



## Research Article

# Prevalence of Cardiac Autonomic Neuropathy among Type 2 Diabetes Mellitus in a Tertiary Care Centre

Authors

Santhi Thoppappatty Sengottaiyan<sup>1</sup>, Anju Surendran<sup>2</sup>, Suresh Ellappan<sup>3</sup>,  
Palani Kannan<sup>4</sup>

<sup>1</sup>Associate Professor of Medicine, Govt. Kilpauk Medical College, Chennai, India

<sup>2,4</sup>Resident, Govt. Kilpauk Medical College, Chennai, India

<sup>3</sup>Associate professor of Diabetology, Govt. Kilpauk Medical College, Chennai, India

Corresponding Author

**Suresh Ellappan**

Associate Professor of Diabetology, Govt. Kilpauk Medical College, Chennai, India

Email: [esuresh51@gmail.com](mailto:esuresh51@gmail.com) Tel: 9444255801

## Abstract

**Background:** Cardiac Autonomic Neuropathy (CAN) is one of the chronic complications of diabetes mellitus, with potentially dangerous outcomes. Though very frequent, it is one of the most under diagnosed and often overlooked entity.

**Aim:** To study the prevalence of cardiac autonomic neuropathy (CAN) among type 2 diabetes patients using non invasive bedside tests.

**Materials and Methods:** A cross sectional study was conducted among 100 type 2 diabetes patients at our institute, over a period of 6 months. Apart from relevant blood investigations, a detailed history including duration of diabetes, symptoms pertaining to autonomic neuropathy etc. were collected from all patients. A battery of five autonomic function tests using sphygmomanometer, ECG tracings and pulse oxymeter as described by Ewing et al were done in all cases and cardiac autonomic dysfunction score was calculated. IBM.SPSS statistics software was used for statistical analysis. Prevalence of CAN was calculated. Chi-square test was used for categorical variables and p value of 0.05 was considered significant.

**Results:** Among 100 patients in study group 25 had an abnormal CAN score and 43 had borderline values. Prevalence of CAN was 58% in our study group. Chi square tests showed significant relation between duration of diabetes and CAN scores with a p value of 0.000.

**Conclusion:** Prevalence of CAN among type 2 diabetes is fairly high, which was 58% in our study group. There is a significant relation between prevalence of CAN and duration of diabetes.

**Keywords:** Diabetes mellitus, Cardiac Autonomic Neuropathy(CAN), Autonomic dysfunction, Autonomic reflex test.

## Introduction

Diabetes Mellitus is a complex “ Metabolic-Cum-Vascular” disorder which has devastating effects on life expectancy and quality of life of

individuals. India has the largest diabetic population in the world and is infamously dubbed as “The Diabetic capital” of the world, with more than 70 million people living with diabetes and

this number would be beyond 100 million by 2030[ICMR]. Diabetic neuropathy is a common chronic complication of diabetes, specifically diabetic autonomic neuropathy (DAN), which is one of the most distressing but under diagnosed entity. Diabetic neuropathy poses a therapeutic challenge to the treating physician as it has multifactorial pathogenic mechanism and varied clinical presentation, the major factor being hyperglycemia, long duration of diabetes, microvascular injury, genetic susceptibility, auto immune factors and bad life style practices. Polyol pathway, loss of vascular autoregulation in chronic hyperglycemics, microvascular injury due to decreased endoneural blood flow, deficient neurotrophic factors (NGF,IGF-I) all are behind the pathogenesis of neuropathy. Diabetes patients having CAN carries an increased risk for developing coronary artery disease(CAD) and is also associated with poor prognosis once they develop CAD. There is no “circadian variation” (morning increase in MI) of acute cardiovascular events in diabetic patients with CAN. “Diabetic patients with CAN are prone for sudden painless death due to ischemic myocardial infarction, rhythm disturbances, heart failure and rapid progression of diabetic nephropathy which cause further more damage to the myocardium by elevated BUN and other parameters”<sup>[1]</sup>. Classification of diabetic neuropathy includes rapidly reversible neuropathy, focal, multifocal neuropathy and generalised symmetric peripheral neuropathy. CAN comes under generalised symmetric neuropathy along with gastrointestinal, genitor-urinary and sudomotor disturbances <sup>[2]</sup>. Cardiovascular autonomic neuropathy (CAN) one among DAN causes damage to sympathetic and parasympathetic fibres of heart which causes alteration in the control of heart rate as loss of heart rate variability (HRV) during deep breathing and blood pressure<sup>[3]</sup> resulting in postural hypotension, resting tachycardia, exercise intolerance ,altered sweating response, ,painless and symptomless myocardial infarction and sudden cardiac death . Autonomic dysfunction not

only affects daily activities of diabetic individuals, but it may even cause potentially life threatening outcomes ranging from silent myocardial infarction to sudden cardiac death. CAN contributes to poor prognosis of coronary artery disease in diabetes. Early recognition of asymptomatic cardiac dysautonomia helps in delaying or arresting its progression. CAN is usually detected at a subclinical stage by means of several autonomic reflex testing<sup>[4]</sup>. These autonomic function tests are mostly non invasive and do not require sophisticated equipments Therefore, it has very important clinical and prognostic relevance. This study is aimed to find out the prevalence of cardiac autonomic neuropathy among diabetics,its early recognition using simple bedside tests and its relation with duration of diabetes.

#### **Aim**

To diagnose cardiac autonomic neuropathy in Type 2 diabetes mellitus and its prevalence with non invasive bed side autonomic reflex testing in our tertiary care centre.

#### **Materials and Methods**

A Cross sectional study is conducted to evaluate the prevalence of cardiac autonomic neuropathy among 100 Type 2 Diabetes Mellitus patients, both males and females with the simple bedside autonomic reflex tests. *Inclusion criteria*; All cases of Type 2 diabetes mellitus diagnosed according to World Health Organisation (WHO) criteria are included in the study regardless the duration of diabetes. *Exclusion criteria*; patients with history of Type 1 diabetes, diabetic retinopathy, hypertension, coronary artery disease, renal dysfunction, electrolyte imbalances like hypocalcaemia or hypokalemia , and drugs affecting autonomic tone are excluded from the study. A detailed clinical history including duration of diabetes ,symptoms pertaining to autonomic dysfunction are elicited from all patients along with physical examination and relevant blood investigations.All are subjected to a

battery of five autonomic function tests as described by Ewing et al and a score of 0 – 2 were assigned to each test<sup>[5]</sup>. The same 100 patients were tested after obtaining proper informed consent, with 10 minutes interval after each manoeuvre. CARTs (cardiovascular autonomic reflex testing) are done after avoiding confounding factors. Patients are advised to avoid strenuous exercises in the preceding 24 hours of tests. Caffeine, alcoholic beverages, smoking, and alcohol are avoided at least 2 hours before testing. Testing are done at fasting or after 2 hours after a light meal. In patients who are on insulin therapy, tests are done at least 2 hours after taking short-acting insulin, and not during time of hypoglycemia or hyperglycemia.

The following are the tests for detecting Cardiac Autonomic Neuropathy<sup>[6,7,8,9,10]</sup>:

1) Blood pressure change during standing; Blood pressure recording is done when the subject is made to lie down and again 2 minutes after standing up. The difference in systolic pressure from lying to standing is a measure of orthostatic hypotension.

2) Change in heart rate to Valsalva manoeuvre; Patient blows in to the rubber tubing of a modified sphygmomanometer to raise the pressure to 40 mm of Hg and a long strip ECG in lead II is taken during the test. Ratio of longest to shortest R-R interval is measured and mean ratio is obtained.

3) Change in heart rate to deep breathing; ECG is recorded continuously while patient is taking breath at a regular rate of 6-12 breaths/min. A difference in heart rate between expiration and inspiration is noted.

4) Blood pressure change to sustained handgrip; Subject is asked to press a ball in his or her left hand for about 5 minutes. Rise in the diastolic blood pressure after sustained hand grip is noted and graded accordingly.

5) Heart rate response to standing; R-R interval is measured at beats 15 and 30 after patient stands. A 30:15 ratio is calculated.

#### EWINGS AUTONOMIC FUNCTION TESTS

#### AND SCORING<sup>[5]</sup>

Score	HR change to Deep breathing	HR response to Valsalva ratio	HR variability to standing	BP variability to hand grip	BP change during standing
0	≥15	≥1.21	≥1.04	≥16	≤10
1	11- 14	1.11 - 1.20	1.01 -1.03	11-15	10- 29
2	≤10	<1..20	≤1	≤10	≥30 mm

Each test is graded as

Score 0 – normal; Score 1- borderline ;Score 2 – abnormal

1. An overall score of ‘0’ or ‘1’ is considered normal
2. Score 2,3,4 are considered borderline abnormal
3. Score ≥5 is judged is abnormal autonomic function

For analysis of frequency of data in descriptive statistics, continuous variables were analysed using mean and standard deviation and categorical variables were analysed as percentage. The collected data were analysed with IBM.SPSS statistics software 23 Version. Prevalence of cardiac autonomic neuropathy in diabetes mellitus was calculated. Chi-square test was used to find association among categorical variables and p value of 0.05 is considered as significant level.

#### Results

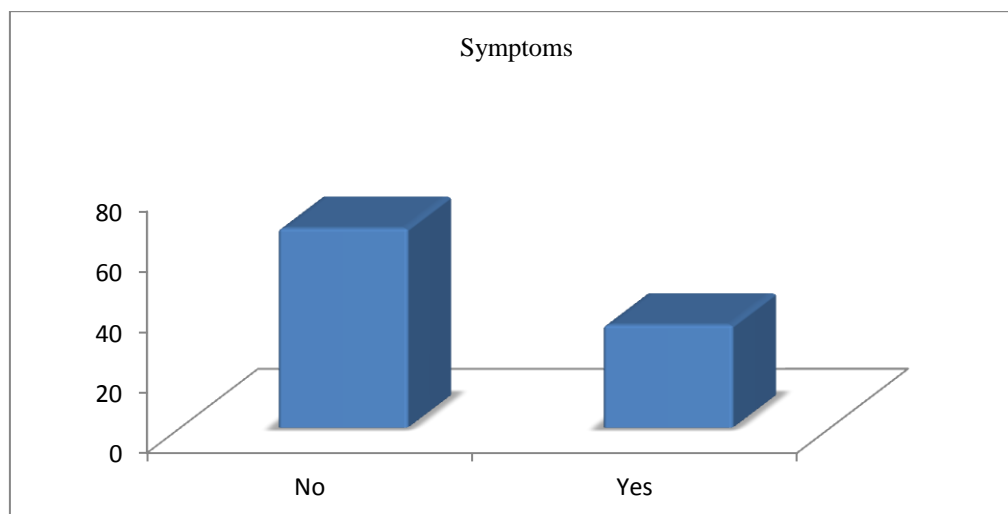
Among 100 patients included in the study, 34 patients had symptoms related to diabetic autonomic neuropathy (Table 1, Fig.1) and the remaining 66 are asymptomatic clinically. Overall, among 100 patients in the study group, 8 people had abnormal CAN score results (score 2) for heart rate variability to deep breathing (Table 2, Figure 2), 15 had abnormal results for heart rate response to Valsalva (Table 3, Figure 3), 15 showed abnormal results for heart rate response to standing (Table 4, Figure 4), 7 had abnormal results for BP response to hand grip (Table 5, Figure 5), 5 had abnormal BP response to standing (Table 6, Figure 6) respectively. Among 100 patients, 25 had an abnormal CAN Score, 43 had borderline thus resulting in a prevalence rate of 68% for cardiac autonomic neuropathy as shown in Table 7 / Fig 7.

Among the study group of 100 based on the duration of diabetes, 4.8% of <5yrs duration of diabetics, 18.9% of 5-10 yrs duration of diabetics and 53.8% of >10yrs duration of diabetics showed abnormal CAN scoring ,showing an increased prevalence of cardiac autonomic neuropathy with increasing duration of diabetes(Table 8, Figure 8). Chi square tests showed there is a significant relation between duration of diabetes and CAN scores with a p value of 0.000 as shown in Table 9.

**Table 1:** Symptoms of autonomic neuropathy

Symptoms	Frequency	Percent	Valid Percent	Cumulative Percent
No	66	66.0	66.0	66.0
Yes	34	34.0	34.0	100.0
Total	100	100.0	100.0	

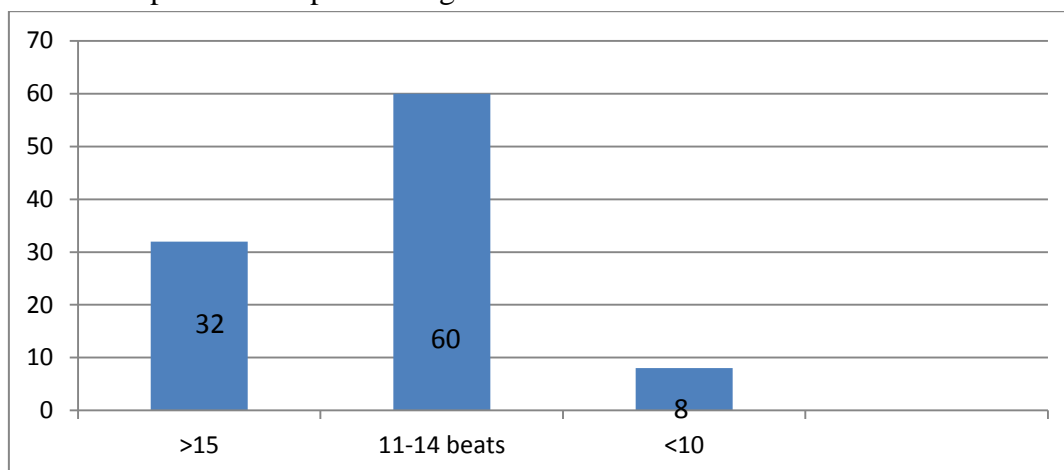
**Figure 1:**



**Table 2:** Heart rate response to deep breathing

Heart rate difference	Frequency	Percent	Valid Percent	Cumulative Percent
≥15	32	32.0	32.0	32.0
11 - 14	60	60.0	60.0	92.0
≤10	8	8.0	8.0	100.0
Total	100	100.0	100.0	

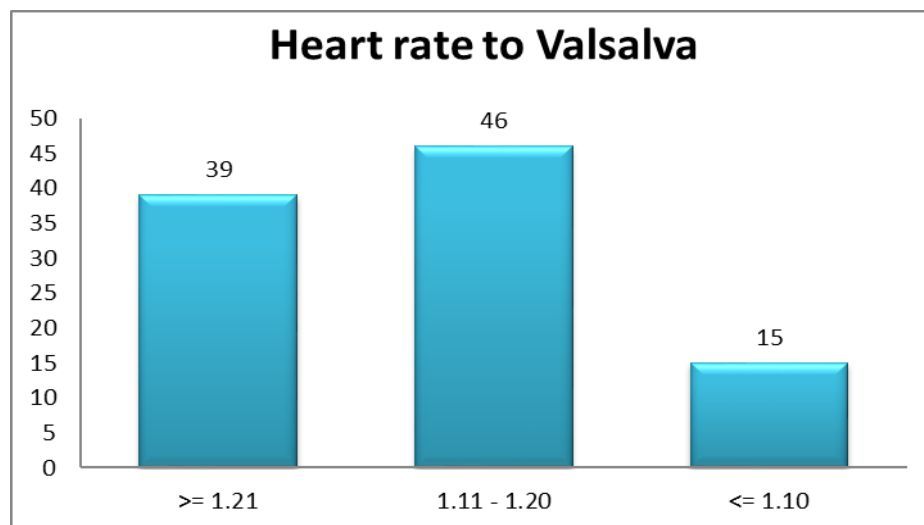
**Figure 2:** Heart rate response to deep breathing



**Table 3:** Heart rate response to Valsalva

Heart rate ratio	Frequency	Percent	Valid Percent	Cumulative Percent
$\geq 1.21$	39	39.0	39.0	39.0
1.11 - 1.20	46	46.0	46.0	85.0
$\leq 1.10$	15	15.0	15.0	100.0
Total	100	100.0	100.0	

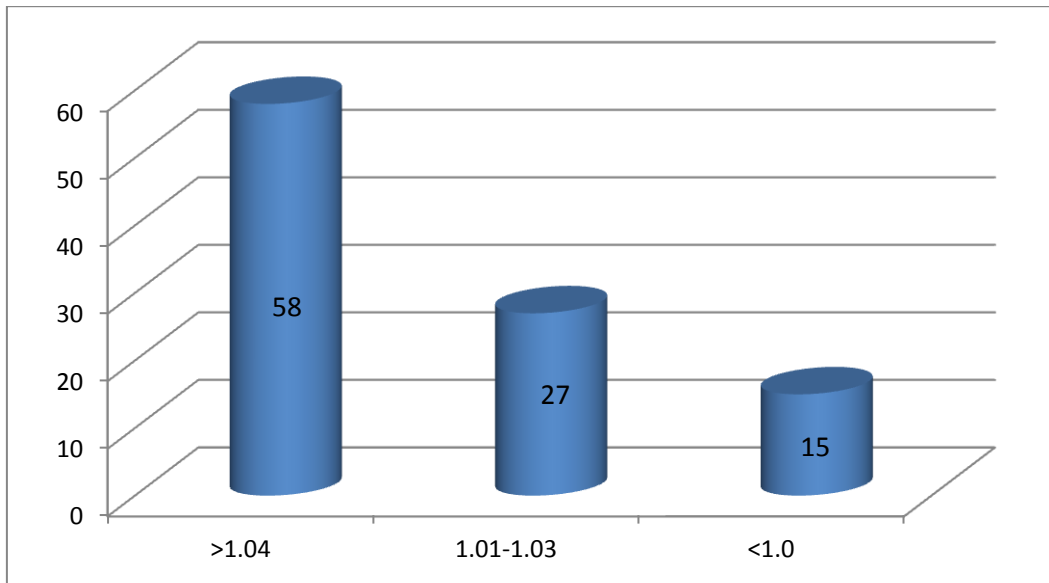
**Figure 3**



**Table 4:** Heart rate response to standing

Heart rate ratio	Frequency	Percent	Valid Percent	Cumulative Percent
$\geq 1.04$	58	58.0	58.0	58.0
1.01 - 1.03	27	27.0	27.0	85.0
$\leq 1.0$	15	15.0	15.0	100.0
Total	100	100.0	100.0	

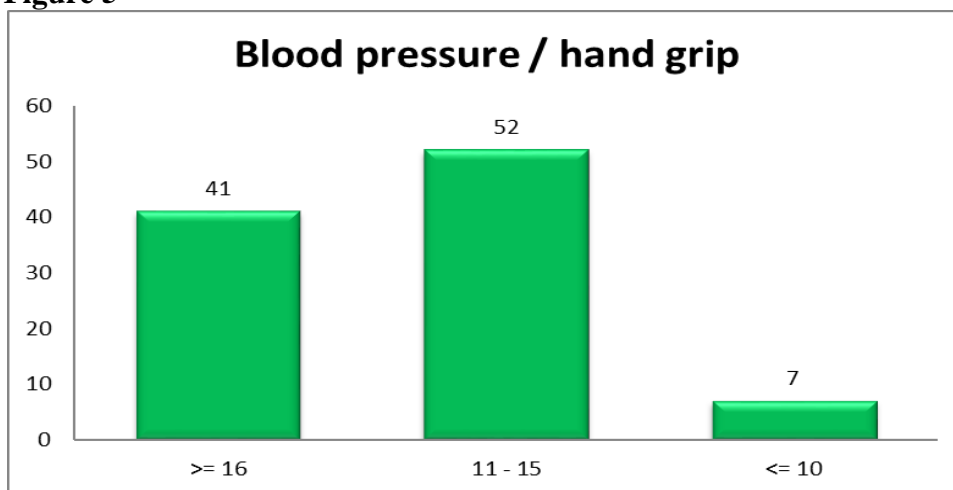
**Figure 4:** Heart rate response to standing



**Table 5:** BP RESPONSE TO HAND GRIP

BP Response	Frequency	Percent	Valid Percent	Cumulative Percent
≥ 16	41	41.0	41.0	41.0
11 - 15	52	52.0	52.0	93.0
≤10	7	7.0	7.0	100.0
Total	100	100.0	100.0	

**Figure 5**



**Table 6:** BP RESPONSE TO STANDING

BP Response/standing	Frequency	Percent	Valid Percent	Cumulative Percent
≤10	48	48.0	48.0	48.0
11 - 29	47	47.0	47.0	95.0
≥ 30	5	5.0	5.0	100.0
Total	100	100.0	100.0	

Figure 6:

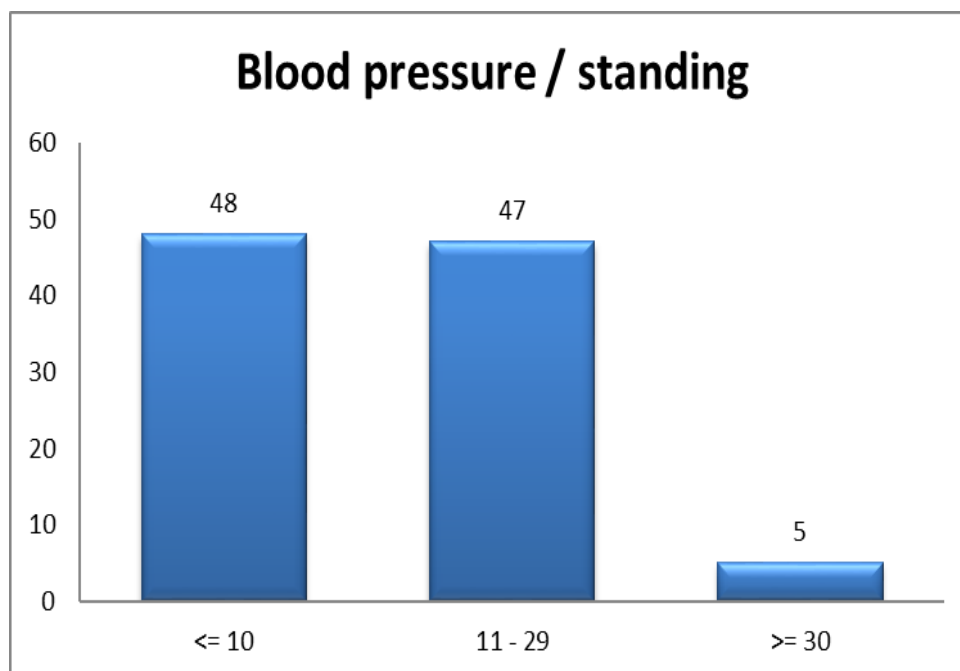
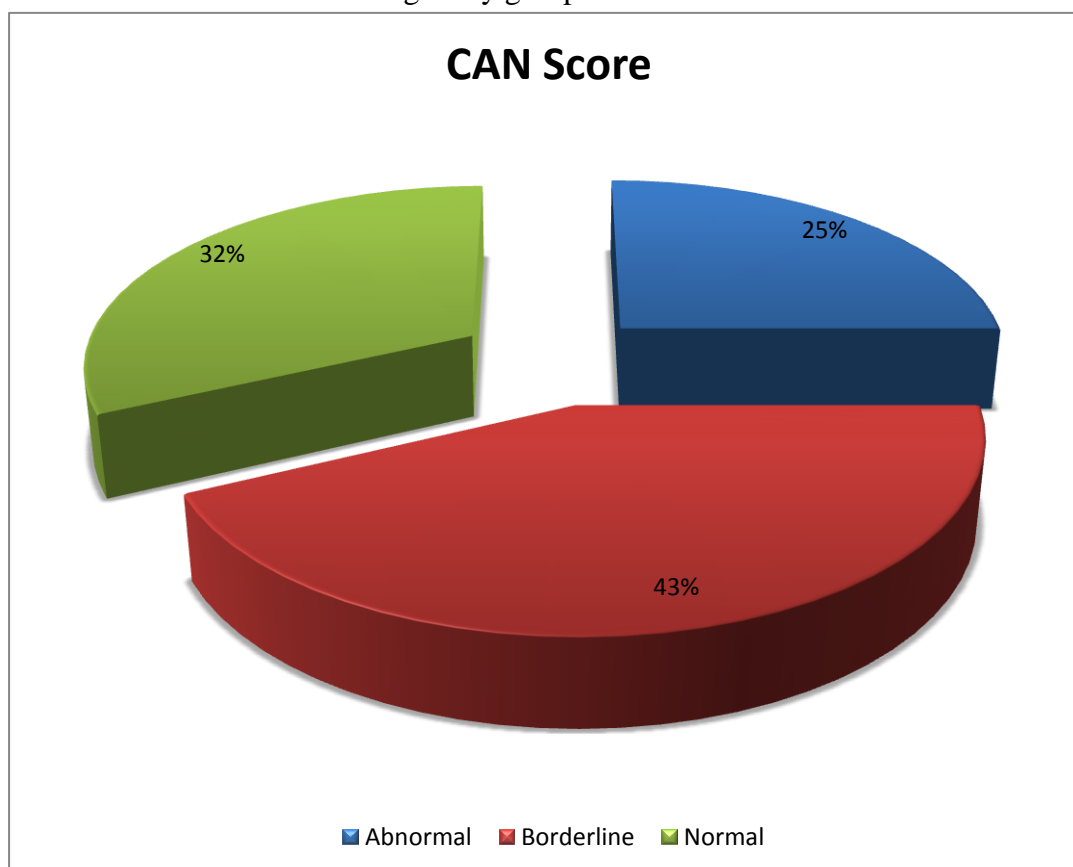


Table 7: Distribution of CAN score among study group

CAN Score	Frequency	Percent	Valid Percent	Cumulative Percent
Abnormal	25	25.0	25.0	25.0
Borderline	43	43.0	43.0	68.0
Normal	32	32.0	32.0	100.0
Total	100	100.0	100.0	

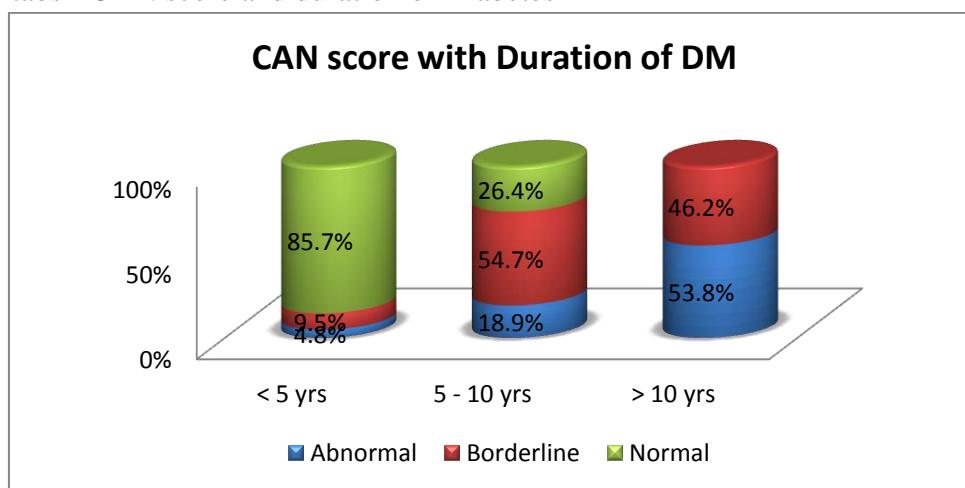
Figure 7: Distribution of CAN score among study group



**Table 8:** Cross tabs - CAN score and duration of Diabetes

CAN score		Duration of diabetes			Total
		<5 yrs	5-10 yrs	>10 yrs	
Abnormal	Count	1	10	14	25
	% with duration of diabetes	4.8%	18.9%	53.8%	25%
Borderline	Count	2	29	12	43
	% with duration of diabetes	9.5%	54.7%	46.2%	43%
Normal	Count	18	14	0	32
	% with duration of diabetes	85.7%	26.4%	0.0%	32%
Total	Count	21	53	26	100
	% with duration of diabetes	100%	100%	100%	100%

**Figure 8:** Cross tabs - CAN score and duration of Diabetes



**Table 9:** Chi-square test

	Value	df	Asymp.Sig (2-sided)
Pearson Chi-Square	47.888 <sup>a</sup>	4	.000
Likelihood Ratio	52.284	4	.000
Linear-by-Linear Association	36.830	1	.000
N of Valid Cases	100		

a.0 cells (.0%) have expected count less than 5. The minimum expected count is 5.25.

**Discussion**

Diabetic autonomic neuropathy poses a therapeutic challenge to the treating physician as it has multi factorial pathogenic mechanism and also has varied clinical presentation. Cardiovascular autonomic neuropathy (CAN) can be detected at subclinical stage using battery of autonomic tests rather than single test which assesses both parasympathetic and sympathetic components of autonomic nervous system. In our study, 100 patients of type 2 diabetes irrespective

of duration of diabetes were evaluated for evidence of cardiovascular autonomic neuropathy using simple bed side autonomic reflex tests. Symptoms pertaining to autonomic neuropathy were specifically asked in history, which showed only 34 patients had symptoms pertaining to autonomic neuropathy. The overall prevalence of cardiac autonomic neuropathy in our study was 68%, with 43% having borderline autonomic dysfunction and 25% having severe autonomic dysfunction. This clearly shows that many



asymptomatic cases can be detected early using these autonomic reflex testing. Among these reflex tests heart rate response to standing and heart rate response to valsalva were affected in maximum number of patients. Prevalence of autonomic neuropathy showed an increasing trend with increasing duration of diabetes, which was correlating with previous similar studies done by mohan et al<sup>[11]</sup> which showed 53.8% of patients with more than 10 years of diabetes had abnormal CAN score. Cessation of smoking, tailored exercise programs, body stockings and gravity suits useful in patients with orthostatic hypotension aimed at improvement in peripheral vascular resistance, high sodium diet, elevation of head end while sleeping gives symptomatic relief. "Staged" posture changing, Standing on crossed legs, dorsiflexing the feet or doing handgrip exercises before standing all these non pharmacological measures are suggested to the diagnosed patients. Pharmacological measures like strict glycaemia control<sup>[12,13,10]</sup>, effective blood pressure monitoring with ACE inhibitors and beta blockers and dyslipidemia correction with statins, aspirin, use of antioxidant, alpha lipoic acid in slowing or reversing progression of neuropathies are also initiated as indicated.

### Conclusion

Prevalence of Subclinical autonomic neuropathy in diabetics is 68%, higher than it was suspected and is assuming greater clinical implications due its higher morbidity and mortality. These simple bedside tests are an objective guide to diagnose at an early stage, halting the progression, and also to modify the life style and exercise programmes for achieving the quality life in these patients.

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### Conflict of interest

All authors contributed equally in developing the manuscript.

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