



CARDIAC AUTONOMIC NEUROPATHY IN DIABETES MELLITUS PATIENTS – STUDY IN TERTIARY CARE CENTER .

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is a serious complication of uncontrolled sugars in type 2 diabetes mellitus. **Aim and objectives** - To study the risk factors and prevalence of CAN in diabetes mellitus patients. **Place of study** – Department of General Medicine, Kamineni Institute of Medical Sciences, Narketpally. **Duration of study**- October 2019 – September 2020. **Study design**- Cross sectional study. **Methods** – 100 patients with type 2 diabetes mellitus of age range 40-75years were studied. Based on clinical, metabolic and biochemistry profile, they were categorized into four groups based on Ewing's criteria. **Results**- Out of 100 patients, 62 were male and 38 were female. Mean age was 51

KEYWORDS : Cardiovascular autonomic neuropathy, diabetes mellitus, diabetic nephropathy, Ewing's criteria .

Background and introduction –

Diabetes is one of the fastest growing global health emergencies of 21st century. In 2019, it is estimated that 463 million people have diabetes and this number is projected to reach 578 million by 2030 and 700 million by 2045^(1,2). Diabetes is a chronic condition that occurs when there are raised blood glucose levels either due to decreased insulin secretion or resistance to insulin action or combination of both. India leads the world with largest number of diabetic patients, hence called “Diabetes capital of the world”⁽³⁾.

Cardiac autonomic neuropathy (CAN) due to diabetes mellitus, is a serious complication which is mostly overlooked and under diagnosed . It is associated with 5 fold increased risk of cardiovascular mortality and morbidity. Although it is a common complication, it is initially subclinical and becomes symptomatic in the later stages of the disease. Early detection of patients with CAN and early initiation of interventions for life style modification, glycemic control and other risk factors delays the progression of CAN⁽³⁾. Hence this study has been designed to investigate the risk factors and prevalence of CAN in type 2 DM patients in a tertiary care center.

Patients and methods –

- **STUDY DESIGN** : Cross sectional study.
- **STUDY SETTING** : Admitted and out-patients with type 2 diabetes mellitus patients in the Department of General Medicine, Kamineni institute of medical Sciences , Narketpally.
- **STUDY DURATION** : OCTOBER 2019 - SEPTEMBER 2020
- **SAMPLE SIZE** : Type2 Diabetes Mellitus – 100 Patients
- **ETHICAL COMMITTEE APPROVAL** : Obtained
- **PATIENT CONSENT** : Informed consent was obtained
- **FINANCIAL SUPPORT** : Nil
- **CONFLICT OF INTEREST** : Nil

INCLUSION CRITERIA :

Patients, of age group 40-75years and who completed a standardized interview and a detailed physical examination and classified as having type2 DM according to the American Diabetes Association (ADA)⁽⁴⁾ are included.

EXCLUSION CRITERIA :

- Other diseases associated with autonomic nervous system (thyroid dysfunction, severe systemic diseases like cardiac, pulmonary, renal pathologies and malignancy).

- Those who had history of hypoglycemia in the preceding 24 hours.
- Patients who are on medications like β -blockers, sympathomimetics, vasodilators, diuretics.
- Patients with underlying cardiac disease like CAD, MI, heart failure and arrhythmias.
- Patients who are uncooperative and not willing for study.

Selection of the study subjects-

After obtaining informed consent, all patients underwent a thorough physical examination including measurement of height, weight, BMI, resting heart rate, blood pressure. In all patients blood samples were sent for analysis. Serum creatinine, blood glucose, fasting lipid profile were analyzed using ERB full auto analyzer. HbA1c was determined by high-performance liquid chromatography. eGFR was calculated using MDRD formula⁽⁶⁾. Urine protein was analyzed using auto analyzer. Retinopathy was evaluated by direct ophthalmoscope. Peripheral neuropathy assessment was quantified by the neuropathic disability score. Data was analyzed with MINITAB 15 statistical software. Cross tabulation and chi square analysis were done using variables obtained.

Tests for evaluation of autonomic nervous system were performed on all patients.

Tests for parasympathetic damage:

1. Resting heart rate: A resting heart rate > 100 beats per minute is considered abnormal.
2. Heart rate response to deep breathing: The patient was made to lie supine and take normal breathing for 2 minutes. Then he was asked to breath deeply at 6 breaths per minute. Continuous ECG recording was obtained to look for heart rate variability. The expiration: inspiration (E:I) difference was calculated as the difference between the longest R-R interval during expiration to the shortest R-R interval during inspiration. E:I difference of <1.1 was considered abnormal.
3. Heart rate response to standing (30:15 ratio): patient was asked to lie supine for 3 minutes and then asked to stand up. A continuous ECG was recorded and 30:15 ratio was calculated by taking ratio of R-R interval at 30th beat and at 15th beat after standing. A 30:15 ratio <1.01 was considered abnormal.
4. Valsalva ratio: the patient was asked to blow into a mouth piece connected to a manometer so as to maintain pressure up to 40mmHg and maintain it for 15s and a

continuous ECG recording was done. After 30s ECG was monitored again for 15s. The valsalva ratio was calculated as longest R-R interval after release to shortest R-R interval during maneuver. A valsalva ratio of <1.1 was considered abnormal.

• Test for sympathetic damage:

1. Blood pressure response to standing: patient's BP was recorded in supine position and then asked him to stand for 2minutes and BP was recorded. A decline in SBP $\geq 20\text{mmHg}$ was considered abnormal.
2. Blood pressure response to sustained hand grip: the patient was asked to apply pressure by hand grip with dominant arm for 3 times. Highest of the 3 recordings was considered maximum voluntary contraction. He was then instructed to maintain hand grip steadily at 30% of maximum contraction for as long as possible to a maximum of 5minutes. Blood pressure was measured on non exercising arm at rest and at the end of grip. The normal response is a rise of DBP $> 16\text{mmHg}$, and $\leq 10\text{mmHg}$ was considered abnormal.

Table - 1 : Cardiac autonomic reflex test based on Ewing's criteria.

Tests reflecting parasympathetic function	Normal	Borderline	Abnormal
Resting heart rate	<100	-	100
Heart rate response to deep breathing (E:I ratio)	>1.1	-	1.1
Heart rate response to standing (30:15 ratio)	1.04	1.01-1.03	1.01
Heart rate response to valsalva maneuver	1.21	1.11-1.20	1.01
Tests reflecting sympathetic system			
Blood pressure response to standing	10mmHg	11-19mmHg	20mmHg
Blood pressure to sustained hand grip	16mmHg	11-15mmHg	10mmHg

The results were then categorized into 4 groups(7):

- Normal
- Early CAN
- Definite CAN
- Severe or advanced CAN.

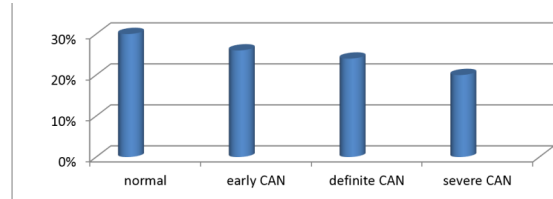
Analysis of data:

Statistical analysis was done using MINITAB 15 software. All the data is presented as mean or percentages. Continuous variables were compared by the chi square test. A P value <0.05 was considered statistically significant.

RESULTS:

Out of 100 patients 62 were male and 38 were female. The mean age of patients was 51 ± 11 years (range 40-75 years). The mean duration of diabetes was 8 ± 6 years. All the patients in the study group were categorized into 4 groups normal, early CAN, definite CAN, severe or advanced CAN. Out of 100 patients normal (without CAN) 30%, early CAN -26%, definite CAN 24%, severe CAN 20%. The patients with CAN were older ($P = 0.005$), had longer diabetic duration ($P = 0.0003$). They had diabetic nephropathy with high creatinine ($P = 0.001$) and low eGFR ($P=0.005$) compared to patients without CAN. The prevalence of severe CAN was seen in patients with mean duration of diabetes of 16 ± 5 years. Other complications in patients with CAN like peripheral neuropathy were seen in 69 patients (98.54%), diabetic nephropathy in 65 patients (92.86%), diabetic retinopathy in 64 patients (91.43%), erectile dysfunction in men in 8 patients (12.35%) and gastrointestinal symptoms in 14 (21.53%). Some people have combination of symptoms involving 2 or 3 systems.

Figure 1 : Prevalence of CAN in type 2 diabetes mellitus patients in study group.



In patients without CAN peripheral neuropathy was seen in 10 patients (33.33%), diabetic nephropathy in 2 (6.67%), retinopathy in 2 (6.67%) patients, gastrointestinal symptoms in 2 (5.71) which is very less compared to patients with CAN.

Table – 2 : Prevalence of complications of type 2 diabetes mellitus in study group.

complication	CAN present (%)	CAN absent (%)	Chi-square test (P)
Peripheral neuropathy	69(98.54)	10(33.33)	<0.023
Diabetic nephropathy	65(92.86)	2(6.67)	<0.001
Diabetic retinopathy	64(91.43)	2(6.67)	<0.001

Among the cardiovascular autonomic reflex test (CART), resting tachycardia was present in 30 patients (46.15%), abnormal heart rate response to deep breathing (E:I ratio) is seen in 45 patients (69.23%), abnormal heart rate response to standing (30:15 ratio) is seen in 36 patients (55.38%) and abnormal heart rate response to valsalva maneuver is seen in 32 patients (49.23%), orthostatic hypotension in 8 patients (12.31%) and abnormal blood pressure response to sustained hand grip is seen in 11 patients (16.92%).

DISCUSSION: Pathogenesis –

The pathogenesis of CAN is complex and multifactorial . It is due to complex interactions among degree of glycemic control, disease duration, diabetic nephropathy and systolic and diastolic blood pressure. Hyperglycemia induced activation of polyol pathway causes direct neuronal damage and activation of protein kinase C leading to vasoconstriction and decreased neuronal blood flow. Other mechanisms involved are increased oxidative stress, free radical production, dysfunction of nitric oxide, autoimmune mechanisms. Accumulation of AGEs (Advanced Glycation End products) leads to now hypoxia and altered nerve function⁽⁸⁾.

In our study out of 100 patients with type 2 diabetes mellitus 70 patients had CAN (70%), of which 45 were male (64.29%) and 25 were female(35.71%) showing no much significant differences in prevalence of CAN between two genders. Early CAN was present in 26%, definite CAN in 24% and severe CAN in 20%. The prevalence of CAN was in accordance with the study by Birajdar et.al (58%)⁽⁹⁾, Ewing et.al (69.3%)⁽¹⁰⁾, Nijhawan et.al (60%)⁽¹¹⁾, Aggarwal et.al (70%)⁽¹²⁾, Ashok K.Bhuyan, Abhamoni Baro et.al (70%)⁽¹³⁾.

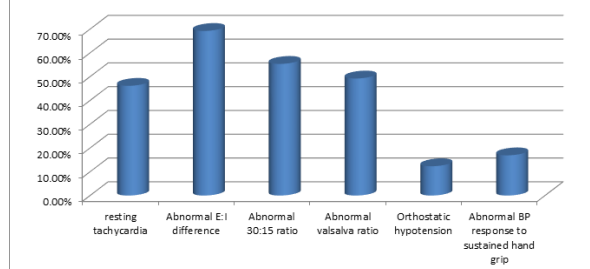
The mean age of study group was 51 ± 11 (range 40-75 years). Ratio of male to female with CAN was 1.8 : 1.

The incidence of peripheral neuropathy in patients with CAN was 98.54%, diabetic retinopathy was 91.43%, diabetic nephropathy 92.86% which is comparable with study by Birajdar et.al⁽⁹⁾ showing peripheral neuropathy (58%), diabetic nephropathy (8%), diabetic retinopathy (56%). Kudrimoti et.al⁽¹⁴⁾ reported peripheral neuropathy in 62.5%, diabetic nephropathy in 31.4% and study by Patel and Shrivastava⁽¹⁵⁾ showed retinopathy in 24.36% and nephropathy in 62.5%.

Valeni P et.al(16)and Kemppler et.al(17) showed a significant correlation between prevalence of CAN and duration of diabetes ($P = 0.026$ and $P < 0.001$ respectively). Tankhiwala et.al(18) also found linear relationship between the duration of diabetes and autonomic dysfunction. In our study most patients with CAN are with a duration of > 5 years.

In the present study resting tachycardia was seen in 30 patients (46.15%), abnormal E:I ratio was seen in 45 patients (69.23%) and abnormal heart rate response to standing (30 : 15) was seen in 36 patients (55.38%), abnormal heart rate response to valsalva was present in 32 patients (49.23%), orthostatic hypotension in 8 patients (12.31%) and abnormal blood pressure response to sustained hand grip was seen in 11 patients (16.92%).

Figure 2: Distribution of abnormal cardiovascular autonomic reflex tests in study population.



In our study E:I ratio was noticed as most common abnormality whereas, in study by Birajdar et.al⁽⁹⁾ E:I was noticed in 24% patients with CAN, 22.9% patients with CAN in study by Kudrimoti et.al⁽¹⁴⁾, 56% of patients have abnormal E:I ratio in Ashok K.Bhuyan , Abhamoni Baro et.al⁽¹³⁾ study. Patnaik et.al⁽¹⁹⁾ reported E:I ratio abnormal in 85.71%.

The heart rate response to standing (30:15 ratio) was found abnormal in 36 patients (55.38%) in our study, which is comparable with study by Kudrimoti et.al⁽¹⁴⁾, Sharma et.al^(38%)⁽²⁰⁾, Ewing et.al⁽¹⁰⁾(60%).

The heart rate response to valsalva maneuver was found to be abnormal in 32 patients (49.23%) which is comparable with study by Gupta et.al⁽²¹⁾ (36.72%), Sharma et.al⁽²⁰⁾ (38%), Patnaik et.al⁽¹⁹⁾(40%), Levin et.al^(62%).

In the present study postural hypotension was seen in 8 patients with CAN (12.31%). Incidence of postural hypotension in study by Gupta et.al⁽²¹⁾(5.7%), Sharma et.al⁽²⁰⁾ (6%), Kudrimoti et.al⁽¹⁴⁾ (17.14%).

In the present study blood pressure response to sustained hand grip in patients with CAN was found in 11 patients (16.92%) which is comparable with study by Ewing et.al⁽¹⁰⁾ (26.22%)⁽¹⁰⁾, Sharma et.al⁽²⁰⁾ (10%).

CONCLUSION :

Our study found that CAN is a most common microvascular complication in type 2 diabetes mellitus .duration of diabetes, age ,diabetic nephropathy(low GFR ,high creatinine) ,glycemic control are significant determinants of CAN. Hence early detection, and management of glycemic control may prevent complications of diabetes.

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