



PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS ASSOCIATION WITH OTHER MICROANGIOPATHIES

Diabetology

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ABSTRACT

BACKGROUND: Cardiac autonomic dysfunction is the most overlooked complication of Diabetes mellitus leading to increase mortality, arrhythmias and sudden cardiac death. Retinopathy is the common microvascular complication of Diabetes along with Neuropathy and Nephropathy, is the most significant risk factor in predicting the presence of cardiac autonomic dysfunction in patients with type2 diabetes. Diabetic Retinopathy is a strong predictor for CAN.

METHODS: Necessary data was collected from the medical archives of 100 diabetic patients registered in a tertiary care hospital of Madhya Pradesh.

RESULTS: The mean age of the patients was 52.48±12 years. Out of 100 diabetic patients 57 were female and 43 were male. Cardiac autonomic neuropathy (CAN) was found in 37 % of patients as per Ewings Criteria, and 26 % of them had retinopathy. The mean urine microalbuminuria was significantly higher in CAN positive patients as compare to negative patients. CAN positivity was strongly associated with duration of disease and also with poor glycemc control.

CONCLUSIONS: Prevalence of cardiac autonomic neuropathy is 37% in our study, which was evaluated by cardiac autonomic function tests, and is positively correlated with duration and other microvascular complication including retinopathy, of type2 Diabetes Mellitus. Early detection of CAN is imperative for successful intervention as it is most over looked complication which has got significant impact on quality and survival of life in people with Diabetes.

KEYWORDS

Cardiac autonomic Neuropathy, Diabetes Mellitus, Retinopathy

INTRODUCTION:

India is known as “Diabetes capital of the world” due to largest population of diabetic subjects. At present, there are 69 million diabetic patients in India. The Indian population with diabetes mellitus type 2 is expected to rise to 101 million by 2030¹. Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia either immune-mediated (Type 1 diabetes), insulin resistance (Type 2), gestational or others (environment, genetic defects, infections, and certain drugs) accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins.²

The injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy)³.

Diabetic neuropathy is a clinically manifest or subclinical disease of the peripheral nerves as a sequel of diabetes mellitus without other pathogenetic causes affecting both the somatic and the autonomous nervous system. In addition to sensorimotor diabetic neuropathy, diabetic autonomic neuropathy is the most frequent disease in the peripheral nervous system. Organs involved in it are Cardiovascular system, gastrointestinal tract, urogenital tract, neuroendocrine system and respiratory System⁴.

It has found that 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had cardiac autonomic dysfunction associated with a high risk of cardiac arrhythmias and with sudden death. It is the complication of diabetes which is common but frequently overlooked and it results in diverse spectrum of clinical manifestations ranging from impairment of exercise intolerance to sudden cardiac death⁵.

METHODS AND MATERIALS:

The present study entitled “Prevalence of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus and its association with other microangiopathies” was carried out on type 2 diabetic patients in a tertiary care center of Madhya Pradesh.

Present study was carried out in tertiary care center on 100 type2

diabetic patients as defined according to ADA criteria⁶. It was a prospective and observational study.

EXCLUSION CRITERIA- patient his/her not willing to provide written voluntary informed consent for participation in the study and/or were Chronic alcoholics, Amyloidosis, Connective Tissue Disorders, Chronic Renal Failure, uncontrolled hypertension, Heart failure, Cirrhosis of liver, Chronic GBS and patients with Macroalbuminuria.

METHODOLOGY-

- Cardiac autonomic functions tests were applied⁷.
 - Tests reflecting cardiac parasympathetic damage which included heart-rate response to Valsalva maneuver, heart-rate (R-R interval) variation during deep breathing and immediate heart-rate response to standing.
 - Tests reflecting sympathetic damage like Blood-pressure response to standing, Blood-pressure response to sustained handgrip.
- Diabetic Retinopathy was tested by ophthalmoscope and microalbuminuria was screened by routine and microscopic examination. It was done by turbidmetric immunoassay by measuring antigen-antibody reaction by the end point method.
- ECG

Outcome measures were evaluated by EWINGS CRITERIA⁸

Tests reflecting parasympathetic function	Normal	Borderline	Abnormal
1. Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	>1.21	1.11-1.20	<1.10
2. Heart-rate (R-R interval) variation during deep breathing	>15 beats/min	11-14 beats/min	<10 beats/min
3. Immediate heart-rate response to standing (30:15 ratio)	> 1.04	1.01-1.03	< 1.00
Tests reflecting sympathetic function			
1. Blood-pressure response to standing	<10 mm Hg	11-29 mmHg	>30mmHg
2. Blood-pressure response to sustained handgrip	> 16 mm Hg	11-15mm Hg	<10 mm Hg

Normal = all tests normal or 1 test borderline.

Early = one of the three heart rate tests abnormal or two borderline.
 Definite = two heart tests abnormal.

Severe = two heart tests abnormal + one or both BP tests abnormal

STATISTICAL ANALYSIS-was done by mean, median mode, 'p' test, chi square test

RESULTS:

In the present study, out of 100 cases studied 43% were male and 57% were female.

Patients were matched according to their age. Maximum numbers of patients i.e. 35% were in the age group 41-50 year and minimum between 71-80. The mean ages of the patients was 53.07±12.70 years.

Out of 100 type2 Diabetes Mellitus patients 37% patients had cardiac autonomic neuropathy according to Ewings Criteria and rest 63% were negative. Out of total 37% who were positive for CAN, mostly (26%) had 2 tests abnormal while only 1 patient had 4 tests abnormal.

Graph 1 –Prevalence of CAN in study population

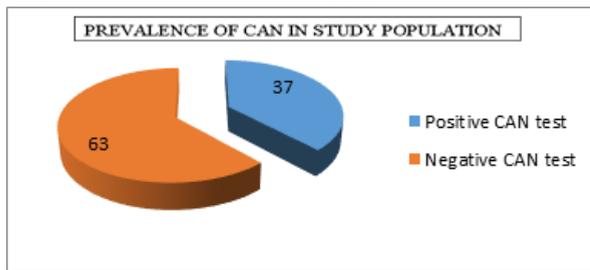


Table1: Distribution of patients according to the number of abnormal cardiovascular autonomic Neuropathy test

ABNORMAL TEST	NO. OF CASES	PERCENTAGE (%)
Two abnormal CV reflex	25	68.42%
Three abnormal CV reflex	11	28.94%
Four abnormal CV reflex	1	2.64%
Total	37	100%

Table 2: Association of CAN with duration of Diabetes Mellitus Type2

		Duration of diabetes mellitus			Total (N=100)	P Value
		Group 1 (≤5 yrs)	Group 2 (5-10 yrs)	Group 3 (≥10yrs)		
Result	Negative	39 (65.0%)	24 (70.6%)	0 (0.0%)	63 (63.0%)	0.004
	Positive	21 (35.0%)	10 (29.4%)	6 (100.0%)	37 (37.0%)	
Total		60 (100.0%)	34 (100.0%)	6 (100.0%)	100 (100.0%)	

The above table (Table 2) shows relationship between cardiac autonomic neuropathy with duration of diabetes mellitus. It was found that patient who had duration of disease more than 10yrs were 6 patients all of them had CAN tests positive as compared to other group who had negative results with P value being 0.004 which was statistically significant (2=11.159, df=2, p<0.05) showing that CAN is dependent on the duration of diabetes.

TABLE 3: Association of mean urine microalbuminuria with CAN results

CAN TEST (N=100)	[Mean±SD]	't' Value	P Value
Positive	17.03 ± 7.07	2.816, df=98	0.006*
Negative	13.84 ± 4.26		

By applying unpaired 't' test comparison was done between mean urine microalbumin value and CAN test results. It was found the mean urine microalbumin value between the two groups was higher in the positive group as compared to negative group P value came to be 0.006 which statistically significant (P<0.05).

TABLE 4: Association of presence diabetic retinopathy with CAN

		CAN TEST			P value
		Negative	Positive	Total (N=100)	
Diabetic retinopathy (N=100)	Negative	45 (71.4%)	14 (37.8%)	59 (59.0%)	0.001
	Positive	18 (28.6%)	23 (62.2%)	41 (41.0%)	
Total		63 (100%)	37 (100%)	100 (100%)	

On comparing the CAN result with the patients having diabetic retinopathy, out of 37 patients who were positive for CAN test 23(62.2%) were also having diabetic retinopathy. So association between them was found to be statistically significant (P < 0.05, 2=10.873, df=1) P value being 0.001.

TABLE 5- Comparison of HbA1c in relation to CAN

		HbA1c		Total (N=100)	P value
		Group A (<6.5)	Group B (≥ 6.5)		
CAN TEST (N=100)	Negative	20 (76.9%)	43 (58.1%)	63 (63.0%)	0.087
	Positive	6 (23.1%)	31 (41.9%)	37 (37.0%)	
Total		26 (100%)	74 (100%)	100 (100%)	

On comparing the CAN test with HBAIC value 74 patients who had HBAIC more than 6.5 , 43(58.1%) had CAN test negative and 31(41.9%) were positive which was less as compared to negative one, association between them was found to be statistically not significant P value being 0.087, showing that CAN test is not associated with HbA1c levels.

DISCUSSION:

Diabetic Autonomic Neuropathy (DAN) accounts for silent myocardial infarction and shortens the lifespan by resulting in death in 25%– 50% of diabetic patients within 5–10 years of DAN. The present report discusses the clinical manifestations (eg, resting tachycardia, orthostasis, exercise intolerance, intraoperative cardiovascular liability, silent myocardial infarction [MI], and increased risk of mortality) in the presence of CAN. Cardiovascular complications are the most common cause of morbidity and mortality in diabetic patients. The mechanisms by which CAN leads to increased mortality remain obscure. A number of studies have shown an increased risk of CAN in diabetic patients showing a prolonged QT interval, leading to speculation that CAN might also predispose to malignant ventricular arrhythmias and to sudden death from cardiac arrest caused by torsades de pointes, as in long QT syndrome⁹. It is difficult to determine the independent effects of CAN on mortality because of the coexistence of cardiovascular disease (CVD). Trial data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including formation of advanced glycation end products, increased oxidative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, and activation of genes involved in neuronal damage¹⁰. Several agents have become available for the correction of functional defects in the autonomic nervous system. Studies have shown improvement of HRV with graded exercise, using a variety of cardioactive drugs as well as intensification of treatment for the multiple risk factors for autonomic neuropathy that are shared with those for macrovascular disease.

CONCLUSION:

Our study was a prospective and observational study which revealed prevalence of cardiac autonomic neuropathy to be 37% which was evaluated by cardiac autonomic function tests and it positively correlated with duration of type2 Diabetes Mellitus, early detection of CAN is imperative for successful intervention as it is most over looked complication which has got significant impact on quality and survival of life in people with Diabetes. CAN is associated with a poor prognosis and may result in severe orthostasis, postural hypotension, exercise intolerance, enhanced intraoperative instability, and an increased incidence of silent MI and ischemia. It may be attributable to a functional abnormality or to organic structural damage to the different components of the autonomic nervous system.

We also found statistically significant association with other microvascular complications including retinopathy and microalbuminuria. It is of utmost importance to analyze the high risk cases as CAN tests as it can uncover autonomic neuropathy even in asymptomatic state and early detection can prevent patient with risk of adverse outcomes like sudden cardiac death.

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