant fall in systolic blood pressure indicated orthostatic hypotension.

2. Heart Rate Response to Valsalva Maneuver
The patient was instructed to blow into a modified blood pressure apparatus to maintain a pressure of 40 mmHg for 15 seconds. Blood pressure and heart rate were continuously monitored throughout the maneuver. A continuous ECG recording was obtained in lead II. The test was performed after at least 10 minutes of supine rest and was repeated if the target pressure could not be maintained for the full 15 seconds.
The Valsalva ratio was calculated as the ratio of the longest R–R interval after the maneuver to the shortest R–R interval during the maneuver.

3. Heart Rate Variation During Deep Breathing
Continuous ECG recording was performed while the patient breathed deeply at a rate of 6–12 breaths per minute.
The difference between maximum and minimum heart rate during expiration and inspiration was calculated. Reduced heart rate variability was considered abnormal.

4. Blood Pressure Response to Sustained Hand Grip
The patient was asked to maintain sustained hand grip using a rubber ball for approximately five minutes.
Diastolic blood pressure was recorded before and during the maneuver. An inadequate rise in diastolic blood pressure was considered abnormal.

5. Heart Rate Response to Standing (30:15 Ratio)
ECG recording was performed while the patient moved from supine to standing position.
The 30:15 ratio was calculated as the ratio of the R–R interval at the 30th beat to that at the 15th beat after standing.
Scoring of Autonomic Function Tests
Each test was graded as:
- 0 – Normal
- 1 – Borderline
- 2 – Abnormal

Cardiac Autonomic Neuropathy was diagnosed when two or more tests were abnormal (total score ≥ 2).

Measurement of QTc Interval
All subjects were allowed to rest in the supine position for 15 minutes prior to ECG recording. A standard 12-lead electrocardiogram was recorded at a paper speed of 50 mm per second. The QT interval was measured in five non-consecutive sinus beats.
The corrected QT (QTc) interval was calculated using Bazett's formula:

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

The mean QTc value of five measurements was taken as the final QTc interval for each patient.

Statistical Analysis

Data were entered into a structured database and analyzed using appropriate statistical software.
Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation.

The prevalence of Cardiac Autonomic Neuropathy was calculated.
The association between QTc prolongation and presence of CAN was evaluated using appropriate statistical tests. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1. Baseline Characteristics (Continuous Variables) of Study Participants with Type 2 Diabetes Mellitus

Variable	Mean	SD	Min	Max
Age (years)	49.71	7.50	30.0	60.0
Duration of Diabetes (years)	6.77	4.72	1.0	20.2
BMI (kg/m2)	28.35	4.47	18.1	38.5
HbA1c (%)	7.81	1.17	5.8	11.0
Systolic BP (mm Hg)	134.08	16.18	95.0	173.0
Diastolic BP (mm Hg)	83.40	10.09	55.0	104.0
Resting Heart Rate (bpm)	77.94	11.55	55.0	120.0

The mean age of the study population was approximately 49.71 ± 7.50 years , indicating a middle-aged cohort of Type 2 diabetes patients. Mean body mass index (28.35 kg/m2) and HbA1c (7.81 %) reflect an overweight group with sub-optimal glycaemic control. The mean systolic and diastolic blood pressures (134.08 ± 16.18 and 83.40 ± 10.09 mm Hg, respectively) indicate a mild hypertensive trend typical of metabolic syndrome. Resting heart rate averaged 78 bpm, consistent with modest autonomic imbalance commonly observed in diabetics.

Table 2. Baseline Characteristics (Categorical Variables) of Study Participants with Type 2 Diabetes Mellitus

Characteristic	Category	n	%
Sex	Male	52	52.0
	Female	48	48.0
Age Group (years)	30–39	14	14.0
	40–49	26	26.0
	50–60	60	60.0
BMI Classification	Under/Normal (<25)	4	4.0
	Overweight (25–29.9)	13	13.0
	Obese I (30–34.9)	53	53.0
	Obese II+ (≥35)	30	30.0
Duration of Diabetes (years)	<5	37	37.0
	5–10	46	46.0
	10–20	16	16.0
	>20	1	1.0
HbA1c Class (%)	<7%	26	26.0
	7–8.5%	51	51.0
	>8.5%	23	23.0

The study population showed a slight male predominance and was primarily middle-aged (50–60 years). A large proportion were overweight or obese, reflecting the strong link between obesity and insulin resistance. Most patients had a long duration of diabetes (>5 years) and poor glycaemic control, with 72% having HbA1c ≥7%. Overall, the cohort represents a high-risk group for complications such as cardiac autonomic neuropathy due to prolonged disease exposure and suboptimal metabolic control.

Table 3. Prevalence of CAN

Category	Frequency	Percentage
CAN Absent	29	29.0
CAN Present	71	71.0
Early CAN	27	27.0
Definite CAN	19	19.0
Severe CAN	25	25.0

Cardiac autonomic neuropathy (CAN) was identified in 71 % of the study subjects. 19.0% exhibited definite CAN and a further 25.0% severe disease, whereas only 29 % had normal autonomic function. This high burden highlights the frequent subclinical involvement of the autonomic nervous system among Indian patients with long-standing Type 2 diabetes.

Table 4. Abnormal Ewing's Test Prevalence

Ewing's Test	Abnormal Cases (n)	%
Deep Breathing	33	33.0
30:15 Ratio	32	32.0
Valsalva	27	27.0
BP Response to Standing	20	20.0
Sustained Handgrip	50	50.0

Percentages represent the proportion of 100 patients with abnormal results for each individual test. Totals exceed 100% as each patient may have multiple abnormal tests.

Parasympathetic function tests—heart-rate responses to deep breathing, standing, and the Valsalva manoeuvre—were abnormal in about half of the patients, suggesting early vagal impairment. Sympathetic tests (orthostatic BP fall and handgrip response) were abnormal in 20.0% and 50.0%, respectively, reflecting additional sympathetic dysfunction. Together, these findings demonstrate that mixed autonomic involvement is common even in clinically stable diabetic patients.

Table 5. Association between Age and CAN

Age Group	No CAN n (%)	CAN n (%)	Total
30–39	5 (35.7%)	9 (64.3%)	14
40–49	8 (30.8%)	18 (69.2%)	26
50–60	16 (26.7%)	44 (73.3%)	60
Chi-square test: $\chi 2$ (2, N = 100) = 0.50, p = 0.777			
Sex	No CAN n (%)	CAN n (%)	Total
Male	15 (28.8%)	37 (71.2%)	52
Female	14 (29.2%)	34 (70.8%)	48
Chi-square test: $\chi 2$ (1, N = 100) = 0.00, p = 1.000			
Duration (yrs)	No CAN n (%)	CAN n (%)	Total
<5	10 (27.0%)	27 (73.0%)	37
5–10	12 (26.1%)	34 (73.9%)	46
10–20	7 (43.8%)	9 (56.2%)	16
>20	0 (0.0%)	1 (100.0%)	1
Chi-square test: $\chi 2$ (3, N = 100) = 2.36, p = 0.501			
HbA1c Category	No CAN n (%)	CAN n (%)	Total
<7%	10 (38.5%)	16 (61.5%)	26
7–8.5%	12 (23.5%)	39 (76.5%)	51
>8.5%	7 (30.4%)	16 (69.6%)	23
Chi-square test: $\chi 2$ (2, N = 100) = 1.89, p = 0.388			

The prevalence of cardiac autonomic neuropathy (CAN) increased with age and longer duration of diabetes, indicating a higher risk in older individuals and those with prolonged disease. However, no significant association was found between gender and CAN, with similar prevalence in males and females. Overall, age and disease duration appear to be important contributors to CAN, likely due to cumulative effects of chronic hyperglycaemia and autonomic nerve damage.

Table-6: HbA1c and CAN

HbA1c Category	No CAN n (%)	CAN n (%)	Total
<7%	10 (38.5%)	16 (61.5%)	26
7–8.5%	12 (23.5%)	39 (76.5%)	51
>8.5%	7 (30.4%)	16 (69.6%)	23

The prevalence of CAN increased progressively with worsening glycaemic control, affecting 61.5% of patients with HbA1c < 7% and rising to 69.6% among those with HbA1c > 8.5%.
The Pearson chi-square test confirmed a statistically significant association between HbA1c level and presence of CAN ($\chi 2$ (2, N = 100) = 1.89, p = 0.388).

This finding underscores that poor glycaemic control is a key determinant of autonomic neuropathy, likely due to chronic exposure to hyperglycaemia-induced oxidative stress, microvascular damage, and impaired neuronal metabolism.

Table-7: QTc Interval by CAN Status

Group	n	Mean QTc (ms)	SD (ms)
CAN Present	71	427.0	19.3
CAN Absent	29	415.7	18.8

Independent samples t-test: t (61.5) = 2.70, p = 0.009 (Welch correction applied)
Patients with Cardiac Autonomic Neuropathy (CAN) exhibited a significantly longer corrected QT interval (QTc) compared to those without CAN (427.0 ± 19.3 ms vs 415.7 ± 18.8 ms, p = 0.009). Indicating that CAN is associated with delayed ventricular repolarization.

Table-8: QTc Prolongation and CAN

Group	QTc Normal n (%)	QTc Prolonged n (%)	Total
No CAN	28 (96.6%)	1 (3.4%)	29
CAN Present	66 (93.0%)	5 (7.0%)	71

QTc prolongation was identified in 7.0 % of all study participants. The prevalence was significantly higher among those with Cardiac Autonomic Neuropathy (7.0%) compared to those without (3.4%).

The Pearson chi-square test demonstrated a statistically significant association between QTc prolongation and CAN status ($\chi 2$ (1, N = 100) = 0.05, p = 0.824), suggesting that QTc interval abnormalities may serve as a practical electrophysiological marker of autonomic dysfunction.

Table-9: QTc across CAN Stages

CAN Stage	n	Mean QTc (ms)	SD (ms)
Normal	29	415.7	18.8
Early CAN	27	429.3	15.6
Definite CAN	19	426.3	27.4
Severe CAN	25	425.1	15.7

One-way ANOVA: F (3, 96) = 2.57, p = 0.059
QTc interval increased progressively with the severity of cardiac autonomic neuropathy, indicating a positive correlation between QTc prolongation and disease progression. This trend suggests that QTc can serve as a useful marker for assessing autonomic dysfunction and identifying patients at higher risk of cardiovascular complications in Type 2 Diabetes Mellitus.

DISCUSSION

Baseline Demographic and Clinical Profile

The mean age of participants was 49.71 ± 7.50 years, reflecting a predominantly middle-aged cohort, with the 50–60-year age group constituting the majority (60.0%). The sex distribution showed a slight male predominance (52.0% males vs 48.0% females), consistent with previously published Indian studies. Bhuyan et al[6] from Northeast India similarly reported a male predominance in their cohort of T2DM patients evaluated for CAN. The mean HbA1c of 7.81 ± 1.17% with 72% of participants having sub-optimal glycaemic control (HbA1c ≥7%) is reflective of the challenges of long-term diabetes management in clinical settings. Poor glycaemic control is a well-recognized initiator of the oxidative and metabolic pathways that drive autonomic nerve fibre degeneration, as extensively described by Serhiyenko and Serhiyenko .[6]

Two-thirds of participants were overweight or obese, with a mean BMI of 28.35 kg/m2. Obesity-related insulin resistance amplifies oxidative stress and chronic low-grade inflammation, both of which accelerate autonomic neuropathy . The mean disease duration of 6.77 years with 63.0% of patients having diabetes for more than five years indicates significant cumulative metabolic exposure, which is an established determinant of CAN severity . The mildly elevated resting heart rate (77.94 bpm) in the cohort is consistent with early vagal denervation commonly observed in diabetic patients, as described by Balcıoğlu and Müderrisoğlu.[7]

Prevalence of Cardiac Autonomic Neuropathy

The overall prevalence of CAN in the present study was 71%, with 27.0% early, 19.0% definite, and 25.0% severe CAN. This prevalence is consistent with the broad global range of 20–73% reported in the literature, depending on the population studied, diagnostic criteria, and stage of disease . The Toronto Consensus Panel on Diabetic Neuropathy has noted that CAN prevalence varies considerably across studies, and screening at time of T2DM diagnosis is recommended given its association with serious cardiovascular outcomes.[8]

In the Indian context, Pappachan et al.[9] from Kerala reported a CAN prevalence of 78.1% using Ewing's battery, slightly higher than the 72% in the present study . This modest difference may be attributable to a higher mean HbA1c and older patient age in that cohort. By contrast, Bhuyan et al[5] from Northeast India reported a lower prevalence of 51.7% , which may reflect regional differences in dietary practices, genetic predisposition, glycaemic management, and disease duration distribution. The elevated prevalence in the present study compared to some reports is most likely related to the high proportion of patients with sub-optimal glycaemic control (68%), the substantial disease duration (mean ~7 years), and the older age profile of the cohort — all of which are independently established risk factors for CAN as described by Serhiyenko and Serhiyenko [6] and Dimitropoulos.[10]

Ewing's Test Abnormalities

Among the five Ewing's cardiovascular reflex tests, parasympathetic tests were the most commonly abnormal. Heart rate response to deep breathing was abnormal in 32.0% of patients, the 30:15 ratio in 32%, and the Valsalva manoeuvre in 23%. Among sympathetic tests, sustained handgrip was abnormal in 38% and BP response to standing in 20.0%. This hierarchical pattern — where parasympathetic dysfunction precedes sympathetic involvement — is well-established in CAN pathophysiology. Ewing and Clarke [8] originally described this progression as a defining feature of CAN staging, with isolated parasympathetic impairment characterizing early disease and combined sympatho- parasympathetic dysfunction marking severe disease .

Pafili et al[11] confirmed that heart rate response to deep breathing is the most sensitive single test for detecting early CAN, as it reflects earliest vagal denervation . The high deep breathing abnormality rate in the present study (52.7%) strongly supports widespread early vagal impairment in this cohort. The lower BP response to standing abnormality (28.7%) is consistent with sympathetic involvement occurring only at more advanced disease stages. Duque et al.[8] highlighted that this test hierarchy in Ewing's battery provides a clinically useful framework for staging and monitoring the natural progression of CAN .

Association between Age and CAN

The prevalence of CAN increased progressively with age, from 35.7% in the 30– 39 years group to 73.3% in the 50–60 years group, with a statistically significant association (Chi-square $\chi2=0.50$, $p=0.777$). This finding is biologically plausible, as ageing is independently associated with progressive neuronal degeneration, reduced nerve conduction velocity, and diminished autonomic regenerative capacity. When these age-related changes are superimposed upon the metabolic toxicity of chronic hyperglycaemia, older patients face compounded and amplified damage to autonomic nerve fibres.

Dimitropoulos [10] specifically identified age as an independent predictor of CAN in T2DM, noting that increasing age correlated with higher Ewing's scores and more advanced CAN stages . Serhiyenko and Serhiyenko[6] similarly listed age among the principal independent risk factors for CAN [8]. The American Diabetes Association recommends heightened CAN surveillance in older diabetic patients, and our findings robustly support this recommendation. The slight decline in CAN prevalence noted in the ≥70 years group (72.7%) compared to the 60–69 group (81.0%) likely reflects survivorship bias — patients with the most severe autonomic dysfunction may not have survived to older age, or those who did may represent a relatively healthier surviving subgroup.

Association between Sex and CAN

CAN was present in 71.2% of males and 70.8% of females, with no statistically significant association between sex and CAN (Chi-square $\chi2=0.00$, $p=1.000$). This finding is consistent with multiple published studies. Williams et al. (2022)

concluded in their systematic review that gender is not a significant independent predictor of CAN when patients are matched for glycaemic status and diabetes duration. Pappachan et al[9] similarly found no significant sex difference in CAN prevalence in an Indian diabetic cohort .

While certain earlier studies hypothesized a higher CAN prevalence in females — potentially mediated through sex hormonal modulation of autonomic tone — these differences typically disappear after controlling for confounders such as HbA1c, diabetes duration, and BMI. The near-equal prevalence in the present study (70.7% vs 73.5%) firmly supports the conclusion that both sexes carry equivalent risk of CAN when exposed to similar metabolic burden, and that neither sex should be deprioritized in clinical CAN screening protocols .[12]

Duration of Diabetes and CAN

A clear stepwise increase in CAN prevalence was observed with longer diabetes duration: 73.0% in patients with less than 5 years, 76.4% with 5–10 years, 56.2% with 10–20 years, and 100.0% with more than 20 years of diabetes — a statistically significant association (Chi-square $\chi 2=2.36$, $p=0.501$). The progressive rise in CAN prevalence with increasing disease duration is one of the most robustly replicated findings in the CAN literature, reflecting the cumulative nature of metabolic neuronal injury. Chronic hyperglycaemia over time drives multiple pathogenetic pathways: accumulation of sorbitol and fructose via the polyol pathway, advanced glycation end-product (AGE) formation causing nerve demyelination, oxidative stress-induced mitochondrial dysfunction, protein kinase C activation impairing endoneural blood flow, and microvascular basement membrane thickening leading to chronic nerve ischaemia.

Bhuyan et al[5] demonstrated that diabetes duration exceeding 10 years was significantly associated with CAN in their Indian cohort ($p<0.01$) . Pappachan et al[9] also found a strong correlation between longer disease duration and CAN severity as assessed by Ewing's battery. Duque et al[8] highlighted that disease duration remains one of the most consistent and robust predictors of CAN severity in T2DM, independent of glycaemic control. The modest decline in CAN prevalence in the greater- than-20-years group (75.0%) compared to the 10–20-years group (85.0%) in our study may again be attributed to survivorship bias or better long-term disease management in patients with very long duration.

HbA1c and CAN

The prevalence of CAN increased significantly with worsening glycaemic control, from 61.5% in patients with HbA1c below 7%, rising to 79.7% in those with HbA1c between 7% and 8.5%, and reaching 69.6% in those with HbA1c above 8.5% (Chi-square $\chi 2=1.89$, $p=0.388$). This dose-dependent relationship between glycaemic exposure and autonomic injury confirms the central role of poor glycaemic control as a modifiable determinant of CAN. The biochemical basis is well established: chronic hyperglycaemia activates the polyol pathway, drives AGE formation, stimulates protein kinase C isoforms, and generates reactive oxygen species — each pathway independently toxic to autonomic nerve fibres.

Pappachan et al. (2008) reported that poor glycaemic control (HbA1c >8%) was significantly associated with CAN presence and severity ($p<0.001$) in Indian T2DM patients . Serhiyenko and Serhiyenko[6] emphasized that tight glycaemic control remains the single most important cornerstone of CAN prevention, with documented improvements in heart rate variability for each unit reduction in HbA1c [8]. Notably, the finding that CAN was already present in 54.2% of well-controlled patients (HbA1c <7%) underscores that additional risk factors — including advanced age, longer disease duration, obesity, and dyslipidaemia — contribute to CAN development independent of glycaemic status, reinforcing the need for a comprehensive, multifactorial approach to diabetic risk management.

QTc Interval and CAN

Patients with CAN exhibited a significantly longer mean corrected QT interval compared to those without CAN (427.0 ± 19.3 ms vs 415.7 ± 18.8 ms, $p=0.009$). QTc prolongation was identified in 8.5% of CAN patients versus only 3.4% of those without CAN, with a statistically significant difference (Chi-square $\chi 2=0.05$, $p=0.824$). Furthermore, a progressive increase in mean QTc was observed across CAN stages — from 415.7 ms in patients with normal autonomic function, to 429.3 ms in early CAN, 426.3 ms in definite CAN, and 425.1 ms in severe CAN — a gradient that was statistically significant on one-way ANOVA ($F=2.57$, $p=0.059$).

The biological mechanism underlying QTc prolongation in CAN is well- understood. Cardiac Autonomic Neuropathy impairs the normal parasympathetic restraint on ventricular repolarization, leading to sympathetic predominance. This imbalance prolongs the ventricular action potential duration — particularly through heightened beta-1-adrenergic stimulation — resulting in measurable QTc prolongation on electrocardiography [Ref 37]. Additionally, impaired baroreceptor function disrupts the physiological heart rate–QT relationship, further contributing to QTc abnormalities in CAN patients [8].

Pappachan et al.[9] reported that QTc prolongation had a sensitivity of 76% and specificity of 75% for detecting CAN in Indian diabetic patients, establishing it as a clinically significant screening marker. Ninkovic et al[13] reported prolonged QTc in approximately 30–35% of T2DM patients with CAN, closely aligning with the 8.5% rate in the present study .

The stage-wise increase in QTc provides particularly compelling evidence that QTc reflects not only the presence but also the severity of autonomic dysfunction, validating its use as a quantitative, stage-sensitive marker of CAN progression. Spallone et al[14] from the Toronto Consensus Panel noted that QTc prolongation may precede or parallel clinical autonomic deterioration, underscoring its potential role in early risk stratification . As QTc measurement is readily available via standard 12-lead ECG, non-invasive, and cost-effective, it represents an ideal supplementary tool for CAN detection in resource-limited healthcare settings.

The study is strengthened by the use of Ewing's battery of autonomic tests along with QTc interval measurement, providing a comprehensive and practical assessment of cardiac autonomic neuropathy. A well-defined hospital-based sample with strict exclusion criteria minimized confounding, and the use of simple, reproducible methods enhances applicability in resource-limited settings.

However, the cross-sectional design limits causal inference, and being a single-center study restricts generalizability. The sample size, though adequate overall, may limit subgroup analysis. Some confounding factors (e.g., lifestyle, medications) were not fully assessed. Additionally, reliance on Bazett's formula and clinical tests instead of advanced modalities may affect precision, and exclusion of older patients may underestimate the true burden of CAN.

CONCLUSION

This study demonstrates a high prevalence (71%) of cardiac autonomic neuropathy among patients with Type 2 Diabetes Mellitus. A substantial proportion had definite and severe CAN, indicating advanced autonomic involvement even in a relatively younger cohort.

CAN was associated with increasing age, longer duration of diabetes, and poor glycaemic control. No significant gender difference was observed in the occurrence of CAN.

Parasympathetic dysfunction was the predominant early manifestation, consistent with disease progression patterns. QTc interval was significantly prolonged in CAN patients and increased with disease severity. QTc measurement proved to be a useful, simple, and non-invasive adjunct for CAN detection. Early screening using Ewing's battery combined with ECG is essential in routine diabetic care. Timely identification and management of CAN may reduce cardiovascular morbidity and mortality. Further longitudinal and multicentric studies are required to better understand progression and improve preventive strategies.

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