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## Evaluation of Autonomic Neuropathy Affecting the Cardiovascular System in Type II Diabetes

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### ABSTRACT

Diabetes Mellitus (DM) is a significant health concern in India, characterized as a modern-day epidemic, with the potential to affect multiple organs and lead to various complications. Cardiac autonomic neuropathy (CAN) represents one of the serious yet often overlooked complications of diabetes. This study aims to ascertain the prevalence of CAN in diabetic patients and investigate its correlation with the duration of DM and glycemic control. One hundred thirty four diabetic patients were included based on predetermined criteria. Demographic information, medical history, and clinical examinations were recorded. CAN assessment involved three tests for parasympathetic and two tests for sympathetic function, with patients categorized as normal, early CAN, definite CAN, or severe CAN according to Ewing's criteria. The prevalence of CAN among the study population was 60%. Individuals with CAN exhibited significantly longer durations of diabetes and higher HbA1c levels compared to those with normal cardiac autonomic function. CAN showed a significant association with DM duration and glycemic control, but not with age. CAN patients presented with background retinopathy, various retinopathies, maculopathy and clinical symptoms such as diabetic foot, cataracts, muscle wasting, and tingling. CAN emerges as a prevalent and often asymptomatic consequence of diabetes. Hence, routine screening for CAN is recommended for all diabetic patients to facilitate early detection and intervention.

## INTRODUCTION

The World Health Organization (WHO) has issued a warning indicating that the number of diabetes cases in India may more than double by the year 2030, escalating from 32 million presently to 80 million<sup>[1]</sup>. Individuals with diabetes mellitus, whether type 1 or type 2, face an elevated risk of developing cardiovascular disease (CVD), accounting for over 60 percent of mortality among diabetic patients. Those with type 2 diabetes exhibit a threefold higher mortality risk from coronary heart disease compared to non-diabetic individuals. Additionally, diabetic individuals commonly present with a cluster of cardiovascular risk factors, collectively augmenting the likelihood of CVD. These factors include obesity, hypertension, dyslipidemia, physical inactivity, and cardiovascular autonomic neuropathy (CAN), an often under diagnosed consequence of diabetes and a significant contributor to cardiovascular risk<sup>[2-4]</sup>.

CAN denotes dysfunction of nerves enervated by the autonomic nervous system (ANS), which regulates cardiac and vascular functions. Reported prevalence rates of CAN in type 2 diabetes range between 31% and 73%, and between 17% and 66% in type 1 diabetes, varying due to diverse research methodologies and diagnostic criteria. Presence of CAN in diabetic individuals correlates with an elevated risk of cardiovascular mortality over a five-year span. Symptomatic manifestations such as resting tachycardia, postural hypotension, exercise intolerance, silent myocardial ischemia or infarction, and alterations in left ventricular systolic and diastolic function are associated with CAN<sup>[2-4]</sup>.

Diabetes mellitus (DM) exerts significant systemic impacts, affecting multiple organs and precipitating various complications. CAN represents a crucial yet often under-recognized and incompletely understood complication of DM. Early identification of autonomic dysfunction holds promise in identifying high-risk patients for adverse outcomes, facilitating improved glycemic control and reduced morbidity<sup>[5-6]</sup>.

The objectives of this study were to assess the prevalence of cardiovascular autonomic neuropathy among diabetic patients admitted to an Indian tertiary-level hospital, and to investigate the association between cardiovascular autonomic neuropathy in diabetic patients and duration of diabetes, glycemic control (HbA1c), and QTc interval.

## MATERIAL AND METHODS

The study included 134 diabetic patients admitted to an Indian hospital, meeting specific inclusion criteria. These criteria comprised individuals aged over 18 years with a documented duration of diabetes mellitus (DM) of at least 5 years, who provided written informed consent for participation. Exclusion criteria

were applied to patients with chronic renal failure, ischemic heart disease, those currently using beta-blockers, individuals with serum electrolyte abnormalities, and those diagnosed with asthma or severe chronic obstructive pulmonary disease. Additionally, patients using medications known to prolong the QT interval were excluded. Non-compliant patients who declined to participate in the study were also excluded.

Demographic information, medical history, physical examination findings, and fundus examination results obtained via direct ophthalmoscopy were recorded using a proforma. Additionally, investigations including fasting blood sugar (FBS), postprandial blood sugar (PPBS), renal function tests (RFT), serum electrolytes, HbA1c levels, urine routine examination, electrocardiogram (ECG), and 2D echocardiography (2D-ECHO) were conducted for each patient.

CAN assessment was performed for each patient using three tests of parasympathetic function namely, R-R interval during deep breathing, Valsalva Ratio, 30:15 ratio, and two tests of sympathetic function, namely SBP response to standing and DBP response to sustained handgrip.

## RESULTS

In this cross-sectional study, 134 diabetic patients were included, with a mean age of  $50.23 \pm 7.9$  years, and the majority falling within the age group of 51-60 years. Among the participants, 72 were male (Table 1).

The mean duration of diabetes mellitus (DM) was  $8.21 \pm 2.32$  years, with patients demonstrating definite and severe cardiac autonomic neuropathy (CAN) having significantly longer durations of DM compared to those with normal cardiac autonomic function. Similarly, HbA1c levels were notably higher in patients with abnormal cardiac autonomic function, showing an increasing trend across the groups of patients with early, definite, and severe CAN. However, there was no statistically significant difference in the mean age of patients with normal versus early, definite, or severe cardiac autonomic dysfunction (Table 2).

Autonomic Function Test results in diabetic patients are presented in (Table 3).

Patients with severe CAN commonly reported symptoms such as numbness and decreased vision, with examination findings including diminished vibration sense and loss of ankle jerk. 'Tingling' was the most frequently reported complaint, followed by 'decreased vision', while 'diminished vibration sense' was the most common finding on examination. The presence of clinical features of peripheral neuropathy was significantly higher in patients with CAN compared to those with normal cardiac autonomic function (Table 4).

Table 1: Demographic characteristics of study patients

Parameter	Normal		Early CAN		Definite CAN		Severe CAN	
	n	%	n	%	n	%	n	%
Age in Years								
<30	0	0.00	3	2.24	2	1.49	4	2.99
31-40	2	1.49	8	5.97	2	1.49	2	1.49
41-50	12	8.96	14	10.45	3	2.24	3	2.24
51-60	22	16.42	16	11.94	7	5.22	10	7.46
61-70	10	7.46	5	3.73	2	1.49	3	2.24
71-80	0	0.00	2	1.49	0	0.00	2	1.49
>80	0	0.00	0	0.00	0	0.00	0	0.00
Gender								
Male	27	20.15	30	22.39	7	5.22	8	5.97
Female	22	16.42	20	14.93	8	5.97	12	8.96

Table 2: Comparison of age, duration of DM and HbA1c levels

Parameter	Normal (mean ± SD)	Early CAN (mean ± SD)	Definite CAN (mean ± SD)	Severe CAN (mean ± SD)	p-Value (mean ± SD)
Age in Years	54.20 ± 9.90	47.50 ± 9.50	49.0 ± 10.0	51.70 ± 8.70	0.58
Diabetes duration; years	6.80 ± 1.10	6.10 ± 1.70	8.90 ± 1.00	11.5 ± 3.50	<0.05
HbA1c, gm dL	7.20 ± 0.63	9.20 ± 2.45	10.7 ± 1.65	14.10 ± 1.35	<0.05

Table 3: Autonomic function test results in DM patients

Autonomic Function Test	Normal	Borderline	Abnormal
R-R interval during deep breathing	69	20	45
Valsalva Ratio	70	44	20
30:15 ratio	109	5	20
SBP response to standing 97	32	5	
DBP response to sustained handgrip	70	32	32

Table 4: Comparison of clinical features in normal and CAN patients

Clinical Features	Normal		CAN		p-value
	n	%	n	%	
Background Retinopathy	3	2.24	52	38.81	<0.05
Burning	3	2.24	54	40.30	<0.05
Callus At Pressure Points	0	0.00	15	11.19	<0.05
Clawing Of Toes	0	0.00	23	17.16	<0.05
Diminished Sense of Pain and Temp	2	1.49	32	23.88	<0.05
Diminished Vibration Sense	3	2.24	64	47.76	<0.05
Loss Of Ankle Jerk	3	2.24	52	38.81	<0.05
Maculopathy	0	0.00	18	13.43	<0.05
Muscle Wasting	0	0.00	17	12.69	<0.05
Numbness	3	2.24	52	38.81	<0.05
Pain	0	0.00	20	14.93	<0.05
Proliferative Retinopathy	0	0.00	17	12.69	<0.05
Tingling	5	3.73	67	50.00	<0.05

## DISCUSSION

Dhumad *et al.* delineated four distinct stages of cardiac autonomic neuropathy (CAN) based on Ewing's criteria: Normal, Early, Definite, and Severe. The Normal stage encompassed patients with negative results across all cardiovascular autonomic tests, whereas the Early stage involved abnormalities in one of the three heart rate (HR) tests. Patients exhibiting abnormalities in two HR tests were categorized as Definite, while those with abnormalities in two HR tests and one or both blood pressure (BP) tests were classified as Severe<sup>[7]</sup>.

Patients with severe CAN and abnormal cardiac autonomic function displayed clinical presentations including diabetic foot, cataracts, muscle wasting, and tingling sensations. The prevalence reported in this study was higher than that observed by Ekta K in New Delhi, while findings were comparable to studies conducted by Pappachan.J.M, possibly due to similarities in patient demographics and hospital settings<sup>[7-11]</sup>. Variations in prevalence may stem from

differences in testing methodologies, instruments utilized, study settings, and geographic regions. Duration of diabetes mellitus was significantly longer in patients with severe CAN compared to those with normal cardiac autonomic function, consistent with findings by P.Valensi<sup>[12]</sup>.

Glycemic control, as assessed by HbA1c levels, significantly differed among patients with normal and various stages of CAN, supporting the association between CAN and elevated HbA1c levels. However, this association was not detected by K.Ekta in their research<sup>[9]</sup>. The QTc interval did not exhibit a statistically significant association with CAN, contrary to findings by M.Veglio<sup>[13]</sup>. Patients with CAN demonstrated an increased risk of vision problems and a higher prevalence of retinopathy, although this difference did not attain statistical significance. Vision loss was reported by all patients diagnosed with severe CAN, suggesting a possible relationship between peripheral neuropathy, retinopathy, and CAN<sup>[13]</sup>.

This cross-sectional study relied on hospital and laboratory records for data collection, lacking longitudinal follow-up to evaluate the impact of glycemic control on CAN progression. Several factors, such as alcohol consumption, chronic renal failure, ischemic heart disease, beta-blocker use, serum electrolyte abnormalities, and respiratory conditions, were exclusion criteria, potentially limiting participant inclusion. Diagnosis of peripheral neuropathy and retinopathy relied on history, clinical examination, and direct ophthalmoscopy, potentially overlooking early manifestations. Utilization of more sensitive diagnostic tools like nerve conduction studies and funds fluorescein angiography could enhance diagnostic accuracy<sup>[12]</sup>.

## CONCLUSION

The study revealed that patient age lacked a significant correlation with cardiac autonomic dysfunction, whereas the duration of diabetes and HbA1c level did show significant correlations. With a prevalence of about sixty percent, CAN emerges as a common complication, often asymptomatic in its early stages. Therefore, routine diagnostic assessments for CAN are recommended for all diabetic patients.

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