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Prevalence of Cardiovascular Autonomic Neuropathy and Its Association with Duration of Type 2 Diabetes Mellitus: A Cross-Sectional Study.

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Abstract

Background: Cardiovascular autonomic neuropathy (CAN) is a common but underrecognized complication of type 2 diabetes mellitus (T2DM) and is associated with increased cardiovascular morbidity and mortality. Early detection using simple cardiovascular autonomic reflex tests may facilitate timely intervention and improve clinical outcomes. This study aimed to determine the prevalence of CAN in patients with T2DM and evaluate its association with the duration of diabetes. ***Methods:*** This hospital based cross-sectional observational study included 130 participants, comprising 100 patients with T2DM and 30 age and sex matched healthy controls. Cardiovascular autonomic function was assessed using five standardized cardiovascular reflex tests: deep breathing difference (DBD), postural tachycardia index (PTI), Valsalva ratio (VR), orthostatic hypotension test (OHT), and sustained handgrip test (SHG). Based on the cumulative autonomic function score, participants were classified as having normal autonomic function, borderline autonomic dysfunction, or definitive cardiovascular autonomic neuropathy. Statistical analysis was performed using the unpaired Student's t-test, chi-square test, and Fisher's exact test, with a p value of <0.05 considered statistically significant. ***Results:*** The mean age of the diabetic and control groups was 50.56 and 53.56 years, respectively, with comparable age and sex distributions. Definitive cardiovascular autonomic neuropathy was present in 47% of diabetic patients, while 24% had borderline autonomic dysfunction. Compared with controls, diabetic patients demonstrated significantly reduced deep breathing difference (11.24 ± 5.94 vs. 18.80 ± 5.16 beats/min; p=0.0001), postural tachycardia index (1.05 ± 0.10 vs. 1.105 ± 0.14; p=0.044), and Valsalva ratio (1.18 ± 0.135 vs. 1.27 ± 0.104; p=0.0012). They also exhibited a significantly greater fall in systolic blood pressure during the orthostatic hypotension test (12.25 ± 7.94 vs. 7.60 ± 3.80 mmHg; p=0.002) and a reduced diastolic blood pressure response during the sustained handgrip test (12.69 ± 5.91 vs. 17.17 ± 3.91 mmHg; p<0.05). The prevalence of definitive CAN increased from 21% in patients with diabetes duration of less than five years to 41% in those with diabetes duration of 5–10 years and 100% in those with diabetes duration exceeding 10 years (p=0.05). Significant associations were also observed between CAN, prolonged QTc interval, and diabetic retinopathy. ***Conclusions:*** Cardiovascular autonomic neuropathy is highly prevalent among patients with type 2 diabetes mellitus and is strongly associated with longer duration of diabetes. Simple bedside cardiovascular autonomic reflex tests provide an effective, non-invasive, and inexpensive method for early detection of autonomic dysfunction. Routine screening of patients with T2DM, particularly those with longer disease duration or microvascular complications, may facilitate early diagnosis, identify patients at higher risk of cardiovascular complications, and optimize clinical management.

Keywords: Type 2 diabetes mellitus; cardiovascular autonomic neuropathy; diabetic autonomic neuropathy; cardiovascular reflex tests; diabetic retinopathy.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the fastest growing non-communicable diseases worldwide and represents a major public health challenge because of its chronic vascular and neurological complications. Among these complications, diabetic neuropathy is one of the most common, affecting both the peripheral and autonomic nervous systems. Cardiovascular autonomic neuropathy (CAN) is one of the most serious yet underrecognized complications of diabetes mellitus and is associated with increased cardiovascular morbidity and mortality. Despite its clinical importance, CAN often remains undiagnosed because many patients remain asymptomatic until advanced stages of the disease.[1-7]

Cardiovascular autonomic neuropathy results from damage to the autonomic nerve fibers that regulate heart rate, myocardial contractility, and vascular tone. The condition has been associated with resting tachycardia, exercise intolerance, orthostatic hypotension, silent myocardial ischemia, cardiac arrhythmias, prolonged QT interval, and sudden cardiac death. Several longitudinal studies have identified cardiovascular autonomic neuropathy as an independent predictor of cardiovascular events and all-cause mortality in patients with diabetes mellitus, highlighting the importance of early diagnosis and timely management.[1,2,6-10]

The pathogenesis of CAN is multifactorial and involves chronic hyperglycemia-induced metabolic and vascular injury. Persistent hyperglycemia activates several biochemical pathways, including oxidative stress, accumulation of advanced glycation end products, activation of the polyol pathway, protein kinase C activation, and microvascular ischemia, ultimately resulting in autonomic nerve dysfunction. The earliest abnormalities usually involve parasympathetic fibers, followed by sympathetic involvement as the disease progresses. Consequently, cardiovascular autonomic dysfunction may be present even in the absence of overt cardiovascular symptoms, highlighting the need for routine screening in patients with type 2 diabetes mellitus.[4-7,13-15]

The prevalence of CAN varies considerably depending on the diagnostic criteria, duration of diabetes, glycemic control, and study population, with reported rates ranging from approximately 20% in newly diagnosed patients to more than 60% in those with longstanding diabetes. Increasing age, prolonged duration of diabetes, poor glycemic control, hypertension, obesity, dyslipidemia, diabetic retinopathy, nephropathy, and peripheral neuropathy have consistently been identified as important risk factors. Recent evidence also suggests that CAN may develop during prediabetes and early glucose intolerance, highlighting the need for timely cardiovascular autonomic assessment. [2,5,12-18]

Several non-invasive cardiovascular reflex tests described by Ewing and Clarke remain the cornerstone for the clinical assessment of CAN. These bedside tests evaluate both parasympathetic and sympathetic autonomic function by measuring heart rate responses to deep breathing, standing, and the Valsalva maneuver, together with blood pressure responses to standing and sustained handgrip. Owing to their simplicity, reproducibility, and low cost, these tests continue to be recommended for routine clinical evaluation and epidemiological studies, particularly in resource-limited settings.[2,4,5,21,22]

Cardiovascular autonomic neuropathy has also been shown to correlate with other microvascular complications of diabetes, including diabetic retinopathy, and with electrocardiographic abnormalities such as QTc prolongation, both of which may indicate an increased risk of adverse cardiovascular outcomes. Early identification of autonomic dysfunction therefore provides an opportunity for optimizing glycemic control, reducing cardiovascular risk factors, and implementing preventive interventions before irreversible complications develop.[8,9,18-20]

Although several international studies have evaluated CAN, data from Indian populations remain relatively limited, particularly from tertiary care centers where patients often present with long-standing diabetes and multiple complications. Previous Indian studies have reported a high prevalence of CAN using Ewing's cardiovascular reflex tests; however, variations in patient characteristics and study methodology necessitate further evaluation in different clinical settings.[16,23,24]

The present study was undertaken to determine the prevalence of cardiovascular autonomic neuropathy among patients with type 2 diabetes mellitus using simple bedside cardiovascular autonomic function tests and to evaluate its association with the duration of diabetes. In addition, the study assessed the relationship between autonomic dysfunction and selected clinical parameters to facilitate early recognition of CAN in routine clinical practice.

MATERIALS AND METHODS

This hospital based cross-sectional observational study was conducted at a tertiary care hospital in Maharashtra, India. The study was undertaken to determine the prevalence of cardiovascular autonomic neuropathy (CAN) among patients with type 2 diabetes mellitus (T2DM) and to evaluate its association with the duration of diabetes mellitus.
Written informed consent was obtained from all participants prior to enrollment.

The study included 130 participants, comprising 100 consecutive patients with T2DM and 30 age- and sex-matched healthy individuals who served as controls. Patients with a confirmed diagnosis of T2DM, irrespective of the duration of diabetes, were eligible for inclusion. Healthy volunteers with a random blood glucose level of less than 100 mg/dL, who were non-alcoholic and not receiving medications known to influence autonomic function, were recruited as controls. Patients with symptomatic coronary artery disease, end-organ failure, chronic alcoholism, or those receiving antidepressants, antihistamines, anticholinergic drugs, β-agonists, or β-blockers were excluded from the study.

A detailed medical history was obtained from all participants using a predesigned proforma, followed by a comprehensive general and systemic physical examination. Information regarding demographic characteristics, duration of diabetes, treatment history, and clinical features was recorded. Routine laboratory investigations included complete blood count, fasting blood glucose, postprandial blood glucose, liver function tests, kidney function tests, and urine examination. Fundus examination was performed after pupillary dilatation by an ophthalmologist using direct ophthalmoscopy to detect diabetic retinopathy. A standard 12-lead electrocardiogram (ECG) was recorded for every participant, and the corrected QT (QTc) interval was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). A QTc interval of ≥440 ms was considered prolonged.

Cardiovascular autonomic function was assessed using the standardized cardiovascular reflex tests described by Ewing and Clarke. Participants were instructed to avoid tea, coffee, and cola beverages for 12 hours before testing and to consume only a light breakfast at least two hours before evaluation. Following 30 minutes of supine rest, autonomic function testing was performed under standardized conditions.

Parasympathetic function was evaluated by assessing heart rate response to deep breathing, heart rate response to standing (30:15 ratio), and the Valsalva maneuver. During the deep breathing test, participants breathed deeply at a rate of six breaths per minute, and the average difference between the maximum and minimum heart rate during six respiratory cycles was calculated. Heart rate response to standing was determined by calculating the ratio of the longest RR interval around the 30th beat to the shortest RR interval around the 15th beat after standing. The Valsalva ratio was calculated as the ratio of the longest RR interval after release of the maneuver to the shortest RR interval during the maneuver while maintaining an expiratory pressure of 40 mmHg for 15 seconds.

Sympathetic function was assessed by measuring blood pressure response to standing and blood pressure response to sustained handgrip. Orthostatic hypotension was determined by recording the fall in systolic blood pressure after standing from the supine position. The sustained handgrip test was performed by asking participants to maintain approximately 30% of their maximum voluntary contraction for three minutes, and the maximum increase in diastolic blood pressure was recorded.

Each cardiovascular reflex test was interpreted according to the criteria proposed by Ewing and Clarke and classified as normal, borderline, or abnormal. Individual tests were assigned scores of 0, 1, or 2, respectively, resulting in a cumulative autonomic function score ranging from 0 to 10. Participants with a total score of 0–1 were classified as having normal autonomic function, those with scores of 2–4 were considered to have borderline autonomic dysfunction, and those with scores of ≥5 were classified as having definitive cardiovascular autonomic neuropathy.

Data were entered into a master chart and analyzed using standard statistical methods. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Comparisons between the diabetic and control groups were performed using the unpaired Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, where appropriate. The association of cardiovascular autonomic neuropathy with the duration of diabetes, diabetic retinopathy, and prolonged QTc interval was also evaluated. A two-tailed p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 130 participants were enrolled in the study, including 100 patients with type 2 diabetes mellitus (T2DM) and 30 age- and sex-matched healthy controls.

The baseline demographic characteristics of the study participants are summarized in **Table 1**. The mean age of the diabetic group was 50.56 years compared with 53.56 years in the control group, with no statistically significant difference between the groups (p=0.452). Similarly, the sex distribution was comparable, with males comprising 55% of the diabetic group and 56.66% of the control group (p=1.00)

Table 1: Baseline characteristics of study participants

Variable	T2DM (n=100)	Controls (n=30)	*p* value
Mean age (years)	50.56	53.56	0.452
Male sex, n (%)	55 (55%)	17 (56.7%)	1.00
Female sex, n (%)	45 (45%)	13 (43.3%)	1.00

The distribution of diabetic patients according to disease duration is presented in **Table 2**. Among the 100 patients with T2DM, 37% had diabetes for less than five years, 41% had diabetes for 5–10 years, and 22% had diabetes for more than 10 years.

Table 2: Duration of diabetes mellitus among patients with T2DM

Duration of diabetes	n (%)
<5 years	37 (37%)
5–10 years	41 (41%)
>10 years	22 (22%)

Comparison of cardiovascular autonomic reflex tests between diabetic patients and healthy controls is shown in **Table 3**. The mean deep breathing difference (DBD) was significantly lower in diabetic patients than in controls (11.24 ± 5.94 vs. 18.80 ± 5.16 beats/min, p=0.0001). The mean postural tachycardia index (PTI) was also significantly reduced in diabetic patients compared with controls (1.05 ± 0.10 vs. 1.105 ± 0.14, p=0.044). Likewise, the mean Valsalva ratio (VR) was significantly lower among diabetic patients (1.18 ± 0.135 vs. 1.27 ± 0.104, p=0.0012). Sympathetic function tests also demonstrated significant impairment in diabetic patients, with a greater fall in systolic blood pressure during the orthostatic hypotension test (12.25 ± 7.94 mmHg vs. 7.60 ± 3.80 mmHg, p=0.002) and a significantly lower increase in diastolic blood pressure during the sustained handgrip test (12.69 ± 5.91 mmHg vs. 17.17 ± 3.91 mmHg, p<0.05).

Table 3: Comparison of cardiovascular autonomic function tests between diabetic patients and controls

Test	T2DM (Mean ± SD)	Controls (Mean ± SD)	*p* value
Deep breathing difference (beats/min)	11.24 ± 5.94	18.80 ± 5.16	0.0001
Postural tachycardia index (30:15 ratio)	1.05 ± 0.10	1.105 ± 0.14	0.044
Valsalva ratio	1.18 ± 0.135	1.27 ± 0.104	0.0012
Orthostatic hypotension (mmHg fall)	12.25 ± 7.94	7.60 ± 3.80	0.002
Sustained handgrip (mmHg rise)	12.69 ± 5.91	17.17 ± 3.91	<0.05

The overall prevalence of cardiovascular autonomic neuropathy is shown in **Table 4**. Based on the cumulative autonomic function score, 29% of diabetic patients had normal autonomic function, 24% had borderline autonomic dysfunction, and 47% fulfilled the criteria for definitive cardiovascular autonomic neuropathy.

Table 4: Prevalence of cardiovascular autonomic neuropathy in diabetic patients

CAN category	n (%)
Normal autonomic function	29 (29%)
Borderline autonomic dysfunction	24 (24%)
Definitive cardiovascular autonomic neuropathy	47 (47%)

The relationship between duration of diabetes and cardiovascular autonomic neuropathy is presented in **Table 5**. Definitive CAN was observed in 8 (21%) of 37 patients with diabetes duration of less than five years, 17 (41%) of 41 patients with diabetes duration of 5–10 years, and all 22 (100%) patients with diabetes duration exceeding 10 years. This association was statistically significant (p=0.05), indicating a progressive increase in autonomic dysfunction with increasing duration of diabetes

Table 5: Association between duration of diabetes and cardiovascular autonomic neuropathy

Duration of diabetes	Patients with definitive CAN	Percentage
<5 years (n=37)	8	21%
5–10 years (n=41)	17	41%
>10 years (n=22)	22	100%

Chi-square test: p=0.05

The association of cardiovascular autonomic neuropathy with diabetic retinopathy and prolonged QTc interval is summarized in **Table 6**. Among the 47 patients with definitive CAN, 28 (59%) had prolonged QTc intervals. In addition, 20 (80%) of the 25 patients with diabetic retinopathy had definitive cardiovascular autonomic neuropathy, demonstrating a significant association between autonomic dysfunction and diabetic microvascular complications (p=0.0001).

Table 6: Association of cardiovascular autonomic neuropathy with QTc prolongation and diabetic retinopathy

Variable	Patients with definitive CAN	*p* value
Prolonged QTc interval	28/47 (59%)	Significant
Diabetic retinopathy	20/25 (80%)	0.0001

The distribution of individual cardiovascular autonomic reflex test responses is shown in Table 7. Abnormal deep breathing difference was observed in 47% of diabetic patients, followed by abnormal postural tachycardia index in 34%, abnormal sustained handgrip response in 33%, abnormal Valsalva ratio in 27%, and abnormal orthostatic hypotension in 9%. Overall, parasympathetic function tests showed a higher frequency of abnormal responses than sympathetic function tests, suggesting earlier involvement of parasympathetic fibers in patients with type 2 diabetes mellitus

Table 7: Distribution of cardiovascular autonomic reflex test responses among patients with type 2 diabetes mellitus (n = 100)

Cardiovascular autonomic reflex test	Normal, n (%)	Borderline, n (%)	Abnormal, n (%)
Deep Breathing Difference (DBD)	30 (30%)	23 (23%)	47 (47%)
Postural Tachycardia Index (PTI)	53 (53%)	13 (13%)	34 (34%)
Valsalva Ratio (VR)	45 (45%)	28 (28%)	27 (27%)
Orthostatic Hypotension Test (OHT)	60 (60%)	31 (31%)	9 (9%)
Sustained Handgrip Test (SHG)	45 (45%)	22 (22%)	33 (33%)

DISCUSSION

Cardiovascular autonomic neuropathy (CAN) is one of the most common yet frequently overlooked chronic complications of diabetes mellitus. It is associated with impaired autonomic regulation of the cardiovascular system and contributes significantly to increased cardiovascular morbidity, silent myocardial ischemia, life-threatening arrhythmias, and sudden cardiac death. Early detection of CAN is clinically important because patients are often asymptomatic during the initial stages, allowing progression before diagnosis. In the present study, cardiovascular autonomic function was evaluated using standardized cardiovascular reflex tests, and nearly half of the patients with type 2 diabetes mellitus (T2DM) were found to have definitive CAN.

The study and control groups were comparable with respect to age and sex distribution, reducing the likelihood of demographic confounding. The mean age of diabetic patients was 50.56 years, and males constituted 55% of the study population. Similar demographic characteristics have been reported in previous Indian studies evaluating cardiovascular autonomic neuropathy, where the majority of patients were in the fifth and sixth decades of life with a slight male predominance. These findings suggest that the study population is representative of adults commonly affected by T2DM.[16,23,24]

The principal finding of the present study was that 47% of patients with T2DM had definitive cardiovascular autonomic neuropathy, while an additional 24% demonstrated borderline autonomic dysfunction. This prevalence is consistent with reports from tertiary care hospitals, where CAN is commonly observed among patients with long-standing diabetes. The prevalence reported in the literature varies considerably because of differences in study populations, duration of diabetes, glycemic control, diagnostic criteria, and methods used for autonomic assessment. Previous studies have shown that CAN may be present in approximately 20% of newly diagnosed patients and increases substantially with disease progression, reaching more than 60% in patients with longstanding diabetes.[2,5,6,12-18]

Assessment of parasympathetic function demonstrated significant impairment among diabetic patients. The mean deep breathing difference, postural tachycardia index, and Valsalva ratio were all significantly lower than those observed in healthy controls. Abnormal deep breathing difference was the most frequently observed autonomic abnormality, affecting 47% of diabetic patients. These findings are consistent with previous studies showing that parasympathetic dysfunction is the earliest manifestation of diabetic autonomic neuropathy. Parasympathetic fibers are longer and more susceptible to chronic metabolic injury resulting from persistent hyperglycemia, oxidative stress, accumulation of advanced glycation end products, activation of the polyol pathway, and microvascular ischemia. Similar reductions in heart rate variability have been reported by Vinik and Ziegler, Spallone et al., Fisher and Tahrani, and Duque et al., who identified parasympathetic dysfunction as the earliest objective marker of CAN.[1,2,4,6,12,14]

Sympathetic function was also significantly impaired in diabetic patients. Orthostatic hypotension and sustained handgrip responses were abnormal more frequently in diabetic patients than in controls, although these abnormalities were less common than parasympathetic dysfunction. This pattern is consistent with the natural history of diabetic autonomic neuropathy, in which parasympathetic fibers are affected earlier, followed by progressive sympathetic involvement as neuronal damage advances. Similar observations have been reported in studies evaluating Ewing's cardiovascular reflex tests for the diagnosis of CAN. [2,4,13,15,21]

A major finding of the present study was the significant association between duration of diabetes and cardiovascular autonomic neuropathy. Definitive CAN was observed in 21% of patients with diabetes duration of less than five years, 41% of those with diabetes duration between five and ten years, and all patients with diabetes duration exceeding ten years.

These findings emphasize that the risk of autonomic dysfunction increases progressively with prolonged exposure to hyperglycemia. Chronic metabolic disturbances and microvascular damage result in irreversible injury to autonomic nerve fibers, explaining the higher prevalence of CAN among patients with longer disease duration. Similar associations between diabetes duration and autonomic dysfunction have been consistently demonstrated in previous studies.[3,5,7,13,15,16]

The present study also demonstrated significant associations between cardiovascular autonomic neuropathy, diabetic retinopathy, and prolonged QTc interval. Among patients with diabetic retinopathy, 80% had definitive CAN, while 59% of patients with definitive CAN had prolonged QTc intervals. These findings support previous studies demonstrating that CAN frequently coexists with other diabetic microvascular complications and electrocardiographic abnormalities. Diabetic retinopathy reflects generalized microvascular injury, whereas QTc prolongation is a recognized marker of impaired cardiac autonomic regulation and increased risk of ventricular arrhythmias and sudden cardiac death.[8,9,18-20]

The cardiovascular reflex tests described by Ewing and Clarke remain practical, inexpensive, reproducible, and non-invasive methods for assessing autonomic function. Although sophisticated techniques such as heart rate variability analysis, cardiac imaging, and autonomic laboratory testing are available, these bedside tests remain particularly valuable in routine clinical practice and in resource-limited settings because they require minimal equipment and can detect both parasympathetic and sympathetic dysfunction. Their continued clinical relevance has been emphasized in recent consensus recommendations and contemporary reviews.[2,5,13,21,22]

The findings of this study have important clinical implications. Nearly one-half of patients with T2DM had definitive cardiovascular autonomic neuropathy despite many having no overt cardiovascular symptoms. Routine screening using simple cardiovascular reflex tests may facilitate early identification of autonomic dysfunction, particularly in patients with longer duration of diabetes or associated microvascular complications. Early diagnosis provides an opportunity for optimization of glycemic control, aggressive management of cardiovascular risk factors, and regular follow-up, which may delay disease progression and reduce cardiovascular morbidity and mortality.

CONCLUSION

Cardiovascular autonomic neuropathy is a common complication of type 2 diabetes mellitus, with nearly half of the patients in the present study demonstrating definitive autonomic dysfunction. The prevalence of CAN increased significantly with longer duration of diabetes and showed significant associations with diabetic retinopathy and prolonged QTc interval, indicating its close relationship with chronic diabetic complications.

Simple bedside cardiovascular autonomic reflex tests, including deep breathing difference, postural tachycardia index, Valsalva ratio, orthostatic hypotension, and sustained handgrip tests, proved to be effective, non-invasive, and inexpensive tools for the assessment of autonomic function. These tests can facilitate early detection of cardiovascular autonomic dysfunction, particularly in resource-limited settings.

Routine screening for cardiovascular autonomic neuropathy should be considered in patients with type 2 diabetes mellitus, especially those with longer disease duration or evidence of microvascular complications. Early identification and timely intervention may facilitate appropriate clinical management and potentially reduce cardiovascular morbidity and mortality.

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