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Original Research Paper

General Medicine

STUDY OF PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN DIABETIC PATIENTS

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ABSTRACT **Aim & Objective:** The purpose of this study was to study the prevalence of Cardiac Autonomic Neuropathy (CAN) in diabetic patients and its relation to age, gender, duration of diabetes mellitus and glycosylated haemoglobin level (HbA1c). **Methods:** This was a cross sectional study conducted at teaching hospital sample of 100 patients with Type 2 Diabetes Mellitus who were on regular treatment with either insulin &/or oral hypoglycaemic agents were studied. **Conclusion** Our study revealed that CAN is a common microvascular complication in type 2 DM. The duration of diabetes and poor glycemic control are its significant determinants

KEYWORDS : Cardiac autonomic neuropathy, Glycemic control, Type 2 diabetes mellitus.

INTRODUCTION

India is the diabetes capital of the world with 41 million people suffering from diabetes(1). Cardiac autonomic neuropathy (CAN) is often an underdiagnosed and dreaded complication of diabetes mellitus (DM) and is associated with increased mortality and morbidity. The prevalence of CAN is approximately 31–73% in type 2 DM and the annual incidence has been reported to be 2%(2). Pathogenesis of CAN is complex and multifactorial. Hyperglycemia-induced activation of the polyol pathway causes direct neuronal damage and activation of protein kinase C, thereby leading to vasoconstriction and decreased neuronal blood flow. Other mechanisms involved are increased oxidative stress, increased free radical production, dysfunction of nitric oxide production, immune mechanisms, and neurotrophic growth factors deficiency. Accumulation of advanced glycosylation endproducts in the neuronal blood vessels leads to nerve hypoxia and altered nerve function(4).

CAN is initially subclinical and becomes symptomatic only in the later stages of the diabetes. Identifying patients with CAN is crucial as early initiation of intensive interventions like targeting lifestyle changes, glycemic control, and cardiovascular risk factors can slow the progression of CAN and may be reversible if diagnosed soon after the onset(3). There have been only a few Indian studies on CAN in diabetes patients . Therefore, the present study has been designed to investigate the prevalence of CAN involvement in type 2 DM and its relationship with age, gender, duration and HbA1c in our setup.

MATERIALS AND METHODS

This study was a cross-sectional observational study, conducted at teaching hospital. A total of 100 patients of type 2 DM were enrolled in this study. The study was conducted between November 2020 to April 2022. The diagnosis of DM was made by the criteria given by the American Diabetes Association 2016.

Criteria for patient selection

Inclusion Criteria

Subjects with type 2 Diabetes mellitus who are on treatment with either oral hypoglycaemic agents or insulin or both.

Exclusion Criteria

1)Subjects on Beta blockers or Tricyclic antidepressants or anti arrhythmic.

2) Subjects with acute complications of DM i.e; hypoglycaemia, diabetic ketoacidosis, hyperosmolar non ketotic coma.
3) K/C/O Hypertension or newly diagnosed (systolic BP >140 or diastolic BP >90).
4) CAD and heart failure patients.

The study was performed according to the guidelines of the ethics committee of our institute and informed consent was taken from all the patients. Based on inclusion and exclusion criteria patients are selected for this study and are subjected to following clinical test for cardiac autonomic neuropathy score assessment recommended by Bellavere et al.

Scoring system recommended by Bellavere et al(5)

TEST	SCORE		
	0 (Normal)	1(Borderline)	2(Abnormal)
Heart rate variability1	> 15	10-15	<10
Valsalva ratio2	≥ 1.21	1.11-1.20	≤1.10
30:15 ratio3	≥1.04	1.01-1.03	≤1.00
BP response to standing4	≤10mm Hg SBP	11-29 mm Hg	≥ 30mm Hg
BP response to handgrip5	≥16mmHg PBP	11-15 mm Hg	≤ 10mm Hg

1 - Difference between maximum and minimum heart rate in response to deep breathing.
2 - Dividing lengthiest R-R interval of ECG recorded at 15 to 30 sec after withdrawing strain period by smallest R- R interval within 15 sec of ECG recording during strain period of valsalva manoeuvre.
3 - Dividing lengthiest R-R interval of ECG recorded at 15 to 30 sec by smallest R- R interval of ECG recorded within15 sec when the patient is standing.
4 - Difference between the resting and standing systolic BP.
5 - Difference between diastolic BP after isometric exercise to resting BP.

Grading of cardiac autonomic neuropathy is decided based on the value secured from each test done above. The total score is from 0 to 10.

Based on the above test, CAN score was calculated using these 5 variables and patients were categorized into 3 categories.

CAN SCORE	CATEGORY
0-1	No autonomic neuropathy
2-4	Mild autonomic neuropathy
5-10	Severe autonomic neuropathy

Clinical tests for cardiac autonomic neuropathy

Tests Reflecting Mainly Parasympathetic Function

A. Beat to beat Heart rate variability in response to deep breathing –

The patient is made to lie in supine position and takes six breath per sixty second deeply in and out, while ECG is recorded for 1minute. Difference between the maximum and minimum heart rates calculated using R-R interval. 15 bpm difference or more is normal and 10 bpm or less is abnormal.

B. Heart rate in response to Valsalva manoeuvre

Patient in made to lie on bed at resting condition in supine posture, ECG machine is connected, patient is advised to sit and ask him to do valsalva manoeuvre and exhale forcibly for around 15 second with glottis open. Valsalva ratio is studied by dividing the lengthiest R-R interval of ECG recorded 15 to 30second after withdrawing strain period to smallest R-R interval of ECG recorded within15 second during the strain period.

C. Heart rate in response to standing

Patient made to lie down in a bed in resting condition and ECG machine is connected and then patient is made to stand completely. Then the ECG is recorded to calculated 30:15 ratio, which is calculated by dividing lengthiest R-R interval of ECG recorded 15 to 30 sec to the shortest R-R INTERVAL of ECG recorded within fifteen second.

Tests Reflecting Mainly Sympathetic Function

D. systolic BP in response to standing

The subjects resting systolic BP was recorded. The subject was then asked to stand and remain standing unsupported for 3 minutes. The systolic BP was recorded at 2 minutes after standing or before 5 minutes of standing. The difference between the resting and standing BP levels was calculated.

E. Diastolic BP response to sustained hand grip exercise

Individual is advised to squeeze the rubber ball to full extent than hold it for 1 minute. Blood pressure was recorded in the non-exercising arm twice at 30 second interval during the procedure. The maximum reading of the diastolic blood pressure was taken as the final value. Then the rise in diastolic blood pressure was calculated by subtracting resting diastolic blood pressure from this value.

Statistical Analysis

The statistical test used were descriptive analysis distribution analysis by class interval method and Chi-square test of association. The entire statistical analysis was carried out by the statistical package of social sciences (Spss-21). P value <0.05 was considered statistically significant.

RESULTS

Table 1(I): Age of the study patients – descriptive analysis

Age (in yrs)	M	SD
Age	59.52	11.67

M-Mean, S.D – Standard Deviation

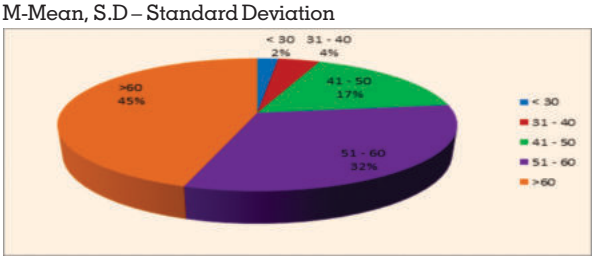

Figure 1: Age distribution

Table 2: Gender distribution **N=100**

Gender	%
Male	58
Female	42
Total	100

%- Percentage

In table 2 gender distribution is presented. The majority of the study patients were male 58%. The proportions of female patients was 42%.

Table: 3 Duration of the condition – descriptive analysis

Duration of the condition	M	S.D
Duration in years	6.99	4.06

M-Mean, S.D – Standard deviation

It is inferred from table 3 that the mean duration of the condition of the study patients was 6.99 ± 4.06 years.

Table: 4 HbA1C Descriptive statistics

	M	S.D
HbA1C	8.07	1.32

M-Mean, S.D-Standard Deviation

It is observed from Table 4 that mean HbA1C of the study patients was 8.07±1.32.

Table: 5 categorization of CAN score – Descriptive statistics

CAN score	%
No autonomic neuropathy (0-1)	61
Mild autonomic neuropathy (2-4)	17
Severe autonomic neuropathy (5-10)	22

%-Percentage

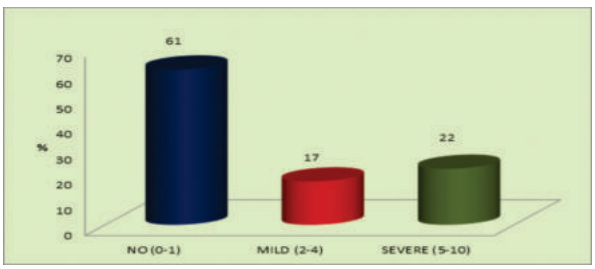

Figure 2: Prevalence of CAN in diabetes

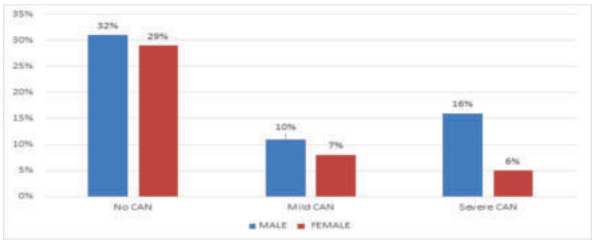

Figure 3: Correlation of CAN vs Gender

In our study there is no significant association of CAN with gender ($p>0.05$).

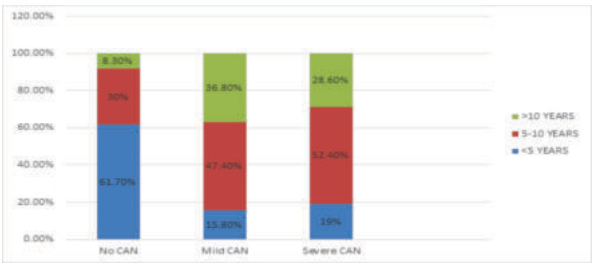

Figure 4: Correlation of CAN with duration of diabetes

In our analysis as shown in figure 4 is that around 61.70% of the subjects with no autonomic neuropathy had diabetes for less than 5 years and around 52.4% of the subjects with duration of DM more than 5 years and 28.60% of patients with duration more than 10 years had severe autonomic neuropathy. It proved that there is statistically significance ($p<0.001$) with duration of DM.

Table: 6 Correlation of Age, duration and HbA1c with CAN

Factors	R	P
Age	0.020	0.841
Duration	0.383	0.001*
HbA1C	0.540	0.001*

r-correlation coefficients, P-Probability value, *-significant

DISCUSSION

Out of 100 patients, 58 were males and 42 were females. The mean age of the study patient was 59.52 ± 11.67 years and it is further noted that the commonest age category was >60 years where 45% of the patients were observed and 51 to 60 years where 32% of the patients were observed. It is inferred from table 3 that the mean duration of the diabetes of the study patients was 6.99 ± 4.06 years. Minimum duration was 1 year and maximum was 20 years. 18% patients were found to have diabetes for more than 10 years. It is observed from Table 4 that mean HbA1C of the study patients was 8.07±1.32.

Patients were divided into three groups: no CAN, mild CAN and severe CAN. It is inferred from table 5 and figure 2 that the prevalence of CAN was 39% in diabetes of which 17% had mild CAN and 22% had severe CAN. Keen H et al(6) in his study found autonomic neuropathy in 32% of the DM subjects, Noronha et al(7) found the CAN in 38. 5% with 11% of subjects having severe autonomic neuropathy. In studies done by Toyry et al(8) and Vinik AI et al(4) CAN was present among 22% and 41% of their patients respectively.

It is inferred from Table 6 that there was significant positive correlation between duration of the diabetes and CAN, $r=0.383$, $P=0.001<0.05$. Hence, as the duration of the disease condition was longer, it was associated with CAN and vice-versa. There was significant positive correlation was observed between HbA1C and CAN, $r=0.540$, $P=0.001<0.05$. Hence, there was significantly higher CAN in patients with higher HbA1C and vice-versa. But no stastically significant correlation of CAN with age group and gender.

There are several risk factors reported in the literature associated with the development of CAN which includes older age, diabetes duration, glycemic control, the presence of microvascular complications, hypertension, dyslipidemia (decreased HDL, increased LDL, and TGs levels), and obesity(9).

In our study longer duration of disease and poor glycemic control was a strong predictor of CAN ($P \leq 0.001$). The positive correlation of CAN and long duration of diabetes have been reported by Ahire et al. who demonstrated that patients having duration of diabetes >5 years are more likely to have definite and severe CAN than in patients with duration of disease <5 years(10). Pappachan et al(11) also showed that incidence of diabetic autonomic neuropathy increased with increasing duration and poor glycaemic control.

Presence of CAN is strongly associated with increased mortality and morbidity such as cerebrovascular disease, coronary artery disease, and silent myocardial ischemia. This has been proven by the results from the European Epidemiology and Prevention of Diabetes (EURODIAB) study and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial(12,13). For early diagnosis and prompt management of CAN, all patients with type 2 DM should be assessed for diabetic neuropathy immediately after diagnosis. Treatment of CAN comprises of symptomatic management as well as effective therapies to slow or reverse its progression. The modalities of treatment include lifestyle modification, intensive glycemic control, antioxidants, and treatment of complications like orthostatic hypotension.

CONCLUSION

Our study revealed that CAN is a common microvascular complication in type 2 DM. The duration of diabetes and poor glycemic control are its significant determinants and hence strict glycemic management at early stages of diabetes may prevent development of CAN. In our setup most of the patients are diagnosed with type 2 DM only after patients become symptomatic and this is due to people ignorance about the disease, especially among the rural-based population. Most often patients presents with one of the diabetes complications, hence diabetic screening should be done for all the patients of more than 30 years for early diagnosis; and by prompt management further complication can be prevented.

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