Original Article

Prevalence of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus

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Abstract

Introduction: Cardiac autonomic neuropathy (CAN) is one of the microvascular complications of diabetes mellitus, which is due to the involvement of autonomic nerve fibers innervating the heart and blood vessels. CAN was found to have a greater degree of morbidity and mortality than their non-CAN counterparts as it is underdiagnosed. Hence, this study aims to determine the prevalence and severity of CAN in type 2 diabetics in the South Indian setting. **Materials and Methods:** Forty-two patients with type 2 diabetes mellitus were enrolled in the study. Patients underwent tests for CAN, with the severity of CAN estimated as a CAN score, which was the sum of the scores of the four cardiovascular autonomic function tests. **Results:** Out of the 42 patients, a total of 36 patients (85.7%) were diagnosed with CAN. Among those with CAN, 24 patients had early CAN (57.1%), and 12 were diagnosed with definite CAN (28.6%). Patients with any form of CAN (early and definite CAN) had higher HbA1c and mean glucose values than those without CAN. CAN was also found to be more severe among older patients with diabetes. **Conclusion:** In the present study, we found that more than 50% of the study population had early CAN and around 28.6% patients had definite CAN indicating higher prevalence of CAN in our population. Also, there was a positive correlation between the severity of CAN and the age of the patients. This study highlights the importance of understanding the importance of screening the diabetic patients for CAN to prevent adverse cardiovascular events.

Keywords: Cardiac autonomic neuropathy, cardiovascular diseases, chronic hyperglycemia, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. It is estimated that more than 400 million people worldwide have diabetes, with approximately 90% of them having type 2 diabetes.[1] Primary care physicians play a crucial role in the management of patients with T2DM, as they are often the first point of contact for individuals with diabetes. Understanding the prevalence of cardiac autonomic neuropathy (CAN) in this patient population is essential for primary care physicians to provide comprehensive care and minimize the associated cardiovascular risks.

Cardiac autonomic neuropathy (CAN) is a common and serious complication of diabetes, particularly in patients with longstanding and poorly controlled T2DM. It is characterized by dysfunction of the autonomic nerves that innervate the heart, leading to abnormalities in heart rate control, blood pressure regulation, and cardiac reflexes. CAN is associated with an increased risk of mortality, arrhythmias, myocardial infarction, and sudden cardiac death.[2]

Recognizing the prevalence of CAN in patients with T2DM is crucial for primary care physicians as it guides screening, diagnosis, and management strategies. Several studies have

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Received: 06-04-2023 **Revised:** 21-06-2023
Accepted: 26-06-2023 **Published:** 30-09-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_609_23

How to cite this article: Karthikeyan A, Manjunath PR, Latha AT, Sultana S. Prevalence of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus. J Family Med Prim Care 2023;12:2070-4.

investigated the prevalence of CAN in patients with T2DM, shedding light on the magnitude of this complication.

Early diagnosis and identification of patients with CAN are imperative to slow its progression and reverse its effects.[3] Hence, this study aims to determine the prevalence of CAN in type 2 diabetic patients in a South Indian setting.

Materials and Methods

A hospital-based prospective study was conducted in an urban tertiary healthcare center for two months after obtaining due clearance from the Institution's Ethics Committee. A total of 42 individuals (age ≥18 years) with type 2 diabetic patients who visited the Endocrinology department of the hospital from July 15, 2022, to September 13, 2022, were recruited. The exclusion criteria included those with a severe medical illness such as severe liver disease (Child-Pugh score >7), thyroid disease (hypothyroidism or hyperthyroidism), malignancies, past medical history of cardiovascular diseases such as myocardial infarction, stroke, coronary, carotid, or lower limb revascularization, those with an eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula of <30 ml/min/1.73 m^2, pregnant women, and type 1 diabetes. Demographic and clinical data were retrieved from the patient's medical records. Patients were informed of the purpose of the study, and consent was obtained while maintaining confidentiality at all stages.

For the assessment of cardiac autonomic neuropathy, patients were advised to avoid smoking, alcohol, and physical activity in the 24 hours prior to the test and avoid intake of food and caffeine 3 hours before the test. Drugs like antihistamines, and beta-blockers, acetaminophen were withheld twelve hours before the examination. CAN testing was performed using the "Diabetic Risk Profiler and Analysis Device" manufactured by Genesis Medical Systems Pvt. Ltd. The tests performed were according to guidelines by Spallone V *et al.* and included the following:

- The sympathetic function test was assessed with systolic blood pressure (SBP) response to standing. The change in systolic blood pressure from a supine position and standing up for 2 minutes was measured manually [Table 1].
- Parasympathetic tests included the heart rate response to deep breathing (exhalation:inhalation ratio) [Table 2]. Heart rate response to standing (30:15 ratio) [Table 3] and the Heart rate response to the Valsalva maneuver (Valsalva ratio) [Table 4].
- The heart rate responses to deep breathing, standing, and Valsalva maneuver was assessed using the "Diabetic Risk Profiler and Analysis Device."

Each normal test was graded as 0, the borderline test as 0.5, and the abnormal test as 1. Based on this, the severity of cardiac autonomic neuropathy (CAN) was quantified using a Cardiac Autonomic Neuropathy Score, which had a minimum score of 0 and a maximum score of 4. A score of 0-0.5 was regarded as absent CAN, 1-1.5 as early CAN, and ≥2 as definite CAN [Table 5].

Table 1: Grading of change in SBP from supine to standing

Difference in SBP (mmHg)	Grading
≥20	Abnormal
11-19	Borderline
≤10	Normal

Table 2: Grading according to E:I (exhalation to inhalation) ratio

E:I Ratio	Grading
≤1.10	Abnormal
1.11-1.20	Borderline
≥1.21	Normal

Table 3: Grading according to 30:15 ratio

30:15 Ratio	Grading
≤1	Abnormal
1.01-1.03	Borderline
≥1.04	Normal

Table 4: Grading according to Valsalva ratio

Valsalva ratio	Grading
≤1.10	Abnormal
1.11-1.20	Borderline
≥1.21	Normal

Table 5: Grading of CAN based on CAN score

CAN score	Grading
0-0.5	ABSENT CAN
1-1.5	EARLY CAN
≥2	DEFINITE CAN

Statistical analysis

Data were entered into a Microsoft Excel data sheet and were analyzed using SPSS 22.0 version software package. Categorical variables were represented in the form of frequency with percentages. The Chi-square test was used as a test of significance for qualitative data. Continuous variables that followed normal distribution were represented as mean and standard deviation, whereas continuous variables not following normal distribution were expressed as median (IQR). An independent *t*-test was used as a test of significance to identify the mean difference between two quantitative variables. One-way ANOVA was used to compare the continuous variables between the three groups of CANs, and the Kruskal–Wallis test was used for variables not following a normal distribution. All the statistical analyses were carried out at a 5% level of significance ($P < 0.05$).

Statistical software

MS Excel, SPSS version 22.0 (IBM SPSS Statistics, Somers, NY, USA) was used to analyze data.

Results

The mean age of all subjects was 52.3 ± 12.7 years, and out of the subjects, 52.4% were men, and 47.6% were women. The median (IQR) duration of diabetes was 6 (1.9 - 12.8) years. The mean Hba1c in the study was 8.77 ± 1.72%. All 42 patients were on oral antidiabetic drugs (metformin, sulfonylureas, DPP4 inhibitors, thiazolidinediones, SGLT2 inhibitors, alpha glucosidase inhibitors), 11 patients were on insulin, 21 patients were on statins, and 10 were on antihypertensive medications (non-beta-blocking drugs).

All patients underwent cardiac autonomic testing and were classified into different categories of severity based on the mentioned criteria. All 42 subjects were classified into three groups based on the tests for cardiovascular autonomic neuropathy. There were as follows:

No CAN (n = 6, 14.3%),

Early CAN (n = 24, 57.1%), and

Definite CAN (n = 12, 28.6%).

Majority of the patients had early CAN, that is, in 24 patients, and 12 patients had definite CAN and only six patients do not have CAN.

Baseline characteristics were assessed, and the association of the various risk factors with the severity of CAN was noted. Patients with any form of CAN (early and definite CAN) tend to be older, with higher HbA1c and mean glucose values. The lipid profile showed a similar trend as well, with higher levels of total cholesterol, triglycerides, LDL and VLDL in patients affected with CAN. It was also noted that although all patients were on oral antidiabetic drugs, a greater percentage of patients affected by CAN needed insulin as compared to the No CAN group [Table 6].

Discussion

Cardiac autonomic neuropathy (CAN) is a significant complication of type 2 diabetes mellitus (T2DM) that can have profound implications for patients' cardiovascular health. As primary care physicians play a crucial role in managing patients with T2DM, understanding the prevalence of CAN is essential to identify and manage this condition effectively.

Several studies have investigated the prevalence of CAN in patients with T2DM, providing valuable insights into the magnitude of this complication. Vinik *et al.*[4] reported a prevalence of approximately 20% depending on the diagnostic. Similarly, Spallone *et al.*[5] estimated a prevalence of 44% in patients with T2DM. These findings highlight the high prevalence of CAN in individuals with T2DM and emphasize the importance of routine screening and early intervention by primary care physicians.

Our findings revealed that among the 42 subjects included in the study, a significant proportion exhibited signs of CAN. The classification of patients based on the severity of CAN indicated that the majority of individuals had early CAN (57.1%), followed by definite CAN (28.6%), whereas only a small percentage did not show any signs of CAN (14.3%).

The association between various baseline characteristics and the severity of CAN was explored in this study. Patients with any form of CAN tended to be older, which is consistent with previous research that suggests an age-related risk for developing autonomic dysfunction.[6] This finding highlights the importance of regular screening for CAN in older patients with T2DM. Furthermore, patients with CAN exhibited higher HbA1c and mean glucose values, indicating poorer glycemic control. Poor glycemic control has been consistently linked to the development and progression of CAN, emphasizing the need for optimal diabetes management to mitigate the risk of autonomic neuropathy.[2]

In a recent study based on the North Indian population by Bhuyan AK *et al.*, similar results were obtained with CAN patients

Table 6: Baseline characteristics according to the presence of cardiovascular autonomic neuropathy (n=42)

		Absent CAN (n=6, 14.3%)	Early CAN (n=24, 57.1%)	Definite CAN (n=12, 28.6%)	P
Age Mean (SD)		49.83 (12.79)	49.88 (12.50)	58.33 (11.95)	0.149
Sex	Male	3 (13.6%)	15 (68.2%)	4 (18.2%)	0.254
	Female	3 (15.0%)	9 (45.0%)	8 (40.0%)	
Hba1c, % Mean (SD)		8.0 (1.5)	9.13 (1.8)	8.58 (1.4)	0.296
Plasma Glucose, mg/dl Mean (SD)		179.7 (42.5)	223.6 (51.9)	202.7 (47.1)	0.145
Total Cholesterol, mg/dl Mean (SD)		147.1 (23.7)	180.4 (44.7)	176.3 (37.7)	0.211
Triglycerides, mg/dl Mean (SD)		170.7 (112.6)	177.0 (116.0)	167.4 (77.1)	0.966
LDL, mg/dl Mean (SD)		83.3 (29.8)	110.3 (42.0)	100.1 (41.8)	0.337
VLDL, mg/dl Mean (SD)		25.8 (11.8)	32.3 (11.2)	32.0 (10.5)	0.558
Use of Oral Anti-diabetic Drugs		6 (14.3%)	24 (57.1%)	12 (28.6%)	a*
Use of Insulin		2 (18.2%)	4 (36.4%)	5 (45.5%)	0.250

*a. No statistics are computed because Oral Anti-diabetic Drugs (METFORMIN) is a constant

being older with a longer diabetes duration (11.56 vs. 3.13 years) compared to patients without CAN.[7] Chhaya Ahire *et al.* also found a similar positive correlation between the duration of diabetes in the patient and the occurrence of damage to the nerve fibers.[8]

Our study also assessed the lipid profile of the patients, revealing a significant association between dyslipidemia and the presence of CAN. Patients affected by CAN exhibited higher levels of total cholesterol, triglycerides, LDL, and VLDL. These lipid abnormalities have been implicated in the pathogenesis of CAN, as they contribute to endothelial dysfunction and vascular inflammation.[9] Therefore, lipid management should be an integral part of the comprehensive management approach for T2DM patients to reduce the risk of CAN development and progression.

Interestingly, despite all patients being on oral antidiabetic drugs, a greater percentage of individuals affected by CAN required insulin compared to those without CAN. This observation suggests that CAN may represent a more advanced stage of T2DM, requiring intensified treatment strategies. It is crucial to recognize the limitations of oral antidiabetic drugs in managing advanced diabetes complications, including CAN, and consider insulin therapy to optimize glycemic control and potentially slow down the progression of neuropathy.[10]

Although the mechanism for CAN is not fully understood, it is known that damage to the autonomic nerve fibers (that innervate the heart and blood vessels) through oxidative stress, as a result of persistent hyperglycemia and hypoglycemia in diabetes, attributed to its development.[11] Hyperglycemia also leads to direct neuronal damage (via the polyol pathway) and decreased neuronal blood flow (via protein kinase C activation). Neuronal blood supply may also be affected due to the Accumulation of advanced glycosylation end products (AGEs), thereby leading to nerve hypoxia and altered nerve function.[12] Smoking, obesity, and lifestyle are among the risk factors associated with CAN development.

CAN is usually symptomatic and managed along with lifestyle modification, intensive glycemic control, antioxidants, and treatment of orthostatic hypotension.

Although our study provides valuable insights into the prevalence and severity of CAN in T2DM patients, it is important to acknowledge certain limitations. The sample size was relatively small, which may limit the generalizability of our findings. Additionally, the cross-sectional design of the study does not allow for causal relationships to be established. Longitudinal studies with larger cohorts are warranted to confirm the associations observed in this study and further explore the temporal relationship between risk factors and the development of CAN.

Conclusion

The prevalence of CAN in patients with T2DM underscores the importance of primary care physicians' role in screening, diagnosis, and management. The high prevalence of CAN necessitates routine screening to identify patients at risk, initiate appropriate interventions, and collaborate with specialists when needed. By understanding the prevalence and implications of CAN, primary care physicians can play a critical role in reducing the burden of cardiovascular disease in patients with T2DM.

Key points

1. Out of the 42 patients, a total of 36 patients (85.7%) were diagnosed with CAN. Among those with CAN, 24 patients had early CAN (57.1%), and 12 were diagnosed with definite CAN (28.6%).
2. Patients with any form of CAN (early and definite CAN) had higher HbA1c and mean glucose values than those without CAN.
3. CAN was also found to be more severe among older patients with diabetes.
4. The mean age of subjects was 52.3 ± 12.7 years, and out of the subjects, 52.4% were men, and 47.6% were women.
5. The median (IQR) duration of diabetes was 6 (1.9 - 12.8) years, and mean Hba1c in the study was 8.77 ± 1.72%.

Acknowledgement

I would like to thank ICMR for providing the necessary support for the primary research work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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