Original Article

A Study of Cardiac Autonomic Neuropathy in Patients with Type 2 Diabetes Mellitus: A Northeast India Experience

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Abstract

Aim: To investigate the prevalence and the risk factors for cardiac autonomic neuropathy (CAN) in type 2 diabetes mellitus (DM) patients. **Study Design:** Cross-sectional cohort study. **Place and Duration of Study:** This study was conducted in the Department of Endocrinology, Gauhati Medical College and Hospital, Assam, India between December 2016 to March 2018. **Methodology:** We included 100 patients (60 males and 40 females; age range: 36–72 years) with type 2 DM. Their clinical, biochemical, and metabolic parameters were analyzed and assessment of CAN were done based on the Ewing's criteria. **Results:** Out of 100 patients, 60 were males and 40 were females. The mean age of the patients was 53.3 ± 10.37 years (36–72 years) and the mean duration of diabetes was 9.03 ± 6.4 years (6 months–25 years). Patients were divided into two groups: "without CAN" (CAN−) and "with CAN" (CAN+). The prevalence of CAN was 70%, with early CAN in 25%, definite CAN in 24%, and severe CAN in 21% cases The patients with CAN were older ($P = 0.0005$), had longer diabetes duration (11.56 vs. 3.13; $P = 0.0001$), higher creatinine ($P < 0.0001$), and lower estimated glomerular filtration rate (eGFR) ($P = 0.0001$) compared to patients without CAN. Retinopathy, peripheral neuropathy, and nephropathy were common in CAN + patients. On multiple logistic regression analysis, duration of diabetes [odds ratio (OR); 6.7, $P < 0.0001$), older age (OR; 1.07, $P < 0.016$), and lower eGFR (OR; 0.97, $P < 0.03$) were risk factors for CAN. **Conclusion:** CAN is a common microvascular complication in type 2 DM with duration of diabetes, age, and severity of nephropathy being its significant determinants.

Keywords: Cardiac autonomic neuropathy, complication, India, type 2 diabetes mellitus

Introduction

India is the diabetes capital of the world with 41 million Indians suffering from diabetes.[1] Cardiac autonomic neuropathy (CAN) is often an underdiagnosed complication of diabetes mellitus (DM) and is associated with increased mortality and morbidity. The prevalence of CAN is approximately 31–73% in type 2 DM and the annual incidence has been reported to be 2%.[2,3] CAN pathogenesis is complex and multifactorial. CAN is initially subclinical and becomes symptomatic only in the later stages of the disease. Identifying patients with CAN is important as early initiation of intensive interventions targeting lifestyle, glycemic control, and cardiovascular risk factors can slow the progression of CAN and may be reversed if diagnosed soon after onset.[3] There have been only a few Indian studies on CAN in diabetes patients and no such study from Northeast India. Therefore, the present study has been designed to investigate the prevalence and risk factors for CAN involvement in type 2 DM in our setup.

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Methods

This study was a cross-sectional observational study, conducted in the Gauhati Medical College and Hospital, Assam, India. A total of 100 consecutive patients of type 2 DM attending the outpatient department and patients admitted in the endocrinology ward were enrolled in this study. The study was conducted between December 2016 to March 2018. The diagnosis of DM was made by the criteria given by the American Diabetes Association 2016.[4] Exclusion criteria were: (1) other diseases associated with autonomic nervous system affection like thyroid disease (hyperthyroidism/hypothyroidism) and

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severe systemic diseases (cardiac, pulmonary, renal, and malignancy). Those who had a history of hypoglycemia in the preceding 24 h before testing were also excluded from the study. (2) Patients on drugs known to affect autonomic function like beta-blockers, sympathomimetics, vasodilators, diuretics, and antiarrhythmics, (3) patients with underlying cardiac illness like coronary artery disease, ischemic heart disease, rheumatic heart disease, arrhythmia, and cardiac failure, (4) uncooperative and physically disabled patients. Patients were advised to avoid coffee, alcohol, smoking, and also strenuous exercise in the preceding 24 h. The study was performed according to the guidelines of the ethics committee of our institute and informed consent was taken from all the patients.

All patients underwent a thorough physical examination, including measurement of resting heart rate, blood pressure, and body mass index (BMI). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or if the patient used any antihypertensive medications. In all patients blood samples were collected in the morning after an overnight fast. Fasting lipid profile (low-density lipoprotein/LDL, high-density lipoprotein/HDL, triglycerides/TG) and creatinine levels were measured with an automatic analyzer. Glycosylated hemoglobin (HbA1c) was determined by the high-performance liquid chromatography. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study (MDRD) equation.[5] Urine albumin excretion was estimated from the early morning spot urine sample using turbidimetric immunoassay and urine creatinine was estimated using modified Jaffe's method. The urine albumin creatinine ratio was defined as the urinary albumin (in milligram) value divided by the urinary creatinine (in gram) concentration. Diabetic nephropathy was defined by presence of albuminuria (≥30 mg/g creatinine).[6] Diabetic retinopathy was evaluated by an experienced ophthalmologist. Peripheral neuropathy assessment was quantified by the neuropathic disability score (NDS). The sensory parameters were scored as 0 if present and 1 if reduced or absent for each leg separately; ankle reflexes were scored 0 if normal, 1 if present with reinforcement, and 2 if absent. The maximum score was 10 and a score above 2 was considered to have neuropathy.[7]

The cardiac autonomic function was evaluated with the CAN system analyzer (CANS 504) manufactured by the Diabetik Foot Care India Pvt Limited (DFCI), Chennai. It analyzes both sympathetic and parasympathetic autonomic nervous system. The system uses electrocardiogram (ECG) and automatic non-invasive blood pressure measurements to conduct a battery of six tests. Every patient was explained prior to testing and then the tests were performed in a quiet ambient room with dim lighting and room temperature of 24–26°C.

The following tests of the autonomic nervous system were performed in all patients:

Tests reflecting parasympathetic damage:

1. Resting heart rate: A resting heart rate >100 beats per minute was considered abnormal
2. Heart rate variation during deep breathing: The subject was made to lie supine and after 2 min of normal breathing, the patient was asked to breathe deeply at 6 breaths per minute (a rate that produces maximum variation in heart rate). During breathing a continuous ECG recording was obtained. The expiration: inspiration (E:I) difference was calculated as the difference between the longest R-R interval during expiration to the shortest R-R interval during inspiration. E:I difference of <11 was considered abnormal
3. Heart rate response to standing (30:15 ratio): The patient was asked to lie supine quietly for 3 min and then asked to stand up. A continuous ECG was recorded and the 30:15 ratio was calculated by taking the ratio of the R-R interval at 30th beat and at 15th beat after standing. A 30:15 ratio <1.01 was considered abnormal
4. Valsalva ratio: The patient was asked to blow into a mouth piece connected to a manometer so as to keep the pressure up to 40 mmHg and to maintain it for 15 s, while a continuous ECG recording was done. After 30 s ECG was monitored again for 15 s. The Valsalva ratio was calculated as longest R-R interval after release to shortest R-R interval during maneuver. This procedure was avoided in patients with proliferative retinopathy. A Valsalva ratio <1.1 was considered abnormal.

Tests for sympathetic damage:

1. Blood pressure response to standing: Patients were asked to stand in the supine position and remain standing for 2 min. A decline in SBP by ≥20 mmHg was considered abnormal. According to the original Ewing's criteria, fall >30 mmHg was considered abnormal but the criteria was modified according to the current definition of orthostatic hypotension[8]
2. Blood pressure response to sustained handgrip: The subject was asked to apply pressure on a handgrip dynamometer with dominant arm for three times. Highest of three readings was called maximum voluntary contraction. The subject was instructed to maintain handgrip steadily at 30% of maximum contraction for as long as possible to a maximum of 5 min. Blood pressure was measured on non-exercising arm at rest and at the end of grip. The normal response is a rise of DBP by >16 mmHg, whereas a response ≤10 mmHg was considered abnormal.

The results were then categorized into one of the four groups[9]

- Normal
- Early CAN – One abnormal parasympathetic test
- Definite CAN – At least two abnormal parasympathetic tests
- Severe or advanced CAN – Abnormality in both parasympathetic and sympathetic tests.

Statistical analysis

Statistical analysis was done using the SPSS Statistics Version 20. All data are shown as the mean or as percentages.

Continuous variables were compared by unpaired student's *t*-test. Categorical variables were compared by the Chi-square test. Multivariate logistic regression analysis was used to analyze various risk factors associated with CAN. A *P* value <0.05 was considered statistically significant.

Results

A total of 100 patients were enrolled in this study. The mean age of the patients was 53.3 ± 10.37 years (range: 36–72 years). Among them, 60 were male and 40 were female patients. The mean duration of diabetes was 9.03 ± 6.4 years ranging from 6 months to 25 years [Table 1]. Patients were divided into two groups: "without CAN" (CAN−) and "with CAN" (CAN+). The clinical and biochemical characteristics stratified by the presence of autonomic neuropathy are shown in Table 1. The patients with CAN were older ($P = 0.0005$), had longer diabetes duration (11.56 vs. 3.13 years; $P = 0.0001$), higher creatinine ($P < 0.0001$), and significantly lower eGFR ($P = 0.0001$) compared to patients without CAN. The prevalence of retinopathy, peripheral neuropathy, and nephropathy were higher in CAN + patients [Table 2]. No significant differences in sex, BMI, SBP, DBP, HbA1c, LDL, HDL, and TG were found between the two groups.

Of all the 70 patients with CAN, 10 (14.28%) were clinically asymptomatic, 15 (21.4%) complained of only gastrointestinal symptoms, 12 (17.1%) complained of cardiovascular symptoms, 12 (17.1%) of urinary bladder dysfunction or erectile dysfunction in men, 12 (17.1%) had a combination of gastrointestinal and cardiovascular symptoms, and 9 (12.8%) had a combination of symptoms involving all three systems.

The prevalence of CAN was 70%, with early CAN in 25%, definite CAN in 24%, and severe CAN in 21% cases [Figure 1]. The presence of severe CAN was seen with mean duration of diabetes of 13.14 ± 6.49 years. Among the abnormal cardiovascular autonomic reflex test, resting tachycardia (heart rate ≥100 beats per minute) was present in 17%, abnormal E:I difference in 56%, abnormal 30:15 ratio in 42%, abnormal Valsalva ratio in 32%, orthostatic hypotension 11%, and abnormal blood pressure response to sustained handgrip in 19% cases [Figure 2].

Multiple logistic regression analysis [Table 3] with presence of CAN as the dependent variable showed that longer duration of diabetes [odds ratio (OR): 6.7, $P < 0.0001$), older age (OR: 1.07, $P < 0.016$), and lower eGFR (OR: 0.97, $P < 0.03$) were independently associated with CAN but no significant association was found with BMI, blood pressure, HbA1c, and lipids.

Discussion

In our study a total of 70 patients (70%) with type 2 DM had CAN. There were no significant differences in prevalence of CAN between the two sexes. Early CAN was present in 25% cases, definite CAN in 24%, and severe CAN in 21% cases

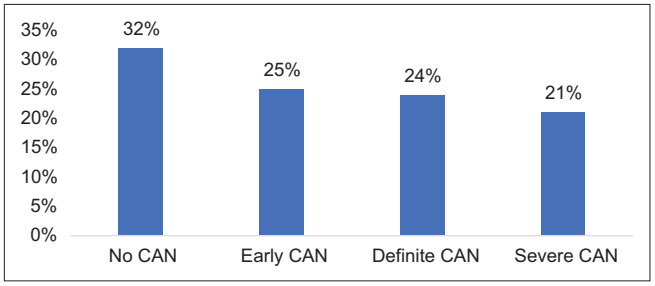

Figure 1: Prevalence of CAN in type 2 diabetes mellitus patients. CAN: Cardiac autonomic neuropathy. Prevalence is expressed as percentage in each group

Table 1: Clinical and biochemical characteristics of the study population

Variables	Mean±SD			*P*
	Total study population (*n*=100)	CAN− (*n*=30)	CAN+ (*n*=70)	
Age (years)	53.3±10.37	47.93±8.51	55.60±10.30	0.0005
Male sex	60 (60%)	44 (62.8%)	16 (53%)	0.37
Duration of diabetes (years)	9.03±6.4	3.13±1.52	11.56±6.15	<0.0001
Weight (kg)	62.1±10.3	62.53±13.09	61.94±9.10	0.7960
BMI (kg/m^2)	23.5±2.7	24.24±3.49	23.28±2.28	0.1043
BP systolic (mmHg)	133.5±11.9	132.67±13.63	133.79±11.18	0.6689
BP diastolic (mmHg)	88.2±7.4	86.67±8.44	88.86±6.92	0.1784
Resting heart rate (beats/min)	85.9±10.5	79.47±5.64	88.70±11.01	<0.0001
HbA1c (NSGP)	10.9±15.5	9.45±2.49	11.55±18.68	0.5424
Creatinine (mg/dl)	0.8±0.3	0.76±0.10	1.01±0.33	<0.0001
eGFR (ml/min/1.73)	81.1±25.8	95.87±14.07	74.85±27.26	0.0001
LDL (mg/dl)	99.5±38.7	101.93±34.72	98.54±34.90	0.6567
HDL (mg/dl)	38.8±10.5	40.17±10.86	38.31±10.45	0.4241
TG (mg/dl)	179.8±80.1	166.33±54.38	185.59±88.71	0.2743

*P<0.05 was considered statistically significant. CAN+: Cardiac autonomic neuropathy present, CAN−: Cardiac autonomic neuropathy absent, BMI: Body mass index, BP: Blood pressure, HbA1c: Glycated hemoglobin, eGFR: Estimated GFR, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride, SD: Standard deviation

Table 2: Prevalence of other microangiopathies in the study population

Microangiopathy	CAN present (%)	CAN absent (%)	Chi-square test (*P*)
Neuropathy	70 (100)	11 (36)	<0.0001
Nephropathy	64 (91)	1 (3)	<0.0001
Retinopathy	64 (91)	1 (3)	<0.0001

*P<0.05 was considered statistically significant. CAN: Cardiac autonomic neuropathy

Table 3: Multivariant logistic regression analysis for assessing predictors of CAN

Variables	Odds ratio (OR)	95% CI	*P*
Model 1			
Age (years)	0.825	0.741-0.918	0.12
Duration of diabetes (years)	6.762	2.385-19.170	<0.001
Model 2			
Age (years)	1.074	1.013-1.138	0.016
BMI (kg/m^2)	0.876	0.733-1.047	0.144
BP systolic (mmHg)	0.975	0.910-1.043	0.458
BP diastolic (mmHg)	1.070	0.964-1.189	0.204
HbA1c (NSGP)	0.931	0.724-1.198	0.580
eGFR (ml/min/1.73)	0.975	0.952-0.998	0.037
LDL (mg/dl)	0.993	0.978-1.007	0.318
HDL (mg/dl)	1.017	0.966-1.070	0.518
TG (mg/dl)	1.004	0.996-1.012	0.308

*P<0.05 was considered statistically significant. CAN+: Cardiac autonomic neuropathy present, CAN−: Cardiac autonomic neuropathy absent, BMI: Body mass index, BP: Blood pressure, HbA1c: Glycated hemoglobin, eGFR: Estimated GFR, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride, OR: Odds ratio, CI: Confidence interval

which is in accordance with the study by Birajdar *et al.*[10] In the study by Birajdar *et al.*, prevalence of CAN was found to be 58% and abnormal 30:15 ratio was the most common CAN abnormality, present in 38% cases.[10] Contrary to that in our study, abnormal E:I difference was the most common CAN abnormality, found in 56% cases. The high prevalence of CAN in our study compared to other studies could be probably due to the fact that we included patients with long duration of diabetes (mean duration –9.03 ± 6.4 years). In our setup most of the patients seek medical advice and are diagnosed with type 2 DM only after patients become symptomatic and this is due to people ignorance about the disease, especially among the rural-based population. Most often patients present with one of the diabetes complications. A similar high prevalence rate of autonomic neuropathy has been reported by Aggarwal *et al.*[11]

The pathogenesis of CAN is complex and multifactorial. Hyperglycemia-induced activation of the polyol pathway cause direct neuronal damage and activation of protein kinase C leading to vasoconstriction and decreased neuronal blood flow. Other mechanisms involved are increased oxidative stress, increased free radical production, dysfunction of nitric oxide

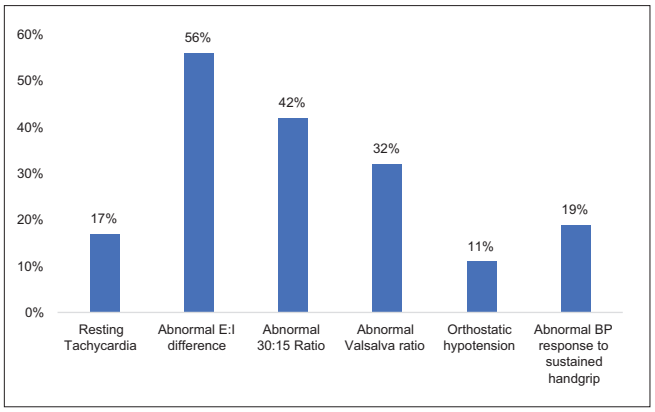

Figure 2: Distribution of abnormal cardiovascular autonomic tests in the study population. E:I: Expiration to inspiration ratio, BP: Blood pressure. Prevalence is expressed as percentage in each group

production, immune mechanisms, and neurotrophic growth factors deficiency. Accumulation of advanced glycosylation endproducts in the neuronal blood vessels leads to nerve hypoxia and altered nerve function.[12]

There are several risk factors reported in the literature associated with the development of CAN which includes older age, diabetes duration, glycemic control, the presence of microvascular complications, hypertension, dyslipidemia (decreased HDL, increased LDL, and TGs levels), and obesity.[13] In our study longer duration of disease was a strong predictor of CAN (OR: 6.7, $P \leq 0.001$). The positive correlation of CAN and long duration of diabetes have been reported by Ahire *et al.* who demonstrated that patients having duration of diabetes >5 years are more likely to have definite and severe CAN than in patients with duration of disease <5 years.[14] However, Ahire *et al.* also found that early CAN was commonly present in patients with shorter duration of disease and concluded that all newly diagnosed type 2 DM patients be screened for CAN. HbA1c was not found to be significantly associated with CAN which suggests that poor short-term glycemic control does not correlate with the prevalence of CAN. The possible explanation could be that in type 2 DM, a single measurement of HbA1c does not reveal the pattern of glycemic control in the last few years, which is responsible for the development of diabetic complications like peripheral neuropathy, retinopathy, and nephropathy.

Because of a common pathophysiology, diabetic microangiopathic complications are closely related to one another. We found CAN to be associated with increasing prevalence of microvascular complications like peripheral neuropathy, nephropathy, and retinopathy. In our study all the patients with CAN also had coexisting peripheral neuropathy and this is in accordance with previous study by Moţăţăianu *et al.*[15] who demonstrated increasing severity of CAN with increasing severity of peripheral neuropathy. In our study both retinopathy and nephropathy were detected in 91% (n = 64) of patients, whereas Moţăţăianu *et al*. reported retinopathy in 72% cases and neuropathy in 92% cases with CAN.[15]

We found a significant association between CAN and diabetic kidney disease. eGFR was found to have negative correlation with prevalence of CAN. The renal glomeruli and tubules are innervated by the sympathetic nerve and it is well known that parasympathetic involvement precedes sympathetic neuropathy in CAN which results in a relative sympathetic over activity.[16] So, this imbalance of autonomic system can affect renal homeostasis involving renal blood flow and filtration which can accelerate the progression to renal dysfunction. In the study by Yun *et al.* definite CAN had a significantly higher (2.62 times) risk for new onset chronic kidney disease than patients with normal autonomic function.[16] Thus, we suggested that low eGFR could be an important predictor of CAN.

Presence of CAN is strongly associated with increased mortality and morbidity such as stroke, coronary artery disease, and silent myocardial ischemia. This has been confirmed by the results from the European Epidemiology and Prevention of Diabetes (EURODIAB) study and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[17,18] For early diagnosis and prompt management of CAN, ADA 2018 has recommended that all patients with type 2 DM should be assessed for diabetic neuropathy starting at diagnosis.[19] Treatment of CAN comprises of symptomatic management as well as effective therapies to slow or reverse its progression. The modalities of treatment include lifestyle modification, intensive glycemic control, antioxidants, and treatment of orthostatic hypotension. The limitation of our study is that the sample size was small and hence, results cannot be applied to the general population.

Conclusion

Our study revealed that CAN is a common microvascular complication in type 2 DM. The duration of diabetes, age, and severity of nephropathy are its significant determinants and hence optimal glycemic management at early stages of diabetes may prevent development of CAN.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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