

Determinants of Cardiac Autonomic Neuropathy Among Patients with Diabetic Peripheral Neuropathy: A Facility-based Cross-Sectional Study

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Abstract

Introduction. Cardiac Autonomic Neuropathy (CAN) is frequently an underdiagnosed consequence of Diabetes Mellitus (DM), increasing the risk of cardiac arrhythmia, silent myocardial ischemia and sudden cardiac death. Diabetic Peripheral Neuropathy (DPN) is a common consequence of diabetes. We aimed to study the proportion of CAN among patients with DPN and identify the predictors of CAN in these patients.

Methodology. This is a hospital-based cross-sectional study conducted over a six-month period. A total of 60 DM patients with nerve conduction study-proven DPN, who fulfilled the inclusion and exclusion criteria, were enrolled in the study. CAN was assessed using both parasympathetic and sympathetic tests. A p -value of <0.05 was considered significant.

Results. The study included a total of 60 patients with diabetic peripheral neuropathy, out of whom 19 (32%) had CAN. Out of the 19 patients with CAN, 11 had severe CAN. There was no statistically significant association between the severity of DPN and CAN ($p = 0.162$). Logistic regression analysis (Model 3) showed that when adjusted for symptoms, risk factors, hypertension and a specific ECG finding (left atrial enlargement), the determinants of CAN were the presence of motor symptoms, being overweight or obese and the presence of left atrial enlargement.

Conclusion. Among this cohort of persons with DM who all had DPN, CAN was found in one-third (32%) of the sample. Patients with DPN who are overweight/obese, have motor neuropathy or have left atrial enlargement have the most significant risk for developing CAN and may be recommended for its screening. Given that CAN is a frequently overlooked condition, each early diagnosis of CAN may potentially prevent its debilitating complications and even fatal outcomes.

Key words: *cardiac autonomic neuropathy, diabetic peripheral neuropathy, diabetes mellitus, heart rate variability, orthostatic hypotension*

INTRODUCTION

Diabetes Mellitus has become rampant and is the root cause of many complications. In comparison to people without the condition, those with diabetes have a roughly two-fold increased risk of cardiovascular disease and may lose about six to seven years of life.¹ Cardiac Autonomic Neuropathy (CAN) is a frequently underdiagnosed consequence of Diabetes. It is characterized by dysfunction of the autonomic nerves that innervate the heart, resulting in abnormalities in heart rate control, blood pressure regulation, and cardiac reflexes, leading to increased risk of mortality, arrhythmias, myocardial infarction, and sudden cardiac death.² Diabetic Peripheral Neuropathy (DPN) is a common consequence of diabetes that can present in many forms such as pain, numbness, tingling and burning sensation. It was found that the prevalence of CAN was relatively high in patients with DPN and its

severity worsens with worsening peripheral neuropathy.³ The studies on the prevalence of CAN and its predictors among patients with DPN are very few, and to the best of our knowledge, this study is probably the first in India. In this study, we have assessed the proportion of CAN among patients with DPN and its predictors.

METHODOLOGY

This is a hospital-based cross-sectional study conducted in a tertiary care hospital in Puducherry, India. A total of 90 patients aged 30-70 years, of both sexes, with proven type 2 diabetes mellitus (T2DM) (according to ADA criteria), who were either on or not on regular anti-diabetic drugs or insulin were sequentially enrolled in the study from our inpatient wards and outpatient General Medicine clinic. A minimum sample size of 60 patients was determined using a prevalence of 85.7% based on the study by Karthikeyan

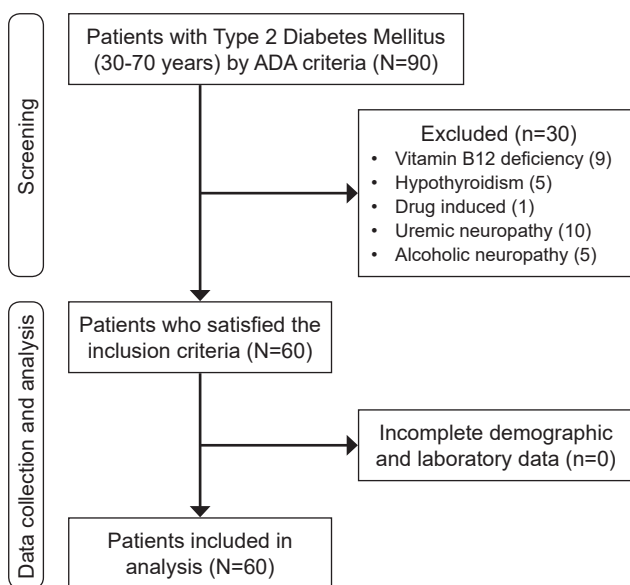


Figure 1. Flowchart of patient recruitment process.

et al.,² with a 95% confidence interval and an absolute precision of 8.86%, as calculated using Open Epi software. We sequentially recruited the patients from March 2023 to September 2023 using the inclusion criteria and identified patients with DPN using nerve conduction studies (NCS). Patients with other causes of peripheral neuropathy (such as vitamin B12 deficiency, hypothyroidism, drug-induced, toxin exposure, infections, alcohol consumption, uremic neuropathy and malignancy), those on pacemakers, those with sepsis and patients on anti-arrhythmic or antidepressant medications were excluded. A summary of the patient recruitment flowchart is shown in Figure 1.

After obtaining written consent, the patients were interviewed and examined by the principal investigator and a questionnaire with the required details was completed. The Toronto Clinical Scoring System (TCSS) was used both as a screening tool and to calculate the severity of Peripheral Neuropathy. The total score ranges from 0 to 19; a score of 0-5 means no PN, 6-8 is mild PN, 9-11 is moderate PN and 12-19 is severe PN.⁴ Fasting blood samples were collected and other evaluations were conducted at least 2 hours after waking up. HbA1c, serum lipid profile, serum urea, serum creatinine, liver function tests and thyroid-stimulating hormone (TSH) levels were determined from a 3 mL venous blood sample drawn from the patient by a trained nurse. The sample was sent to the biochemistry lab within 1 hour for analysis. The HbA1c estimation and serum lipid profile were done using the High-performance Liquid Chromatography method. The diagnosis of diabetes was based on the criteria established by the American Diabetes Association.⁵ After applying the exclusion criteria, the patients who had PN on the TCSS scale were subjected to nerve conduction studies. The patients with positive results in the NCS were included in our study.

Before being examined, the patients were asked to refrain from taking their anti-hypertensive drugs for the necessary

amount of time based on the duration of action of their drugs. Height was measured using a metal stadiometer with a precision of 0.5 cm in a typical standing posture without shoes. Meanwhile, weight was recorded using a digital scale with an accuracy of 100 g while wearing the least amount of clothing. The blood pressure was measured with a standard mercury sphygmomanometer after 15 minutes of rest. The heart rate and blood pressure were examined in the right hand in a supine and standing position.

A continuous electrocardiogram (ECG) was taken from each individual in two modes: the patient breathed deeply 6 times per minute and the ECG was recorded continuously for 1 minute in the supine position. The time of inspiration and expiration was marked on the ECG tape. The RR intervals were calculated based on the continuous ECG tape.⁶ The autonomic dysfunction was analyzed using parasympathetic and sympathetic cardiovascular reflex tests such as at-rest tachycardia (heart rate more than 100 beats per minute after 15 minutes of rest in a supine position); beat-to-beat heart rate variability (patient lies down and takes 6 breaths per minute and is considered abnormal when the expiration to inspiration RR interval ratio is more than 1.17); and, orthostatic hypotension (both systolic and diastolic blood pressures (BP) were measured with the patient in supine position and then repeated after standing for 3 minutes, whereby a reduction in systolic BP by 20 mmHg or diastolic BP by 10 mmHg after standing is considered abnormal).⁷ The criteria for diagnosis of CAN include:

1. Definite or confirmed CAN – the presence of any two abnormal cardiovascular reflex tests.
2. Severe or advanced CAN – definite CAN and the additional presence of orthostatic hypotension.⁸

Statistical analysis

Data was entered into Microsoft Excel and checked for errors. Descriptive statistics are presented as a mean \pm standard deviation (SD) for continuous variables and as proportions or percentages for categorical variables. The Chi-square test was used to study the association between variables. The independent t-test was used to compare continuous variables between the two groups. Logistic regression was done to examine the predictors of CAN.

Ethics

This research has been reviewed and approved by the Institutional Ethics Committee of the tertiary care hospital where the study was conducted. The research has been designed and implemented in accordance with the committee's recommendations.

RESULTS

The study included a total of 60 patients with DPN who underwent testing for CAN. They were divided into two groups based on the presence of CAN: 41 (68%) patients

Table 1. Proportion of Cardiac Autonomic Neuropathy

Variables	Total = 60, n (%)
Cardiac Autonomic Neuropathy	
Definite CAN	8 (13.3)
Severe CAN	11 (18.3)
Total	19 (31.6)
Based on age distribution (in years)	
30-39	0 (0.0)
40-49	2 (3.3)
50-59	8 (13.3)
≥60	9 (15.0)
Gender	
Male	14 (23.3)
Female	5 (8.3)

with no CAN and 19 (32%) with CAN. Of the 19 patients with CAN, 11 (18%) had severe CAN (Table 1).

Among the study population, 42 (70%) were male and 18 (30%) were female. The mean age of the study population was 56.3 ± 9.6 years. The demographic profile showed no statistically significant difference in age distribution between the groups, with a mean age of 58.5 ± 7.8 years in the CAN group and 55.3 ± 10.3 years in the normal group ($p = 0.234$). Similarly, there was no statistically significant difference in gender distribution, with males constituting 73.7% (n=14) in the CAN group and 68.3% (n=28) in the normal group, and females constituting 26.3% (n=5) in the CAN group and 31.7% (n=13) in the normal group ($p = 0.672$) (Table 2).

The analysis of the duration of diabetes among the CAN group and the normal group did not show any statistically significant association ($p = 0.432$). Of the 60 patients who underwent TCSS scoring for DPN, 29 (48.3%) were found

to have mild, 28 (46.7%) moderate and 3 (5%) severe DPN. However, there was no statistically significant association between the severity of DPN and the occurrence or severity of CAN ($p = 0.162$) (Table 3).

The analysis of various symptoms of the patients did not show any statistically significant association with CAN. The motor symptoms were predominantly present in the CAN group (47.4%, n = 9) compared to the normal group (24.4%, n = 10) ($p = 0.075$). There was no statistically significant association between CAN and smoking ($p = 0.676$) or obesity ($p = 0.055$). The analysis of various comorbidities showed no statistically significant association between CAN and hypertension ($p = 0.337$) or dyslipidemia ($p = 0.631$). The prevalence of obesity was comparatively higher in the CAN group (33.3%, n = 6) than in the normal group (12.2%, n = 5). Orthostatic hypotension was present in 68.4% (n = 13) of the CAN group compared to only 9.8% (n = 4) of the normal group, a statistically significant difference ($p < 0.001$) (Table 4).

The analysis of laboratory parameters showed no statistically significant association between CAN and eGFR ($p = 0.470$), TyG index ($p = 0.494$), total cholesterol ($p = 0.965$), triglycerides ($p = 0.288$), HDL ($p = 0.906$) or LDL ($p = 0.904$). The mean HbA1c of the study population was 9.9 ± 1.9 , while the CAN group had a mean of 9.6 ± 1.8 and the normal group had a mean of 10.0 ± 2.0 . No statistically significant association was found between CAN and HbA1c ($p = 0.515$) (Table 5).

Analysis of the ECG showed that the following findings were predominantly observed in the CAN group: wide QRS (CAN 15.8% vs. normal 2.4%), left atrial enlargement (CAN 63.2% vs. normal 43.9%) and corrected QT interval ≥ 430 ms

Table 2. Age and gender profile of the participants

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Age (in years)	56.3 ± 9.6	58.5 ± 7.8	55.3 ± 10.3	0.234 [#]
Age distribution (in years)				
30-39	3 (5.0)	0 (0.0)	3 (7.3)	-
40-49	10 (16.7)	2 (10.5)	8 (19.5)	
50-59	21 (35.0)	8 (42.1)	13 (31.7)	
≥60	26 (43.3)	9 (47.4)	17 (41.5)	
Gender				
Male	42 (70.0)	14 (73.7)	28 (68.3)	0.672 [*]
Female	18 (30.0)	5 (26.3)	13 (31.7)	

[#]Independent sample t-test; ^{*}Chi-square test

Table 3. Diabetic status and severity of diabetic neuropathy according to TCSS

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Duration of diabetes (in years)				
<5	13 (21.7)	2 (10.5)	11 (26.8)	0.432 [*]
5-10	32 (53.3)	11 (57.9)	21 (51.2)	
11-20	11 (18.3)	5 (26.3)	6 (14.6)	
>20	4 (6.7)	1 (5.3)	3 (7.3)	
TCSS Scoring				
Mild	29 (48.3)	6 (31.6)	23 (56.1)	0.162 [*]
Moderate	28 (46.7)	13 (68.4)	15 (36.6)	
Severe	3 (5.0)	0 (0.0)	3 (7.3)	

^{*}Chi-square test; [^]Yates' corrected

(CAN 47.4% vs. normal 41.4%). However, no statistically significant association was found between CAN and any specific ECG findings in our study (Table 6).

The odds-ratio analysis using logistic regression revealed that males have 1.62 (95% CI 0.44-5.91) times the odds of developing CAN compared to females, but this difference was not statistically significant ($p = 0.461$). The odds of

Table 4. Symptoms, risk factors and comorbidity profile of participants

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Symptoms and risk factors				
Numbness	50 (83.3)	16 (84.2)	34 (82.9)	0.901
Pricking pain	17 (28.3)	4 (21.1)	13 (31.7)	0.394
Motor symptoms	19 (31.7)	9 (47.4)	10 (24.4)	0.075
Giddiness	7 (11.7)	3 (15.8)	4 (9.8)	0.498
Altered bowel/bladder	7 (11.7)	3 (15.8)	4 (9.8)	0.498
Overweight/obesity [§]	11 (18.6)	6 (33.3)	5 (12.2)	0.055
Smoking	5 (8.3)	2 (10.5)	3 (7.3)	0.676
Other comorbidities				
Hypertension	21 (35.0)	5 (26.3)	16 (39.0)	0.337
Dyslipidemia	15 (25.0)	4 (21.1)	11 (26.8)	0.631
Orthostatic hypotension	17 (28.3)	13 (68.4)	4 (9.8)	<0.001

*Chi-square test; [§]one missing value

Table 5. Laboratory parameters

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Estimated GFR				
≥100 ml/s	7 (11.7)	3 (15.8)	4 (9.7)	0.470 [^]
80-99 ml/s	18 (30.0)	3 (15.8)	15 (36.6)	
60-79 ml/s	17 (28.3)	8 (42.1)	9 (22.0)	
<60 ml/s	18 (30.0)	5 (26.3)	13 (31.7)	
TyG index				
4.0-4.9	28 (46.7)	11 (57.9)	17 (41.4)	0.494 [*]
5-5.4	20 (33.3)	5 (26.3)	15 (36.6)	
≥5.5	12 (20.0)	3 (15.8)	9 (22.0)	
HbA1c				
Mean ± SD	9.9 ± 1.9	9.6 ± 1.8	10.0 ± 2.0	0.515 [#]
6.6-9.5 %	29 (48.3)	11 (57.9)	18 (43.9)	0.600 [*]
9.6-12.5 %	23 (38.4)	6 (31.6)	17 (41.5)	
>12.5 %	8 (13.3)	2 (10.5)	6 (14.6)	
Lipid profile				
Total cholesterol	169.2 ± 55.1	169.7 ± 62.5	169.0 ± 52.2	0.965 [#]
Triglyceride	176.5 ± 100.6	156.1 ± 119.5	185.9 ± 90.5	0.288 [#]
HDL	37.1 ± 9.8	36.9 ± 8.3	37.2 ± 10.5	0.906 [#]
LDL	96.4 ± 38.4	95.5 ± 37.9	96.8 ± 39.1	0.904 [#]

[#]Independent sample t-test; ^{*}Chi-square test; [^]Yates' corrected

Table 6. ECG findings

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Normal ECG	52 (86.7)	16 (84.2)	36 (87.8)	0.974 [^]
Prolonged PR interval	0 (0.0)	0 (0.0)	0 (0.0)	-
QRS duration				
Narrow	56 (93.3)	16 (84.2)	40 (97.6)	0.169 [^]
Wide	4 (6.7)	3 (15.8)	1 (2.4)	
Left ventricular hypertrophy	3 (5.0)	1 (5.3)	2 (4.9)	0.566 [^]
Left atrium enlargement	30 (50.0)	12 (63.2)	18 (43.9)	0.165
Left axis deviation	17 (28.3)	4 (21.1)	13 (31.7)	0.394
Left bundle branch block	4 (6.7)	0 (0.0)	4 (9.8)	-
Other changes				
Poor R wave progression	6 (10.0)	2 (10.5)	4 (9.8)	0.711 [^]
T wave inversion in precordial leads	1 (1.7)	0 (0.0)	1 (2.4)	-
Low voltage complexes	1 (1.7)	1 (5.3)	0 (0.0)	-
Corrected QT interval (in ms)				
390-409	8 (13.4)	3 (15.8)	5 (12.2)	0.778
410-429	26 (43.3)	7 (36.8)	19 (46.4)	
≥430	26 (43.3)	9 (47.4)	17 (41.4)	

*Chi-square test; [^]Yates' corrected

Table 7. Predictors of Cardiac Autonomic Neuropathy

Variables		Unadjusted OR (95%CI)	p-value	Model 1 Adj. OR (95%CI)	p-value	Model 2 Adj. OR (95%CI)	p-value	Model 3 Adj. OR (95%CI)	p-value
Gender	Male	1.62 (0.44-5.91)	0.461	1.79 (0.45-7.14)	0.404				
	Female	Ref.	-	Ref.	-				
Duration of diabetes (in years)	<5	Ref.	-	Ref.	-				
	5-10	2.61 (0.48-14.11)	0.263	2.05 (0.32-13.08)	0.445				
	11-20	4.58 (0.67-31.19)	0.120	3.38 (0.40-28.40)	0.261				
	>20	1.83 (0.12-27.79)	0.662	1.38 (0.06-30.62)	0.836				
TCSS scoring	Mild	Ref.	-	Ref.	-				
	Moderate	3.06 (0.94-9.94)	0.062	2.41 (0.63-9.15)	0.194				
Symptoms									
	Numbness	1.02 (0.23-4.53)	0.969			0.99 (0.13-7.45)	0.998		
	Pricking pain	0.61 (0.16-2.23)	0.461			0.53 (0.09-2.93)	0.471	0.43 (0.08-2.27)	0.321
	Motor symptoms	3.10 (0.96-9.95)	0.057			8.40 (1.75-40.21)	0.008	7.11 (1.44-34.97)	0.016
	Giddiness	1.15 (0.19-6.96)	0.874			1.34 (0.14-12.14)	0.791		
	Altered bowel/bladder habits	1.85 (0.36-9.28)	0.455			0.96 (0.15-5.96)	0.972		
Risk factors									
	Smoking	1.58 (0.24-10.39)	0.632			0.15 (0.54-45.54)	0.157	2.87 (0.29-28.09)	0.363
	Overweight/obesity	3.64 (0.92-13.95)	0.064			10.80 (1.71-67.85)	0.011	21.83 (2.82-168.74)	0.003
Comorbidities									
	Hypertension	0.60 (0.17-2.01)	0.408			0.36 (0.05-2.28)	0.284	0.23 (0.04-1.14)	0.072
	Dyslipidemia	0.77 (0.21-2.88)	0.709			0.44 (0.05-3.37)	0.433		
ECG findings									
	Left atrium enlargement	2.55 (0.80-8.13)	0.112					6.07 (1.07-34.41)	0.041
	Left axis deviation	0.61 (0.16-2.23)	0.461						
	Left ventricular hypertrophy	1.14 (0.09-13.52)	0.913						

developing CAN were higher with a longer duration of diabetes of up to 20 years, with an OR of 2.61 for 5-10 years duration (95% CI 0.48-14.11) ($p = 0.263$) and an OR of 4.58 for diabetes duration of 11 to 20 years (95% CI 0.67-31.19) ($p = 0.120$). In contrast, the odds were lower in patients with diabetes for more than 20 years with an OR of 1.83 (95% CI 0.12-27.79) ($p = 0.662$). The odds of developing CAN were 3.06 (95% CI 0.94-9.94) times higher in patients with moderate DPN compared to those with mild DPN ($p = 0.062$). Among the symptoms, CAN was associated with increased odds of motor symptoms (OR 3.10, 95% CI 0.96-9.95, $p = 0.057$) and decreased odds of pricking pain (OR 0.61, 95% CI 0.16-2.23, $p = 0.461$). Smoking and overweight/obesity were associated with 1.58 times (95% CI 0.24-10.39, $p = 0.632$) and 3.64 times (95% CI 0.92-13.95, $p = 0.064$) the odds of developing CAN, respectively. Both hypertension (OR 0.60, 95% CI 0.17-2.01, $p = 0.408$) and dyslipidemia (OR 0.77, 95% CI 0.21-2.88, $p = 0.709$) were associated with decreased odds of developing CAN. ECG findings like LAE (OR 2.55, 95% CI 0.80-8.13, $p = 0.112$) and LVH (OR 1.14, 95% CI 0.09-13.52, $p = 0.913$) were associated with increased odds of developing CAN whereas left axis deviation (OR 0.61, 95% CI 0.16-2.23, $p = 0.461$) was associated with decreased odds of developing CAN. However, none of the above findings were statistically significant, as p -value was <0.05 (Table 7).

Model 1 of the adjusted odds-ratio analysis using logistic regression included adjustments for gender, duration of diabetes and TCSS scoring. It did not show any statistically significant association between these variables and CAN. Model 2 included adjustments for symptoms, risk factors and comorbidities. It revealed that CAN was significantly

Table 8. Model statistics for multivariable logistic regression

Model	Accuracy	Specificity	Sensitivity	AUC
Model 1	0.711	0.951	0.166	0.708
Model 2	0.779	0.853	0.611	0.804
Model 3	0.813	0.878	0.667	0.838

associated with increased odds of motor symptoms (OR 8.40, 95% CI 1.75-40.21, $p = 0.008$) and overweight/obesity (OR 10.80, 95% CI 1.71-67.85, $p = 0.011$). Model 3 included adjustments for symptoms (pricking pain and motor weakness), risk factors (smoking and overweight/obesity), comorbidities (hypertension) and ECG findings (left atrial enlargement or LAE). It was evident that CAN was significantly associated with increased odds of motor symptoms (OR 7.11, 95% CI 1.44-34.97, $p = 0.016$), overweight/obesity (OR 21.83, 95% CI 2.82-168.74, $p = 0.003$) and LAE (OR 6.07, 95% CI 1.07-34.41, $p = 0.041$) (Table 7).

Model statistics for multivariable logistic regression showed that Model 3 had the highest accuracy (81%), specificity (88%), sensitivity (67%) and AUC (0.838) among all three models (Table 8).

DISCUSSION

The study estimated the proportion of Cardiac Autonomic Neuropathy among patients with DPN and also the predictors of CAN among patients with DPN. The data of 60 DPN patients were studied, 70% of which are male, and the sample mean age was 56.3 ± 9.6 years. CAN was

found to be more prevalent among males; however, no statistically significant age or sex preponderance was seen. Neuropathy is the most prevalent complication of DM,⁹ and our study, based on cardiovascular reflexes, specifically determined the proportion of definite CAN among patients with DPN to be 32% (n = 19). Out of the 32%, 11 patients (18%) had severe CAN. Various studies have shown that the prevalence of CAN in DM patients ranges from 17% to 90% in patients with type 1 DM and 27.5% to 73% in patients with type 2 DM. This wide range is due to the varied study populations and differences in the criteria used to define CAN.¹⁰ The prevalence of CAN in this study was consistent with the overall prevalence of CAN in other studies. However, almost all of the available studies have shown the prevalence of CAN in diabetic patients, whereas our study assessed the proportion of CAN in patients with diabetic peripheral neuropathy. Using more precise instruments such as MIBG scans and PET scans may lead to a higher prevalence of CAN.¹¹⁻¹³ This study utilized a short-term continuous ECG, which is less accurate than 24-hour Holter monitoring of heart rate. Yet, it remains to be a straightforward and non-invasive procedure that can be performed at the bedside. Nevertheless, the tests utilized in our study have reasonably good sensitivity and specificity.¹³⁻¹⁶ The drawback of the tests is that they require the patient's active participation and complete cooperation.¹⁷ Additionally, there is a factor that heart rate variability generally declines with age.^{18,19}

Many studies have shown a direct relationship between the CAN and the duration of diabetes.³ Even though studies have shown that controlling diabetes can prevent or delay the onset of microvascular complications, our study revealed that there was no significant association between CAN and the duration of diabetes, glycemic control (HbA1c) or severity of peripheral neuropathy. This could be attributed to differences in study populations (i.e., patients with DPN and not all patients with diabetes), varying criteria used to define CAN or the underlying glycemic variability (as HbA1c only reflects the glycemic status in the last three months and does not indicate long-term glycemic control in diabetic patients).

QTc prolongation (by Bazett's formula) is a specific yet insensitive marker of Diabetic Autonomic Neuropathy. In our study, there was no significant association between CAN and any specific ECG finding independently of each other. Orthostatic hypotension was present in 68.4% (n = 13) of patients with CAN, which was statistically significant. Thus, orthostatic hypotension is indicative of severe CAN if considered along with other autonomic functions.

Logistic regression analysis (Model 3) showed that when adjusted for symptoms, risk factors, comorbidities (hypertension) and specific ECG findings (left atrial enlargement), the determinants of CAN were the presence of motor symptoms, being overweight or obese and the presence of left atrial enlargement. It was evident from the multivariate logistic regression analysis that Model 3

was the best among all the three models, with the highest accuracy (81%) and AUC (0.838).

Strengths and limitations

A key strength of the study is that all of the examinations and diagnostic procedures were conducted by a single examiner, increasing its internal validity. Limitations include the small sample size, single-center design and the lack of data on the long-term glycemic control and daily fluctuations in blood sugar levels of the patients and absence of follow-up.

CONCLUSION

Among this cohort of persons with T2D who all had DPN, CAN was found in one-third (32%) of the sample. Patients with DPN who are overweight/obese, have motor neuropathy or have left atrial enlargement in 2D-ECHO have the most significant risk for developing CAN and may be recommended for its screening. Given that CAN is a frequently overlooked condition, each early diagnosis of CAN may potentially prevent its debilitating complications and even fatal outcomes.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria

Author Disclosure

The authors declare no conflict of interest.

CRediT Author Statement

BM: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **DG:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding acquisition; **SNH:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **Funding acquisition;** **BAK:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition

Data Availability Statement

Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Funding Source

None.

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