Prevalence of cardiac autonomic neuropathy in type 2 diabetic patients in rural part of Dharmapuri District

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Abstract
Background: Diabetes mellitus is a global epidemic. Prevalence of diabetic cardiac autonomic neuropathy is high and it carries a high mortality rate. Early diagnosis of cardiac autonomic neuropathy helps to identify individuals at risk and prioritize the management. **Aims Of The Study:** To study the prevalence of cardiac autonomic neuropathy in Type 2 diabetic patients by assessing the individuals by(a) Standard autonomic testing and (b) Ansiscope.**Methods:** Patients with Type 2 diabetes who were visiting the OPD of the Medicine Department in Dharmapuri medical college, in the year 2017-2018 were included in the study. Patients were subjected to symptom analysis, clinical examination and laboratory investigations. Eligible cohorts were subjected to standard autonomic testing and testing with Ansiscope. Standard autonomic testing includes (a) Assessing heart rate variability with deep breathing, Valsalva, supine to standing position. (b) Assessing blood pressure variability with supine to standing position. Patients were categorized based on Ewing's criteria for CAN.RESULTS: 19% (n=16) of the study group individuals were newly detected T2DM. Among them, 11 individuals 68.8% were CAN positive by ansiscope and% (13 subjects) by a conventional method. 50 individuals were diabetic for a duration of 1-5 years. Among them, 82% (41 individuals) and 88%(44 subjects) tested positive for autonomic dysfunction by ansiscope and conventional method respectively. 18 subjects who were diabetic for more than 5 years tested 100% positive for autonomic dysfunction by both the methods. **Conclusion:** The prevalence of cardiac autonomic neuropathy is extremely high among diabetics. Poor blood sugar control is significantly associated with CAN. Also, individuals who are unaware of the complications of diabetes have shown a significant association with autonomic dysreflexia. Early screening, early diagnosis, proper education of patients and strict glycemic control help in the arrest of progression of Cardiac Autonomic Neuropathy in Type 2 diabetic population.
Keywords: Diabetes, Cardiac Autonomic Neuropathy, Ansiscope, Autonomic Testing, Ewing's Criteria.

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INTRODUCTION

Change in the lifestyle of people along with globalization in the past century has increased the incidence of diabetes. The number of people with diabetes is expected to increase from 65.1 million in 2013 to 109 million in 2035 in India.[1] Indians develop diabetic complications at an early age. This results in an increase in mortality and morbidity among Indians. Despite a high prevalence of diabetes in Southeast Asian countries, only 5 % of the global health care cost goes towards diabetes care.[2] Prevention of complications associated with diabetes is achieved by primary prevention by modifying risk factors such as insulin resistance and obesity. Diabetic neuropathy a set of clinical syndrome sometimes silent and undetected may be single or combined with signs which are nonspecific, insidious and slow and often diagnosed by exclusion.[3] Neurologic complications occur equally in all types of diabetes – type I, type II and all

other types of diabetes. Peripheral neuropathy can lead to foot complications, such as sores, ulcers, and infections because nerve damage can make you lose feeling in your feet.[4] As a result, you may not notice that your shoes are causing a sore or that you have injured your feet. Nerve damage can also cause problems with balance and coordination, leading to falls and fractures[5]. These problems may make it difficult for you to get around easily, causing you to lose some of your independence. In some people with diabetes, nerve damage causes chronic pain, which can lead to anxiety and depression.[6] One-fourth of patients attending the diabetes clinic had diabetic neuropathy based on the symptoms present. A simple clinical examination like testing for ankle jerk or vibration test revealed a positive test in 50% of individuals.[7] A more sophisticated test for autonomic neuropathy showed a 90% incidence of neuropathy in diabetic patients at diagnosis. Diabetic neuropathy is the most common cause of hospitalization than other known cause of complications. So early diagnosis of cardiac autonomic neuropathy by using simple noninvasive investigation – heart rate variability using ECG helps in the identification of individuals at risk.[8]

MATERIALS METHODS

Patients with Type 2 diabetes who were visiting the OPD of Medicine Department in Dharmapuri medical college, in the year 2017-2018 were included in the study. Patients were subjected to symptom analysis, clinical examination and laboratory investigations. Eligible cohorts were subjected to standard autonomic testing and testing with Ansiscope. Standard autonomic testing includes (a) Assessing heart rate variability with deep breathing, Valsalva, supine to a standing position (b) Assessing blood pressure variability with supine to standing position. Patients were categorized based on Ewing's criteria for CAN. Assessing heart rate variability with 1.Deep breathing.2.valsalva 3.supine to standing position 4.supine to standing. Procedure: Resting ECG was taken for all the patients. Individuals in the study group were subjected to ECG recordings. Preferred lead is lead II. Subjects were made to lie supine comfortably. Then they were asked to take deep breathe evenly at the rate of 6 breaths per minute i.e., 5 seconds for inspiration and 5 seconds for expiration. A continuous ECG was recorded for one minute. The maximum and minimum R-R interval during the respiratory cycle was calculated and converted to beats per minute. The difference between the two and heart rate variation of fewer than 10 beats per minute was taken as abnormal. Then the patient was allowed to lie quietly for another 5 minutes. The patient was made to exhale forcibly into the mouthpiece of manometer sustaining a pressure of 40 mmHg for about 15 seconds and the ECG was recorded continuously. The patient was made to stop the maneuver and the ECG was further recorded post maneuver. The ratio of shortest R-R interval during the maneuver and the longest R-R post-Valsalva was calculated. A ratio of less than 1.10 was considered abnormal. Again the patient was made to lie supine quietly. After about 5 minutes with continuous monitoring, the patient was made to stand. The R-R interval at 15th beat and 30th beat was calculated. The 30:15 ratio of less than1.00 was considered abnormal. For the assessment of the sympathetic function, the patient was made to lie down and his BP recorded. Then he was made to stand up and again BP measurement was made 2 minutes after standing. A fall of systolic Blood Pressure more than 30 mmHg was considered abnormal. Based on the above standard testing patients with 2 or more abnormal test were classified as definite, one of the three heart rate variability test abnormal were classified as early. When individuals with parasympathetic dysfunction along with significant BP fall were classified as severe CAN as per Ewings *et al*. For testing of patients with ansiscope, patients were instructed to lie supine comfortably. The electrodes were connected and after obtaining good ECG signal the test was commenced. At the end of the count of 571 R-R intervals the instrument display the presence/absence of CAN and the severity.

STASTICAL ANALYSIS

A chi-square test was used in order to compare the frequencies of nominal variables. Quantitative variables were compared using a t-test, Mann-Whitney test, when appropriate. Multivariate analysis was carried out using linear regressions. We used as dependent variable the CAN: CAN+ code 1 vs CAN- code 0. We used the Bonferroni correction in order to account for multiple comparisons. The level of statistical significance was set at $p < 0.05$.

RESULTS

Table 1: Sex Distribution

Sex	Frequency	% of Study Group
MALE	30	35.7
FEMALE	54	64.3
TOTAL	84	100

Table: 1 shows Among the total 84 individuals studied 64.3 % were females and 35.7 % were males. A total of 15.5%(13 persons) were smokers and among them, 92.3%(12 persons) and about 100% (13 people) were found to have cardiac autonomic neuropathy by ansiscope and conventional methods respectively.

Table 2: Can Positivity

CAN	Ansiscope		Conventional	
	Frequency	Percentage	Frequency	Percentage
Yes	70	83.3	75	89.3
No	14	16.7	9	10.7
TOTAL	84	100	84	100

Table: 2 27 subjects i.e. 32% were found to have peripheral neuropathy by clinical testing and among them, 92.6% (25 persons) tested positive for autonomic neuropathy by ansiscope and 96.3% (26 persons) by a conventional method

Table 3: Valsalva Ratio

	Frequency	Percentage
NORMAL	16	19
BORDERLINE	45	53.6
ABNORMAL	23	27.4
TOTAL	84	100

Table 3 shows Of the 84 subjects tested 27.4% (23 individuals) had an abnormal Valsalva ratio. 71.4% (60 individuals) had an abnormal inspiratory and expiratory ratio. 63.1% (53 individuals) had abnormal 30:15 ratio. And 4 individuals (4.8%) had significant abnormal orthostatic hypotension

Table 4: Association of various parameters with can

Parameter	% of subjects	Prevalence of CAN		p Value	
		Conventional	Ansiscope	Conventional	Ansiscope
SMOKERS	15.5%	100%	92.3%	0.384	0.58
HYPERTENSION	42.9%	91.9%	86.1%	0.799	0.761
PERIPHERAL NEUROPATHY	32.1%	96.3%	92.6%	0.293	0.210
DURATION OF DIABETES					
a. at diagnosis	19%	81.2%	68.8%		
b.1-5 years	59.5%	88%	82%	0.344	0.106
c.>5 years	21.5%	100%	100%		
UNAWARE	75%	93.7%	85.7%	0.039	0.049
POOR SUGAR CONTROL	33.33%	100%	96.4%	0.026	0.029

Table: 4 shows Of the 84 study subjects 63 (75%) people were not aware of the complications related to diabetes. In the 54 subjects(85.7%) and 59 subjects(93.7%) tested positive for cardiac autonomic neuropathy by ansiscope and conventional methods respectively. This association is found to be statistically significant. A total of 16 subjects (19%) were examined at diagnosis. Among them, 11 individuals 68.8% were CAN positive by ansiscope and81.2 % (13 subjects) by a conventional method. Of the 84 individuals, 50 individuals were diabetic for a duration of 1-5 years. Among them, 82% (41 individuals) and 88%(44 subjects) tested positive for autonomic dysfunction by ansiscope and conventional method respectively. Of the 18 subjects who were diabetic for more than 5 years, were tested 100% positive for autonomic dysfunction by both the methods.28 individuals had poor glycemic control. All individuals with poor glycemic control tested positive for cardiac autonomic dysfunction by

conventional method and 96.4% (27 individuals) tested positive by ansiscope. This association is statistically significant.13.Sensitivity and specificity of the individual test are as follows Valsalva - 86.7% and 66.7%.E: I ratio- 92% and 33.3%30:15 ratio - 92% and 55.6% respectively.

DISCUSSION

Cardiac autonomic neuropathy (CAN) is one of the most overlooked of all serious complications of diabetes. Although silent in the earlier stages, it is a powerful predictor of mortality risk in diabetic patients and is a major challenge for all physicians dealing with people suffering from diabetes.[9] Patients with CAN have a five-fold increased risk of mortality due to a high-risk of cardiac arrhythmias, silent myocardial ischemia, and sudden death. The burden of DM is reflected not only in the increasing number of patients but also in the growing number of premature deaths due

to diabetes. n T1DM, there is clear evidence for genetic predisposition but also strong evidence for an autoimmune mechanism for destruction of the beta cells leading to absolute dependence on insulin treatment.[10] Neurons and pancreatic beta cells have a neuroectodermal origin and therefore share common antigens, especially in the early stage of evolution.[11] Ramachandran *et al* provided epidemiological data that support the implication of autoimmunity in autonomic neuropathy in T1DM by demonstrating the existence of antibodies against the autonomic nervous system (sympathetic ganglion, vagus nerve, adrenal medulla) in T1DM patients with autonomic neuropathy. This study was done to assess the prevalence of cardiac autonomic dysfunction in Type 2 diabetics by ansiscope and conventional methods which assess the heart rate variability.[12] The prevalence rate was 83.3% and 89.3% by ansiscope and conventional methods respectively. Our study included diabetics of less than one year as 'at diagnosis'. 'At diagnosis' 68.8% were CAN positive by ansiscope and 81.2% by a conventional method. In individuals with a duration 1-5 years, 82% and 88% tested positive for autonomic dysfunction by ansiscope and conventional method respectively. Diabetics for more than 5 years, were tested 100% positive for autonomic dysfunction by either of the methods.[13] Shai I *et al* concluded the prevalence of CAN around 51.9%.In the present study though there is an increased percentage positivity of Cardiac Autonomic Dysfunction in individuals with smoking, peripheral neuropathy, duration of diabetes we did not find any significant association. In our study, there is a significant association of CAN positivity in individuals who were unaware of the complications of diabetes. There is a significant positive association of cardiac autonomic dysreflexia in individuals with poor glycemic control in our study. [14]All individuals with poor glycemic control tested positive for Cardiac Autonomic Dysfunction by conventional method and 96.4% tested positive by ansiscope. [15]EURO DIAB study has found that the incidence of autonomic neuropathy is associated with poor glycemic control.[16] stenotype 2 trial has followed up intensively controlled diabetics for 8 years and documented a reduced rate of progression of autonomic neuropathy.[17] The DCCT research group had shown that intensive therapy for diabetics decreases the rate of progression and delays the development of autonomic dysfunction. In our study we have found the heart rate variation with E: I ratio and 30:15 ratio is 92% and is found more sensitive compared to other methods.[18,19,20]

CONCLUSION

The prevalence of cardiac autonomic neuropathy is extremely high among diabetics as shown in our study. Most diabetic patients have significant autonomic dysreflexia even at diagnosis of diabetes. Cardiac autonomic neuropathy is the single important factor which predicts the 5-year mortality rate among diabetics. Poor blood sugar control is significantly associated with CAN and is the single best factor which determines the rate of progression as cited in our study. Also, individuals who are unaware of the complications of diabetes have shown a significant association with autonomic dysreflexia. Early screening, early diagnosis, proper education of patients and strict glycemic control help in the arrest of progression of Cardiac Autonomic Neuropathy in Type 2 diabetic population.

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