

# A study of cardiovascular autonomic neuropathy in the diabetic patients at tertiary health care center

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## Abstract

**Background:** Cardiac autonomic neuropathy (CAN) is one of the major complications of diabetes mellitus. It is also the most under diagnosed and least understood diabetic complications. It generally manifests as exercise intolerance, resting tachycardia and orthostatic hypotension. Diabetic neuropathy progresses from asymptomatic (subclinical) stage to the symptomatic stage with the progression of disease. Factors that may facilitate the process include poor glycaemic control coupled with duration of disease and patient's age. Present study was planned to study cardiovascular autonomic neuropathy in type 2 diabetic patients at a tertiary health care center. **Material and Methods:** The present study was observational, prospective type conducted in the department of medicine, in patients of diabetes mellitus attending the outpatient department and patients admitted in medicine wards. **Results:** In present study, total 130 patients were included. 47 % patients were from above 50 years age group. Most common age group was 51-60 years (28 %) followed by > 60 years (19 %). Male to female ratio was 1.4:1. Most patients had diabetes duration less than 2 years (51 %). In present study, heart rate variation during deep breathing (E: I ratio) was normal in 68% patients, while 32 % patients had abnormal findings. Immediate heart rate response to standing (30:75 ratio) was normal in 59% patients, while 41 % patients had abnormal findings. Valsalva ratio (Normal  $\geq 1.21$ ) was normal in 70% patients, while 30 % patients had abnormal findings. Postural hypotension test (Normal  $\leq 20$  mm of Hg fall in systolic BP) was normal in 88% patients, while 12 % patients had abnormal findings. Blood pressure response to sustained handgrip was normal in 87% patients, while 13% patients had abnormal findings. We noted normal findings in 69 % patients. Abnormal findings such as early parasympathetic disturbance in 31%, definite parasympathetic disturbance in 19% and combined parasympathetic and sympathetic disturbance in 11 %. **Conclusion:** In the present study, the overall prevalence of autonomic neuropathy in type 2 diabetes mellitus was 47%. Cardiac autonomic neuropathy is a preventable condition, requires early diagnosis of diabetes mellitus, good glycaemic control, regular screening and good patient counselling to prevent further morbidity.

**Keywords:** diabetes mellitus, cardiovascular, complication, Cardiac autonomic neuropathy

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## INTRODUCTION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals

currently diagnosed with the disease.<sup>1,2</sup>Advances in the management of diabetes have reduced mortality enormously. Although the acute complications of diabetes such as ketoacidosis coma, hyperosmolar non-ketotic coma, and infections have been overcome, the long-term complication continues to pose a challenge to the management. As per a World Health Organisation's (WHO) report, the burden of diabetes in India was 31.7 million. It is slated to grow further in the years to come.<sup>3,4</sup> Obesity and lack of physical activity is thought to be the primary cause of type 2 diabetes and known to cause chronic complications particularly neuropathy, retinopathy, and nephropathy. Diabetic Autonomic Neuropathy (DAN) is among the least recognized and less understood complication of diabetes mellitus despite its

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significant impact on survival and quality of life in people with diabetes.<sup>5</sup> Cardiac autonomic neuropathy (CAN) is one of the major complications of diabetes mellitus. It is also the most under diagnosed and least understood diabetic complications. It generally manifests as exercise intolerance, resting tachycardia and orthostatic hypotension.<sup>6</sup> The incidence of diabetic neuropathy varies according to the duration of disease and the rigorousness of good glycemic control. In addition, age has been proposed as an accelerant that may hasten the pathological process. Varying incidence and prevalence of CAN are reported in different studies among diabetic patients with the rates ranging from as low as 1.6% in patients with well-controlled diabetes to as high as 90% in those awaiting a pancreas transplant.<sup>7</sup> In the Indian context, limited reports are available that have described the incidence of diabetic neuropathy in Indian population. The incidence ranges from 15–29% in such reports.<sup>8,9</sup> Diabetic neuropathy progresses from asymptomatic (subclinical) stage to the symptomatic stage with the progression of disease. Factors that may facilitate the process include poor glycemic control coupled with duration of disease and patient's age. Present study was planned to study cardiovascular autonomic neuropathy in type 2 diabetic patients at a tertiary health care center.

## **MATERIAL AND METHODS**

The present study was observational, prospective type conducted in the department of medicine, XXX medical college, XXX. Study duration was from January 2019 to November 2019. Institutional ethical committee approval was taken for present study. Study was conducted in patients of diabetes mellitus attending the outpatient department and patients admitted in medicine wards. The patient selection was based on following inclusion and exclusion criteria.

### **Inclusion criteria**

Patients of diabetes mellitus within the age group of 19 to 70 years.

Patients willing to participate in study.

### **Exclusion criteria**

Associated diseases in which autonomic nervous system is affected like, Tabes dorsalis and leprosy etc.

Patients receiving drugs that are known to interfere with cardiac or respiratory function such as beta blockers, sympathomimetic drugs, antihypertensives like alpha methyl dopa, diuretics etc.

Patients with comorbid conditions like ischemic heart disease, rheumatic heart disease, arrhythmia and cardiac failure.

Patients who cannot cooperate for various tests and physically handicapped patients and those unable to stand up quickly and maintain an erect posture.

A written informed consent was taken from all patients for participation in study. After applying above-mentioned inclusion and exclusion criteria we enrolled total 130 cases in the present study. All patients underwent careful history taking and detailed clinical examination to find out signs/symptoms suggestive of autonomic nervous system involvement. After thorough clinical examination, all these patients were subjected for various investigations. Newly detected patients as well as known patients of diabetes mellitus were included in the present study. In all patient's diagnosis of diabetes mellitus was made by criteria given American diabetics association.<sup>10</sup> Necessary laboratory investigations, fundus examination and 12 lead ECG were done in all cases. Special investigations like X-ray chest, CSF examination, etc. were done wherever necessary. Peripheral Neuropathy, retinopathy and nephropathy was diagnosed by using standard procedures.

### **Autonomic function tests**

The tests were explained to the patients before being actually carried out.

Tests reflecting parasympathetic damage:

Heart rate variation during deep breathing (E: I ratio): The subject was made to lie quietly and to breathe deeply at 6 breaths/min. During breathing instantaneous heart rate monitoring was performed electrocardiographically. The expiration: inspiration (E:I ratio) was calculated-as the longest R-R interval during expiration to the mean of shortest R-R interval during inspiration.

Immediate heart rate response to standing (30:75 ratio): The test is simple to use and requires only a standard electrocardiograph and ability of patients to stand-up a continuous ECG recording and measurement of the R-R interval at beat 15 and 30 after standing to give 30:15 ratio.

Valsalva ratio: The patients lay comfortably and resting ECG was recorded for 15 seconds. Later 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 seconds while a continuous ECG recording was done. After 30 seconds ECG was monitored again for 15 sec. The Valsalva ratio was calculated as longest R-R interval after release to shortest R-R interval during manoeuvre. Tests for sympathetic damage

Blood pressure response to standing: When patients stand, 2 min after standing decline in systolic blood pressure by more than 20 mmHg and by more than 10mmHg for diastolic blood pressure is considered abnormal.

Blood pressure response to sustained handgrip: The patient gripped the inflated cuff with dominant arms three times. Highest of three readings was called maximum voluntary contraction. Subject was instructed to maintain handgrip steadily at 30% of maximum contraction for as long as possible to a maximum of 4-5 minutes. Blood pressure was measured on non-exercising arm at rest and at the end of

grip. The change in blood pressure was recorded as difference between resting reading and after test.

The results were then categorized into one of the 4 groups:  
Normal

Early parasympathetic disturbance- One of the three tests of parasympathetic function abnormal

Definite parasympathetic disturbance- With 2 of the three tests of parasympathetic function abnormal

Combined parasympathetic and sympathetic disturbance- When in addition to abnormal parasympathetic disturbance one or both sympathetic tests abnormal.

The collected data was entered using Microsoft excel. Statistical analysis was done using SPSS. Statistical analysis was done using descriptive statistics.

## RESULTS

In present study, total 130 patients were included. 47 % patients were from above 50 years age group. Most common age group was 51-60 years (28 %) followed by > 60 years (19 %). Male to female ratio was 1.4:1. Most patients had diabetes duration less than 2 years (51 %). In present study according to duration of diabetes, we noted 22 % had 3-5 years diabetes duration, others were 12%, 9% and 5% with duration of diabetes as 5-10 years, 11-20 years and >20 years respectively.

**Table 1:** Distribution of diabetic patients with various characteristics.

Variable	Number of patients	Percentage
Age group		
19-30	16	12%
31-40	24	18%
41-50	29	22%
51-60	36	28%
>60	25	19%
Age	43.16 ± 9.22 years	
BMI	25.98 ± 3.84 kg/m <sup>2</sup>	
HbA1c	9.01 ± 3.12 %	
Gender		
Male	76	58%
Female	54	42%
Duration of diabetes (in years)		
0-2	66	51%
3-5	29	22%
5-10	16	12%
11-20	12	9%
>20	7	5%

In present study, heart rate variation during deep breathing (E: I ratio) was normal in 68% patients, while 32 % patients had abnormal findings. Immediate heart rate response to standing (30:75 ratio) was normal in 59% patients, while 41 % patients had abnormal findings. Valsalva ratio (Normal ≥1.21) was normal in 70% patients, while 30 % patients had abnormal findings. The Valsalva ratio was calculated as longest R-R interval after release to shortest R-R interval during manoeuvre. Blood pressure response to standing was measured as when patients stand, 2 min after standing decline in systolic blood pressure by more than 20 mmHg and by more than 10mmHg for diastolic blood pressure is considered abnormal. Postural hypotension test (Normal ≤20 mm of Hg fall in systolic BP) was normal in 88% patients, while 12 % patients had abnormal findings. Blood pressure response to sustained handgrip was normal in 87% patients, while 13% patients had abnormal findings.

**Table 2:** Distribution of patients according to cardiac autonomic neuropathy.

Test	Results	
	Normal	Abnormal
E:I ratio (Normal ≥1.10)	89 (68 %)	41 (32 %)
30:15 ratio (Normal ≥1.04)	77 (59 %)	53 (41 %)
Valsalva ratio (Normal ≥1.21)	91 (70 %)	39 (30 %)
Postural hypotension test (Normal ≤20 mm of Hg falls in systolic BP)	114 (88 %)	16 (12 %)
Sustained handgrip test (Normal ≥16)	113 (87 %)	17 (13 %)

We noted normal findings in 69 % patients. Abnormal findings such as early parasympathetic disturbance in 31%, definite parasympathetic disturbance in 19% and combined parasympathetic and sympathetic disturbance in 11 %.

**Table 3:** Incidence of autonomic neuropathy in diabetes patients.

Results	Number of patients	Percentage
Normal	69	53%
Early parasympathetic disturbance	31	24%
Definite parasympathetic disturbance	19	15%
Combined parasympathetic and sympathetic disturbance	11	8%

## DISCUSSION

Cardiac Autonomic Neuropathy (CAN) results in damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.<sup>11</sup> The mechanisms governing CAN are primarily due to metabolic insult and activation of pro-oxidant factors such as polyol pathway, Protein Kinase C, advanced glycosylation end products, and hexosamine pathway.<sup>12,13</sup> The end-organ damage caused by diabetes is responsible for the increased morbidity and mortality compared with nondiabetics. Unopposed sympathetic activity due to involvement of the vagus nerve results in either resting tachycardia or heart rate variability (HRV). Reduced heart rate variation is earliest indicator of CAN. Normally a postural change from supine to sitting position results in baroreceptor initiated and centrally mediated sympathetic reflex response leading to increase in peripheral vascular resistance and increase in norepinephrine leading to cardiac acceleration. Impaired reflex response and sympathetic efferent neuropathy usually causes fall in peripheral resistance with change in posture and results in orthostatic hypotension. The prevalence of CAN is approximately 31–73% in type 2 DM and the annual incidence has been reported to be 2%. CAN pathogenesis is complex and multifactorial. CAN is initially subclinical and becomes symptomatic only in the later stages of the disease.<sup>14,15</sup> There is no specific algorithm for detecting CAN but, for proper diagnosis of the condition, it is recommended that more than one test is conducted to improve the sensitivity and reliability of the detection. Menon *et al.*<sup>17</sup>, *et al.*<sup>18</sup>, and have found the prevalence of CAN to be 66 and 58 respectively, among patients with type 2 diabetes. In present study a 47 % incidence was noted. Another study from the western part of India revealed parasympathetic dysfunction in 58% subjects and sympathetic dysfunction in 20% of the diabetic patients.<sup>19</sup> The possible explanation to this huge variation in CAN prevalence is the inconsistency in the criteria used to diagnose CAN and significant differences in the study populations, particularly in relation to CAN risk factors (such as age, sex, and DM duration amongst others). We noted normal findings in 69 % patients. Abnormal findings such as early parasympathetic disturbance in 31%, definite parasympathetic disturbance in 19% and combined parasympathetic and sympathetic disturbance in 11 %. Menon *et al.*<sup>17</sup> studied CAN in 74

patients and found a high prevalence of abnormal CARTs (Cardiovascular autonomic reflex tests), sustained handgrip of 81%, E: I ratio of 66.2%, 30 : 15 ratio of 28.3%, and orthostatic hypotension of 13.5%. They estimated possible CAN prevalence to be 31.0% and definite CAN 66.2%. They found that only ten patients had advanced CAN. HRV tests need to be interpreted according to age. When age is taken into account the prevalence rate of CAN does not seem to be influenced by it, while alterations of these tests correlate with diabetes duration.<sup>20</sup> The late stages of CAN are associated to considerable morbidity and an increase in mortality, related to postural hypotension, exercise intolerance, increase in the intraoperative instability. Patients with a CAN diagnosis have an increased risk of cardiovascular mortality due to acute myocardial infarction and sudden death.<sup>21</sup>

## CONCLUSION

In the present study, the overall prevalence of autonomic neuropathy in type 2 diabetes mellitus was 47%. Cardiac autonomic neuropathy is one of the major complications of DM, and this is usually associated with poor prognosis. Cardiac autonomic neuropathy is a preventable condition, requires early diagnosis of diabetes mellitus, good glycemic control, regular screening and good patient counselling to prevent further morbidity.

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