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A Study of Pattern and Prevalence of Cardiovascular Autonomic Neuropathy(CAN) in Type 2 Diabetes Mellitus Patients

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Abstract

Background: Cardiovascular autonomic neuropathy(CAN) is a common underdiagnosed complication in patients with type -2 diabetes mellitus in clinical practice. CAN is associated with increased morbidity and mortality among diabetics. Only few studies are available in literature about pattern and prevalence of CAN among type-2 diabetics in developing countries like India where burden of the disease is high.

Aim : To study the pattern and prevalence of CAN in type 2 Diabetes mellitus patients and to study the sympathetic and parasympathetic abnormalities related to cardiovascular system in patients with type 2 Diabetes mellitus.

Materials and Methods: The study design was observational Retrospective and was conducted at Department of Physiology, Thanjavur Medical college, between april to june 2022. We recruited 80 patients (55 male and 25 female) with type 2 Diabetes mellitus of age 30 years and above from Medicine and Non-Communicable Diseases (NCD) Outpatient Department of Thanjavur Medical college hospital. The study was approved by Institutional Ethical committee(IEC). After getting informed written consent from all the participants, age, duration of diabetes, systolic blood pressure and HbA1c levels were recorded. Patients were made to undergo Autonomic Function Tests(AFT) in Research Laboratory. Assessment of CAN was done retrospectively and scoring was done using three different scoring system namely Ewing's, Bellavere's and AIIMS criterias.

Statistical Analysis and Results: Mean age was 48.86(±5.694) years and duration of diabetes was 108.48(±25.039) months. Mean systolic blood pressure(SBP) was 132.10(±25.039)mmHg and HbA1c level was 8.63(±0.46368). Statistical Analysis was done using unpaired 'T' and Chi-Square tests. The abnormality of single autonomic test ranged from 6% in valsalva ratio to 46.25% in cold pressor test. CAN was found in 14 and 20 patients by Ewings's and Bellavere's criteria respectively. AIIMS criteria revealed 43 patients with isolated sympathetic abnormality and 37with parasympathetic abnormality and 25 with both abnormalities. Duration of diabetes, systolic blood pressure(SBP) and and HbA1c levels were not significantly correlated with autonomic abnormality in our study. Only Valasava Ratio(VR) correlates with autonomic abnormality significantly(P value<0.05).

Conclusion: CAN is a common microvascular abnormality in type 2 diabetes mellitus. We have to highlight the importance of regular testing of autonomic functions in type 2 diabetes mellitus to prevent mortality due to cardiovascular complications.

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Key words: Cardiovascular autonomic neuropathy(CAN), Autonomic function Test(AFT), HbA1c, Valsalva ratio(VR)

Introduction

Dysfunction of the Autonomous Nervous system is an underdiagnosed cause of excessive morbidity and mortality in adults with diabetes. Among Non-Communicable Diseases, Type 2 Diabetes Mellitus(DM) is emerging as a great threat and burden to Indian population as India is becoming world diabetes capital[1].

Complications of Diabetic Autonomic Neuropathy are often missed as symptoms are mild and not life threatening. CAN is the major underdiagnosed complication in type -2 DM as its prevalence is 31-73% and its annual incidence is 2%[1].

Early identification of CAN in type -2 DM patients can lead to early intensive interventions targeting life style, glycemic control and risk factors that can slow the progression of CAN[1]. Common symptoms of CAN which are often missed and under diagnosed are exercise intolerance, resting tachycardia, heat intolerance, arrhythmias, dry skin and orthostatic hypotension[2].

CAN in type -2 DM is the result of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition and systolic and diastolic blood pressure[3].

Materials and Methods

This study was an observational retrospective study, conducted at Department of Physiology, Thanjavur medical college. The study was approved by IEC- 961/2022. Written informed consent were obtained from all study participants. We have selected 80 patients of type 2 DM ofboth sexes of age 30 yrs and above attending Medicine and NCD Outpatient Department. 55 males and 25 females participated in the study. This study was conducted from april to june 2022. Exclusion Criteria were Normal healthy adults, Type 2 diabetics who were newly diagnosed and those with disease less than one year, previous history of coronary artery disease, hepatic, respiratory, renal, cerebrovascular, thyroid or other endocrine abnormalities, previous history of ECG abnormalities and with any history of acute illness within past 48 hrs. Female patients during menstrual cycles were excluded. Patients should not have consumed beverages containing caffeine or alcohol within past 12 hrs and patient should not be on drugs like betablockers or sympathomimetics or vasodilators or diuretics or antiarrhythmics or calcium channel blockers. Patients engaged in strenuous exercise in the preceding 24 hrs were excluded from the study.

Detailed history including treatment, dietary, lifestyle and family histories and duration of DM were recorded. Baseline investigations including SBP in mmHg using mercury Sphygmomanometer was recorded and about 3ml of blood samples were collected from the antecubital vein for HbA1c. HbA1c was analysed using automatic analyser (A1c 2.2 Glycohemoglobin Analyser HLC-723GHb). ECG recording was done using ECG machine (BPL Cardiart 6208 View 3 Channel).

Cardiovascular Autonomic Function tests:

The six autonomic function tests were done for all the patients as per standard protocol[4]. All the tests were done after proper instructions.

1. Deep breathing test: The patient was asked to lie down in the supine position. Lead II ECG was recorded for heart rate and respiration monitoring was done for 30 seconds.The subject was asked to breathe deeply at a rate of six breaths per minute(allowing 5 seconds each for inspiration and expiration). Maximum and minimum heart rate with each respiratory cycle were recorded and average was taken.

2. Valsalva Maneuver:The patient was made to sit comfortably and ECG electrodes were connected and recording was done. The patient was asked to blow or exhale forcefully into the mouthpiece connected to the sphygmomanometer after closing the nostrils with nose clip and was asked to maintain the expiratory pressure at 40mmHg for 10-15 seconds. Recording of ECG was done throughout and 30 seconds before and after the procedure. After 30 seconds,the patient was asked to release the pressure. Valsalva Ratio was calculated from the longest RR interval during phase IV and shortest RR interval during phase II.

3. Handgrip test: Baseline BP was recorded and the patient was asked to press handgrip dynamometer at 30 percent of maximum contraction for 4 minutes. The DBP was recorded at first, second, third and fourth minute of contraction. The rise in the DBP above baseline was recorded.

4. Cold Pressor test: Baseline BP was recorded. The patient was asked to immerse the right hand into the container containing cold water(at or below 4 degree Celsius) for 60 seconds. The DBP was recorded at 30 and 60 seconds. The rise in the DBP above baseline was recorded.

5. Lying to standing test: the patient was asked to lie down in supine position. The basal BP and ECG were recorded. Then the patient was asked to stand immediately within 3 seconds from supine position. ECG was recorded continuously during the procedure at 0.5^{th},1^{st},2^{nd},2.5^{th} and 5^{th} minute.30:15 ratio was calculated from ECG (i.e) ratio of RR interval at 15^{th} beat and RR interval at 30^{th} beat. Record blood pressure at 2^{nd} and 5^{th}minute. The fall in SBP was recorded.

6. Head Up Tilt test: After proper instructions, the patient was asked to lie down in Head –Up tilttable for 5 minutes. Baseline BP and ECG were recorded. Then the patient was made to stand erect 80 degrees passively from supine position within 15 seconds and was maintained in that position for 5 minutes. Immediately heart rate and BP were recorded for 5 minutes. The maximum fall in SBP was recorded.

1. Categorization of patients as per Bellavere criteria[5]

1. Deep breathing test(delta heart rate)

2. Valsalva maneuver(Valsalva Ratio)

3. Lying to standing(30:15 ratio)

The scores were added and CAN was categorized as follows

0-1 = no CAN

2-3 = early CAN

4-6 = definite CAN

2. Categorization of patients as per Ewing´s criteria[6]

All the tests were included except cold pressor test.

The scores were added and CAN was categorized as follows

Normal = all tests normal or one test borderline

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

Definite = two heart rate tests abnormal

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

3. Categorization as per AIIMS criteria[2]

Test for parasympathetic parameters

1. Deep breathing test (delta HR)

2. Valsalva maneuver (VR)

3. Lying to standing (30:15 ratio)

Tests for sympathetic parameters

1. Handgrip test (change in DBP)

2. Cold pressor test (change in DBP)

3. Lying to standing test (change in SBP)

Table 1: Test for Assessment of Autonomic Function

Test	Parameter	Criteria	Category	Score
Deep Breathing test	Delta HR(bpm)	>15	Normal	0
		11-14	Borderline	1
		<10	Abnormal	2
Valsalva Maneuver	VR	>1.21	Normal	0
		1.11-1.20	Borderline	1
		<1.10	Abnormal	2

Test	Parameter	Criteria	Category	Score
Handgrip test	Change in DBP(mmHg)	>16	Normal	0
		11-15	Borderline	1
		<10	Abnormal	2
Cold pressor test	Change in DBP(mmHg)	<10	Normal	0
		11-20	Borderline	1
		>20	Abnormal	2
Head-Up tilt	Fall in SBP(mmHg)	<10	Normal	0
		11-20	Borderline	1
		>20	Abnormal	2
Lying to standing test	30:15 ratio	>1.04	Normal	0
		1.01-1.03	Borderline	1
		<1.01	Abnormal	2

Statistical Analysis

Statistical analysis was done using the SPSS statistics software version 20. All the data were shown as the mean or as percentages. Continuous variables were analysed by Unpaired student´s t-test. Categorical variables were compared by the Chi-square test. P value <0.05 was considered as statistically significant.

Results and Discussion

The mean age of 80 patients who participated in the study was 48.86 ± 5.694 years. Among them, 55 were male and 25 were female which corresponds to 68.8% and 31.3% respectively. Mean duration of diabetes was 108.48 ± 25.039 months. Mean HbA1c value was 8.63 ± 0.46368.Mean systolic blood pressure was 132.10 ± 6.689 mmHg. Out of 80 patients, only 49 patients were able to do all autonomic function tests. All patients were not able to do physical effort related tests like Valsalva Maneuver, Hand grip test and deep breathing test .Valsalva maneuver was not done in patients with diabetic retinopathy. Table II shows results of individual test done in 80 patients. Table III shows the scoring based on Bellavere, Ewing´s and AIIMS criteria respectively. CAN was found in 40,29 and 43 patients according to Bellavere, Ewing's and AIIMS criteria respectively.

Figure I shows bar diagram of genderwise loss of autonomic function in diabetes which shows no specific variation among tests between genders except valsalva maneuver. Table IV shows statistical inference of continuous variable using Unpaired ´t´ test which shows age, duration of diabetes and HbA1c were not significant. Table V shows statistical inference of categorical variable using Chi-square test and correlation coefficient and Pearson's correlation analysis between independent variable.

Table 2: Results of Autonomic Function Test Done in The Patients

Test	Parameter	Total	Borderline	Abnormal	%Abnormal
Deep Breathing test	Delta heart Rate(bpm)	80	28	30	35
Valsalva Maneuver	Valsalva Ratio	50	3	5	6
Handgrip test	Change in diastolic blood pressure(mmHg)	70	32	21	45.71
Cold pressor test	Change in diastolic blood pressure(mmHg)	80	37	17	46.25

Test	Parameter	Total	Borderline	Abnormal	%Abnormal
Head up tilt	Fall in systolic blood pressure(mmHg)	80	10	28	12.5
Lying to standing test	30:15 ratio	80	14	1	17.5

Table 3: Categorization as Per Bellavare,Ewing's and Aiims Criteria

BELLAVRE CRITERIA	**NO OF PATIENTS**	
NORMAL(SCORE 0-1)	40	
EARLY(SCORE 2-3)	20	
DEFINITE(SCORE 4-6)	20	
EWING'S CRITERIA	**NO OF PATIENTS**	
NORMAL	51	
EARLY	15	
DEFINITE	–	
SEVERE	14	
AIIMS CRITERIA	**BORDERLINE**	**ABNORMAL**
PARASYMPATHETIC(IRRESPECTIVE OF SYMPATHETIC STATUS)	29	29
PARASYMPATHETIC BUT NO SYMPATHETIC ABNORMALITY	17	1
SYMPATHETIC(IRRESPECTIVE OF PARASYMPATHETIC STATUS)	17	42
SYMPATHETIC BUT NO PARASYMPATHETIC ABNORMALITY)	17	14
BOTH	10	25

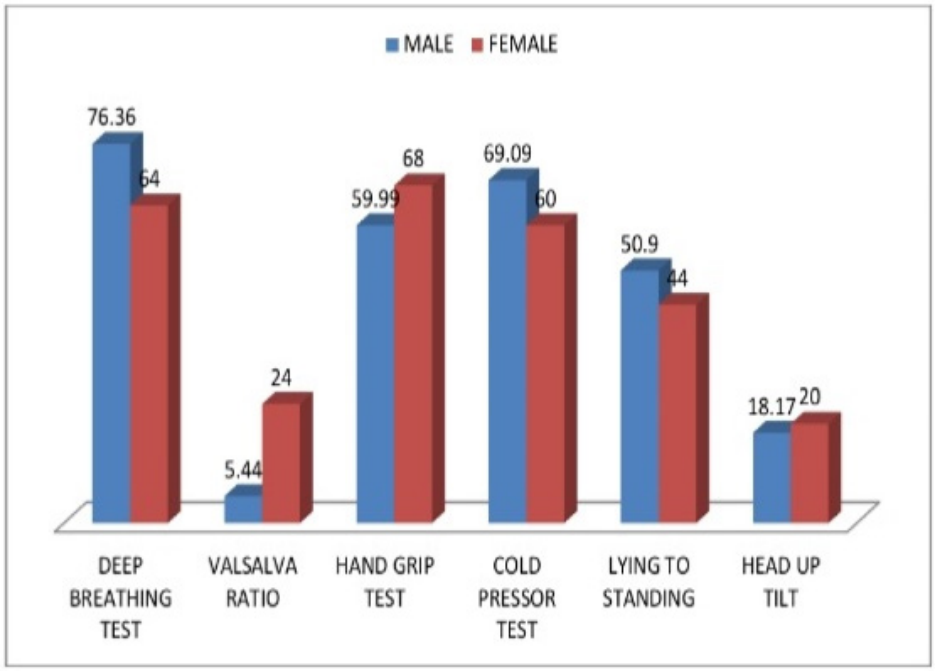

Figure 1 : Genderwise Loss of Autonomic Function in Diabetics

TABLE 4: STATISTICAL INFERENCE BY UNPAIRED´ t´ TEST

SEX	N	Mean	S.D	Statistical inference
SYSTOLIC BP(mmHg)				
Male	55	131.56	6.321	T=1.065 Df=78
Female	25	133.28	7.436	0.290>0.05 Not Significant
HbA1C %				
Male	55	8.6418	.47442	T=0.158 Df=78
Female	25	8.6240	.44840	0.875>0.05 Not Significant
DURATION OF DIABETES(months)				
Male	55	109.38	24.422	T=0.478 Df=78
Female	25	106.48	26.754	0.634>0.05 Not Significant

TABLE 5: STATISTICAL INFERENCE BY CHI-SQUARE TEST AND CORELATION COEFFICIENT

	SEX						Statistical inference
	Male		Female		Total		
	n	%	n	%	n	%	
DEEP BREATHING TEST-							
Abnormal	19	34.5%	9	36.0%	28	35.0%	X^2=0.571 Df=2
Borderline	22	40.0%	8	32.0%	30	37.5%	0.751>0.05
Normal	14	25.5%	8	32.0%	22	27.5%	Not Significant
VALSALVA MANEUVER							
Not able to do test	23	41.8%	7	28.0%	30	37.5%	X^2=8.298 Df=3
Abnormal	1	1.8%	2	8.0%	3	3.8%	0.040<0.05
Borderline	1	1.8%	4	16.0%	5	6.3%	Significant
Normal	30	54.5%	12	48.0%	42	52.5%	
HAND GRIP TEST -							
Not able to do test	8	14.5%	3	12.0%	11	13.8%	X^2=0.979 Df=3
Abnormal	20	36.4%	12	48.0%	32	40.0%	0.806>0.05
Borderline	14	25.5%	5	20.0%	19	23.8%	Not Significant
Normal	13	23.6%	5	20.0%	18	22.5%	
COLD PRESSOR TEST -							
Abnormal	27	49.1%	12	48.0%	39	48.8%	X^2=1.054 Df=2
Borderline	11	20.0%	3	12.0%	14	17.5%	0.590>0.05
Normal	17	30.9%	10	40.0%	27	33.8%	Not Significant
HEAD UP TILT TEST -							
Abnormal	7	12.7%	3	12.0%	10	12.5%	X^2=0.349 Df=2
Borderline	21	38.2%	8	32.0%	29	36.3%	0.840>0.05
Normal	27	49.1%	14	56.0%	41	51.3%	Not Significant
LYING TO STANDING 30:15							
Abnormal	9	16.4%	5	20.0%	14	17.5%	X^2=0.591 Df=2
Borderline	1	1.8%	0	.0%	1	1.3%	0.744>0.05
Normal	45	81.8%	20	80.0%	65	81.3%	Not Significant
Total	55	100.0%	25	100.0%	80	100.0%	

STATISTICAL ANALYSIS BY CORRELATION COEFFICIENT							
INDEPENDENT VARIABLE	**n**	**Mean**	**S.D**		**Age (yrs)**	**Systolic BP (mmHg)**	**Duration of Diabetes (months)**
Age (yrs)	80	48.86	5.694	r	—	.094	.126
				sig.	—	.407	.264
Systolic BP (mmHg)	80	132.10	6.689	r	.094	—	.097
				sig.	.407	—	.393
Duration of Diabetes (months)	80	108.48	25.039	r	.126	.097	—
				sig.	.264	.393	—

Our study reveals sympathetic abnormality was more common than parasympathetic component and abnormality in a single test which varies from 6% in VR to 46.25% in cold pressor test. The study shows only VR correlates significantly with CAN as p value<0.05. The autonomic score does not significantly correlates with age of the patient and duration of diabetes as well as HbA1c level. The age of the patient at which diabetes is diagnosed is variable.

CAN is a serious complication of diabetes that is often associated with poor prognosis and can result in severe postural hypotension, exercise intolerance, enhanced intraoperative instability and increased incidence of myocardial infarction or ischemia and may even predict the development of stroke[7]. According to a meta-analysis, the overall mortality rates over periods up to 10 years were 30.4% for people with diabetes and CAN detected by heart rate variability (HRV) compared with 13.4% without CAN[7].

CAN is the most life threatening complication which results from damage to the autonomic nerves that supply the heart, causing abnormal heart rates and rhythms. The hallmark and earliest indicator of subclinical and symptomatic cardiac autonomic dysfunction is reduced Heart Rate Variability(HRV)[7].

Postural hypotension is the clinical hallmark of CAN in diabetics and is characterized by weakness, faintness, dizziness, visual impairment and even syncope following the change in position from lying to standing[7]. A meta-analysis study revealed an increased risk of silent myocardial ischemia during exercise by 1.96% in people with diabetes and CAN compared with those without CAN[7].

Parasympathetic neuropathy in type -2 diabetics is associated with features of the insulin resistance syndrome[8].

Conclusion

AFTs are simple and cost effective which can be done in routine outpatient services. The purpose of this study is to highlight the importance of testing of autonomic functions during regular outpatient followup in long standing type 2 diabetics. An improvement in autonomic balance by recognition of autonomic imbalance in type 2 diabetics is vital to reduce cardiovascular events and early mortality. Early symptoms and signs of autonomic dysfunction like Valsalva maneuver, resting heart rate, BP responses to standing should be elicited from all type 2 diabetics attending OPD irrespective of duration of disease. Early detection and intervention of CAN is necessary in long standing type 2 diabetics so that rigorous regime including lifestyle modification, physical activity and judicious use of medicines for strict glycemic control can be implemented.

Introduction of new therapeutic agents in treatment regime to improve autonomic functions in type 2 diabetics should be considered. Our participants were motivated to adopt regular treatment and to achieve strict glycemic control and to advocate healthy life style modifications.

Limitations of the Study:

The study was retrospective and was limited to 80 patients. The duration of study period was also very short. The future studies are planned with larger population and with more study duration so that we can able to correlate significantly the duration of diabetes with the autonomic abnormality.

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Conflict of Interest: NIL