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Original Research Paper

Prevalence of Cardiovascular Autonomic Neuropathy Among type 2 Diabetes Mellitus Patients

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ABSTRACT*:*

Background: Cardiac autonomic neuropathy (CAN) is one of the chronic complications of diabetes mellitus with potentially dangerous consequences. Although it is very common, it is one of the most underdiagnosed and often overlooked conditions. **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 of 93 type 2 diabetic patients was performed at our institute over a 12-month period. Detailed medical history was obtained from all patients, including duration of diabetes, symptoms related to autonomic neuropathy, etc. Relevant blood tests were also performed as deemed necessary. A series of five autonomic function tests were performed in all patients using a sphygmomanometer and ECG recordings as described by Ewing et al, and the cardiac autonomic dysfunction score was calculated. GNU PSPP statistics software was used for statistical analysis. Prevalence of CAN was calculated. Chisquare test was used for categorical variables and p value 0f 0.05 was considered significant. **Results:** Among 93 patients in study group 24 had an abnormal CAN score and 39 had borderline values. Prevalence of CAN was 67.7% in our study group. Chi square tests showed significant relation between duration of diabetes and CAN scores with a p value of <0.001. **Conclusion:** Prevalence of CAN among type 2 diabetics is fairly high, which was 67.7% in our study group. There is a significant relation between prevalence of CAN and duration of diabetes.

Keywords: CAN, autonomic neuropathy, diabetes, coronary artery disease

INTRODUCTION:

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common feature of hyperglycemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycemia (1). Type 2 diabetes, which accounts for majority of the cases, can lead to multiorgan complications, broadly divided into microvascular and macrovascular complications (2). Diabetic neuropathy poses a therapeutic challenge to the treating physician as it has multifactorial pathogenic mechanisms and varied clinical presentation, the major factors being hyperglycemia, long duration of diabetes, microvascular injury, genetic susceptibility, auto immune factors and bad life style practices. Classification of diabetic neuropathy includes rapidly reversible neuropathy, focal, multifocal neuropathy and generalized symmetric peripheral neuropathy. 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 (3). Cardiovascular autonomic neuropathy (CAN) comes under generalized symmetric neuropathy along with gastrointestinal, genitor-urinary and sudomotor disturbances. CAN is a severely debilitating yet underdiagnosed condition in patients with diabetes. The prevalence can range from 2.5% (based on the primary prevention cohort in the Diabetes Control and Complications Trial) to as high as 90% of patients with type 1 diabetes. Clinical manifestations range from orthostasis to myocardial infarction (4). Silent ischemia in diabetic patients may result from CAN. Altered pain thresholds, subthreshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms (5). Clinical manifestations of CAN depend on disease progression. Decreased HR variability is the earliest manifestation in subclinical CAN. In clinical CAN, resting tachycardia and decreased exercise tolerance may be observed in the

early stages as sympathetic tone increases. Orthostatic hypotension and sympathetic denervation of the heart are manifestations of severe CAN. Other symptoms such as dizziness, syncope, visual disturbances, frequent falls, and nocturnal hypertension due to a paradoxical increase in sympathetic tone may also be observed at CAN (6,7). CAN may cause potentially life-threatening outcomes ranging from silent myocardial infarction to sudden cardiac death probably due to ventricular arrhythmias (8).CAN contributes to poor prognosis of coronary artery disease in diabetics. Early recognition of asymptomatic cardiac dysautonomia may help in delaying or arresting its progression (9). CAN is usually detected at a subclinical stage by various tests of autonomic reflexes (10). The American Diabetes Association recommends the use of Ewing tests in the diagnosis of CAN (11). These autonomic function tests are noninvasive and do not require sophisticated equipment, making them of great clinical and prognostic importance. The aim of this study is to determine the prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus patients, its early detection with simple bedside tests, and its association with duration of diabetes. This study may help in identifying individuals with asymptomatic CAN, who would be at a greater risk of developing life threatening complications, so that specific steps can be taken for their prevention.

AIM:

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

METHODOLOGY:

A Cross sectional study is conducted to evaluate the prevalence of cardiac autonomic neuropathy among 93 Type 2 Diabetes Mellitus patients, both males and females, with the simple bedside autonomic reflex tests.

Inclusion criteria:

- Diagnosed Type 2 Diabetes Mellitus patients according to WHO criteria who are already on treatment.

Exclusion Criteria:

- Known Coronary Artery disease
- Systemic Hypertension
- Documented valvular heart disease
- Clinical Heart failure
- Age above 60 years.
- Electrolyte imbalance (hypocalcemia, hypokalemia)
- Patients who are on drugs that would interfere with the autonomic functions.
- Recent myocardial infarction
- Recent eye operation or major surgery

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. A series of five autonomic function tests were performed (as described by Ewing and Clarke et al.). Autonomic neuropathy tests were performed in the outpatient clinic and in the hospital ward, using a 12-lead ECG monitor, a pulse oximeter, and a BP device. Patients were tested after obtaining proper informed consent, with an interval of 10 minutes after each manoeuvre. Patients were advised to avoid strenuous exercise in the 24 hours before testing. Caffeine, alcoholic beverages and smoking were avoided at least 2 hours before testing. Testing was performed fasting or 2 hours after a light meal. In patients receiving insulin therapy, testing was performed at least 2 hours after taking a short-acting insulin and not during the period of hypoglycemia or hyperglycemia.

The following 5 tests for detecting Cardiac Autonomic Neuropathy were done (12,13, 14):

1. **Blood pressure for postural or orthostatic hypotension:**
   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:**
   This test can be done using a slightly modified BP apparatus. Patient blows into the rubber tubing to raise the pressure to 40 mm Hg, a long strip ECG in lead II is taken. The ratio between the longest and shortest R-R interval is measured and the mean ratio is determined.

3. **Deep breathing associated changes in Heart Rate:**
   The ECG is recorded continuously while the patient breathes at a regular rate of 6-12 breaths/min. A difference of heart rate of <15 beats/min between expiration and inspiration is taken as abnormal.

4. **Blood pressure changes during sustained hand grip:**
Subject is given a ball and is asked to press the ball in his or her left hand for about 5 minutes. Failure of diastolic blood pressure to rise more than 15 mm of Hg is considered as an abnormal finding and graded accordingly.

5. **Heart rate response to standing:**
R-R interval is measured at beats 15 and 30 on ECG. 30:15 R-R interval ratio is then calculated.

Ewing's autonomic function tests and scoring

Score	Heart rate variability to Deep breathing	Heart rate response to Valsalva ratio	Heart rate variability to standing ratio	BP Variability to handgrip (mmHg)	BP Change during standing (mmHg)
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

Each test is graded as:

- Score0 –normal
- Score 1-borderline
- Score 2–abnormal

1. An overall score of '0'or'1'is considered normal.
2. Scores 2,3,4 are considered borderline autonomic function.
3. Score ≥5 is judged as 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 GNU PSPP statistics software 1.62 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*:*

Gender distribution

	Frequency	Percent
Females	40	43.0%
Males	53	57.0%
Total	93	100.0%

Duration of diabetes

Duration of DM (yrs)	Frequency	Percent
<5yrs	20	21.5
5-10yrs	43	46.2
>10yrs	30	32.3
Total	93	100.0

Among 93 patients from the study group, highest number of patients had duration of 5-10 yrs.

CARDIOVASCULAR AUTONOMIC REFLEX TESTS:

Heart rate response to deep breathing

Heart rate difference	Frequency	Percent
≥15	28	30.1
11- 14	57	61.3
≤10	8	8.6
Total	93	100.0

Among 93 patients tested, 8 had abnormal scores and 57 had borderline scores and 28 had normal scores.

Heart rate response to Valsalva

Heart rate ratio	Frequency	Percent
≥1.21	36	38.7
1.11-1.20	43	46.2
≤1.10	14	15.1
Total	93	100.0

The test returned normal score for 36 patients, borderline scores for 43 patients and abnormal scores for 14 patients.

BP response to standing

BP Response/standing	Frequency
≤10	44
11-29	44
≥ 30	5
Total	93

Among the 93 tested patients, 44 had a normal response, 44 had borderline and 5 had abnormal response.

BP response to Handgrip

BP Response	Frequency
≥ 16	39
11-15	47
≤10	7
Total	93

Among the 93 patients tested for BP response to Handgrip, 39 patients had normal response, 47 had borderline response and 7 had abnormal response.

Heart rate response to standing

Heart rate ratio	Frequency
≥1.04	54
1.01-1.03	25
≤1.0	14
Total	93

Out of 93 patients tested for abnormal heart rate response to standing, 54 patients had a normal score, 25 had borderline scores and 14 had abnormal scores.

Summary of CAN test Results:

Overall, among 93 patients in the study**, 5** patients had abnormal results (score 2) for heart rate variability to deep breathing**, 14** had abnormal results for heart rate response to Valsalva**, 5** showed abnormal results for heart rate response to standing, **5** had abnormal results for BP response to hand grip and **5** had abnormal BP response to standing respectively.

CAN score-frequency distribution

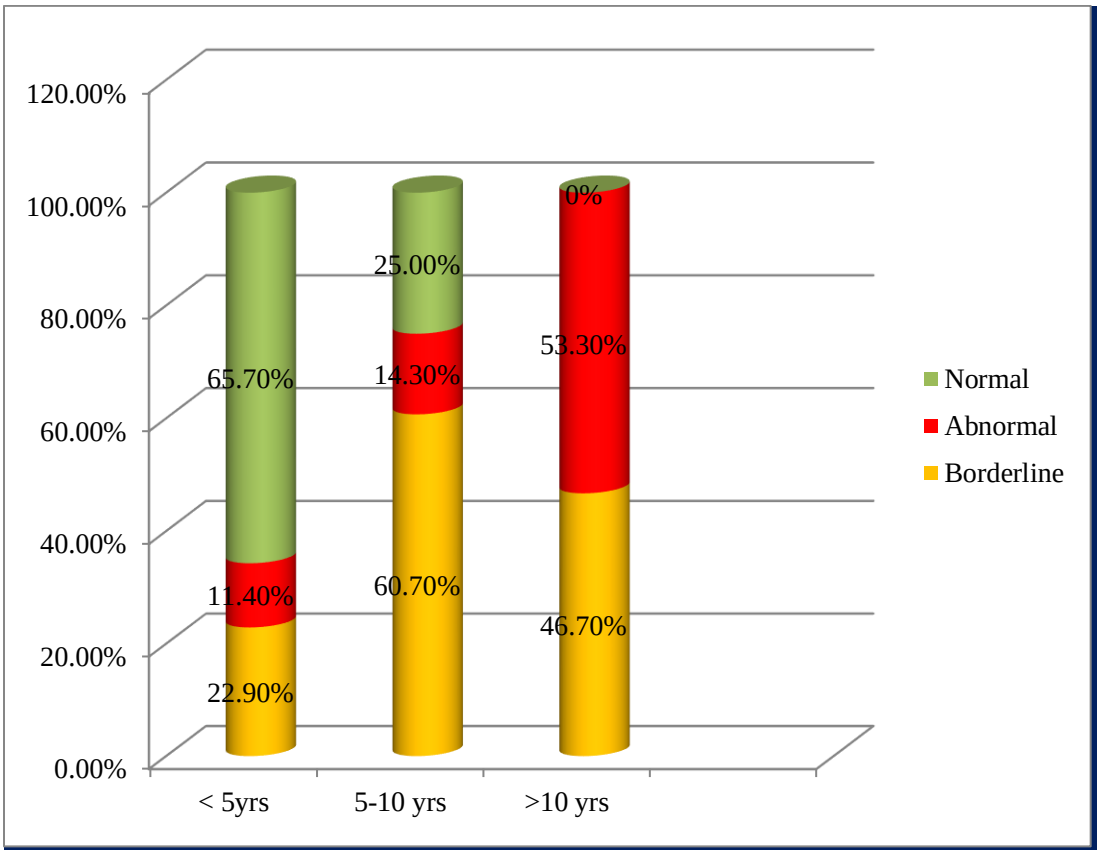
CAN Score	Frequency
Abnormal	24
Borderline	39
Normal	30
Total	93

Among 93 patients, 24 had an abnormal CAN Score, 39 had borderline and 30 had normal CAN Score.

Cross tabs-CAN score and duration of DM

			Duration of DM(yrs)			total
			<5	5-10	>10	
CAN Score	abnormal	Frequency	4	4	16	24
		Percentage	11.4%	14.3%	53.3%	25.8%
	Borderline	frequency	8	17	14	39
		Percentage	22.9%	60.7%	46.7%	41.9%
	Normal	Frequency	23	7	0	30
		Percentage	65.7%	25.0%	0%	32.3%
total		Count	35	28	30	93
		Percentage	37.6%	30.1%	32.3%	100%
		Total	100%	100%	100%	100%

CAN Score with duration of DM



Chi-Square Tests:

	Value	df	Asymptotic Sig.(2-tailed)
Pearson Chi-Square	**40.88**	**4**	**.0001**
Likelihood Ratio	**47.01**	**4**	**.0001**
N of Valid Cases	**93**		

Among the 93, 11.4% of <5years diabetics, 14.3% of 5-10 years diabetics and 53.3%of >10 years diabetics showed abnormal CAN score. Chi-square tests showed there is a significant relation between duration of DM and CAN scores.

DISCUSSION*:*

Diabetic autonomic neuropathy presents a therapeutic challenge to the treating physician because it has a multi-factorial pathogenic mechanism and also usually manifests late. Cardiovascular autonomic neuropathy (CAN) can be detected at the subclinical stage by performing a series of autonomic tests rather than a single test that detects both the parasympathetic and sympathetic components of the autonomic nervous system. In our study, 93 patients with type 2 diabetes were evaluated for signs of cardiovascular autonomic neuropathy using simple bedside autonomic reflex testing, regardless of the duration of diabetes. The medical history specifically asked about for symptoms of autonomic neuropathy, which revealed that only 33 patients had symptoms of autonomic neuropathy. The overall prevalence of cardiac autonomic neuropathy in our study was 67.7%, with 41.9% having borderline autonomic dysfunction and 25.8% having severe autonomic dysfunction. 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 (15) which showed that 53.8% of patients with more than 10 years

of diabetes had abnormal CAN score. Satchi A, Surendran et al (16) found prevalence of CAN to be 58% among the patients with Type 2 Diabetes Mellitus. Smoking cessation, tailored exercise programs, body stockings, and gravity suits are useful in patients with orthostatic hypotension to improve peripheral vascular resistance, elevation of the head end during sleep may bring symptomatic relief. A gradual change in posture, standing with legs crossed, dorsiflexion of the feet, or grip exercises before standing up; all these non-pharmacological measures are recommended to diagnosed patients. Pharmacological measures such as tight control of blood glucose levels, effective blood pressure control with ACE inhibitors(17) and beta-blockers, and correction of dyslipidemia with statins, aspirin and antioxidants have already been tried for halting the progression.

CONCLUSION:

Prevalence of cardiac autonomic neuropathy in diabetics is 67.7%, which is quite high and significant due to the associated morbidity and mortality. There is a significant relation between prevalence of CAN and its severity with duration of diabetes. These simple bedside tests provide an objective guide for early identification of patients at higher risks of developing life threatening complications of CAN so that steps can be taken to halt disease progression and modify lifestyle and initiate exercise programs to improve the quality of life.

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