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Comparison of cardiac autonomic neuropathy in asymptomatic T2DM and normal individuals

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Abstract

Introduction: The availability of simple, non-invasive tests for cardiovascular autonomic function has supported an extensive clinical and epidemiologic evolution in the investigation of Cardiac autonomic neuropathy. Such data forms a strong body of evidence in detecting and monitoring impaired autonomic function in patients with diabetes. The proposed study aims at detecting the presence of autonomic neuropathy in an early and possibly stills a reversible phase in Type 2 Diabetes Mellitus (T2DM) individuals in comparison to non T2DM normal individuals.

Material and Methods: The cross sectional case control study consisted of 200 subjects, 100 as Cases with T2DM in the age group 35 to 50 years and 100 age and sex matched normal subjects without T2DM as Controls. Resting heart rate, Sinus Arrhythmia and Valsalva Ratio were measured from ECG recorded. Based on these heart rate tests they were grouped into normal, early and definite autonomic neuropathy changes. An informed written consent to participate in the study was taken from the subjects. There was no financial burden on the subjects. The study protocol was approved by the Institutional Ethical Committee. All the quantitative data were summarized and statistically analysed.

Results: The basic characteristics with respect to age did not show any significant difference between the T2DM as compared to normals ($p<0.05$). The HbA1c of diabetics was significantly increased as compared to normals ($p<0.05$). Amongst the T2DM, 90% showed autonomic neuropathy changes. 70% of those with autonomic neuropathy were early and 20% were definite changes. 15% of the normal individuals also showed autonomic neuropathy changes, of which 14% were early and 1% definite changes.

Conclusion: Autonomic dysfunction is prevalent and a serious complication of T2DM. Given the clinical and economic impact of this complication, the present study emphasizes the testing of T2DM individuals for cardiovascular autonomic dysfunction as a part of their standard of care.

Keywords: T2DM, Autonomic neuropathy, ECG, Sinus arrhythmia, valsalva ratio.

Introduction

Diabetes is a common cause of neuropathy that involves motor, sensory, and autonomic nerve fibres. Involvement of autonomic fibres may alter function in the cardiovascular system. Autonomic regulation of both the heart and peripheral circulation may be affected. Diabetic autonomic neuropathy (DAN) is a serious and common complication of Type 2 Diabetes Mellitus (T2DM). DAN has been reported to be associated with an increasing mortality rate[1], and deaths may be sudden and unexplained [2,3]. DAN is best diagnosed by evaluating cardiovascular reflex responses. This has a close correlation with the measures of parasympathetic heart rate control like baroreceptor sensitivity. Severity of DAN can be identified using standard tests of heart rate variability[4] and blood pressure (BP) responses to stimuli, such as deep breathing, the Valsalva maneuver, and the move from lying to standing[5].

In the lower limbs, DAN is associated with foot ulceration[6,7], although other factors, such as impaired sensation and musculoskeletal abnormalities, will also contribute. Foot ulceration is a major cause of morbidity associated with diabetes and sometimes may be the first indication of neuropathy or T2DM which further worsens with the duration of the disease[8,9]. T2DM at diagnosis may already have macro vascular or neuropathic complications[10] and so are the abnormalities in cardiac autonomic function[11,12]. Up to 40% of the diabetic patients show evidence of autonomic dysfunction but very few of them are symptomatic. Autonomic neuropathy involves the heart and symptomatic autonomic neuropathy carries a poor prognosis[13].

Hence, in the present study aims to detect the presence of autonomic neuropathy in asymptomatic T2DM at an early and possibly still reversible phase.

Objectives

1. To compare the presence of autonomic neuropathy in asymptomatic T2DM and normal individuals using Electrocardiograph (ECG).
2. Comparison of age and sex-wise distribution of autonomic neuropathy.
3. To observe the impact of duration of T2DM on autonomic neuropathy.

Materials and Methods

The aim of the study was to asses and to detect the presence of autonomic neuropathy in asymptomatic T2DM at an early and possibly still reversible phase. A cross sectional case control study design was adapted and the duration was 1 year. The study consisted of 200 subjects, 100 as Cases with T2DM, asymptomatic of autonomic neuropathy in the age group 35 to 50 years and 100 age and sex matched normal subjects without T2DM as Controls. Subjects with pre-existing retinal complications/ with refractive errors/ colour blindness/ symptoms of autonomic neuropathy and those on drugs which can have an effect/ interfere with sensation and cardiac functions were excluded from the study.

Methodology: The study was conducted at the Department of Physiology, Sri Siddartha Medical College and Hospital, Tumkur, INDIA. Study subjects who meet the inclusion criteria were chosen from those attending the OPD at Sri Siddartha Medical College and Hospital. Subjects were examined at the Medicine dept, Sri Siddartha Medical College and Hospital to rule out any pre-existing retinal complications/ with refractive errors/ colour blindness/ symptoms of autonomic neuropathy. An informed written consent to participate in the study was taken from the subjects. There was no financial burden on the subjects. The study protocol was approved by the Institutional Ethical Committee.

Inclusion Criteria: Cases of T2DM and normal individuals in the age group 35 to 50 years were included. All subjects, cases and controls had no symptoms of autonomic neuropathy.

Exclusion Criteria: Patients taking medications or affected by the diseases that could influence autonomic nervous function, interfere with the execution or evaluation of cardiovascular tests were excluded.

Procedures involved:

1. **Resting heart rate determination: The subjects were rested in supine position for 15 minutes and then 12-lead ECG recorded. Heart rate is calculated from lead II by using the formula,**

heart rate = 1500 / R-R interval.

2. **Heart rate response to deep breathing (sinus arrhythmia):** The subjects were made to lie quietly and asked to breathe deeply at a rate of six breaths per minute (5 seconds inspiration and 5 seconds expiration, a rate that produces maximum variation in heart rate) and the ECG was recorded in lead II. The maximum (during inspiration) and minimum (during expiration) heart rates during each 10 seconds breathing cycle were calculated from the RR interval. The mean of the differences during 3 successive breathing cycles gives the sinus arrhythmia.
3. **Heart rate response to Valsalva maneuver (Valsalva ratio):** In supine position, subjects were connected to an ECG recorder and asked to forcibly exhale for 15 seconds against a fixed resistance (40 mmHg) using manometer with an open glottis. The Valsalva ratio was determined by dividing the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver in lead II.

Based on observations from the above procedures, the values were categorised as normal / borderline / definite. The observations were categorized into three groups:

1. Normal – all tests normal or one borderline
2. Early Changes- one test abnormal or two borderline
3. Definite Changes – two or more tests abnormal

Test	Normal	Borderline	Definite
Resting heart rate (beats per min)	< 90	90-100	> 100
Sinus Arrhythmia (beats per min)	> = 15	11 -14	< 10
Valsalva Ratio	> = 1.21	1.11 -1.20	< 1.10

Statistical Analysis: All the quantitative data such as age, HbA1c were summarized through descriptive statistics in terms of mean, median and standard deviation. In order to test for differences T2DM and normals, students T test / appropriate non parametric test (if the data do not follow normal distribution) were employed. Significance level of $p<0.05$ was considered.

Results

The cross sectional case control study design was adapted and the study consisted of 200 subjects, 100 as Cases with T2DM in the age group 35 to 50 years and 100 age and sex matched normal subjects without T2DM as Controls.

The T2DM group had a significantly higher HbA1C than the normals ($p < 0.05$) (Table 1).

Table 1: Basic characteristics of the study

Basic characteristics (Mean±SD)	Diabetics (n=15)	Non Diabetics (n=15)	p value
Age (years)	42.50±2.28	41.95±1.67	> 0.05
HbA1c (%)	7.16±1.99	5.76±0.55	< 0.005*

90% of the asymptomatic T2DM, showed autonomic neuropathy changes, of which 70% were early and 20% definite changes. (Table 2)

Table 2: Presence of autonomic neuropathy (%)

	Normal	Autonomic neuropaty			Total
		Early	Definite	Total	
Diabetics	10	70	20	90	100
Non-diabetics	85	15	01	14	100
Total	95	85	21	104	200

15% of the normal individuals showed autonomic neuropathy changes, of which 14% were early and 2% definite changes. (Table 2)

There were no significant differences in observations seen in between males and females either amongst the T2DM or normal groups (P > 0.05) (Table 3).

Table 3: Sex-wise distribution of autonomic neuropathy

	Diabetics			Non-diabetics		
	Normal	Early	Definite	Normal	Early	Definite
Male	08	74	18	86	12	02
Female	10	70	20	82	16	02

Males Vs Female, p value: > 0.05

Autonomic neuropathy changes were progressive with advancing age and duration of T2DM. There were definite autonomic neuropathy changes in T2DM with duration more than 10 years. (Table 4)

Table 4: Autonomic neuropathy with respect to duration of Diabetes (%)

Duration in years	Normal	Early	Definite
0-1	17	83	-
2-4	21	52	27
6-10	-	50	50
>10	-	-	100

Discussion

Cardiac autonomic dysfunction has been observed in T2Dm at the time of diagnosis. In the present study autonomic neuropathy was studied and tested for in asymptomatic T2DM at a possibly early and still reversible phase. Cardiac autonomic neuropathy is best diagnosed by evaluating the cardiovascular reflex responses to various stimuli[14]. These tests are simple, non-invasive and can be performed in the clinic within 30 minutes. Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes[11,12]. However, sub-clinical autonomic dysfunction can occur at an early stage of T2DM. Autonomic neuropathy is related to the age of onset and duration of disease in T2DM.

In the present study, 90% of the asymptomatic T2DM, showed autonomic neuropathy changes, of which 70% were early and 20% definite changes. The findings are suggestive of the metabolic consequences of hyperglycemia rather than the type of diabetes lead to autonomic neuropathy[10]. Also that autonomic neuropathy is equally found in both T2DM and T1DM. Recent studies have suggested that autonomic damage itself may promote the development and progression of nephropathy and retinopathy[15], possibly through a direct effect of nerve damage on the micro-circulation within these organs. Cardiac autonomic neuropathy results from damage to the autonomic nerve fibers that innervate the heart and the blood vessels and results in abnormalities in heart rate control and vascular dynamics[16].

The study also showed that there were definite autonomic neuropathy changes in T2DM with duration more than 10 years. Evidence also suggests that there is worsening of DAN with the duration of disease[17].

The procedures involved in the present study were tests for integrity of autonomic nervous system, Valsalva maneuver and Valsalva ratio. Tests for parasympathetic nervous system are heart rate variation with respiration and heart rate responses to standing. Studies have suggested that the degree of respiratory sinus arrhythmia may be used as a non-invasive indicator of the degree of parasympathetic cardiac control[18]. Reports showed that in diabetics with clinical features of autonomic neuropathy, simple autonomic function tests (Valsalva maneuver) give good guide to prognosis[19] and the abnormal tests are associated with a high mortality. Earlier researchers have compared a single test (heart rate responses to deep breathing) and the five simple, non-invasive cardiovascular reflex tests and showed that one test alone does not distinguish the degree or severity of autonomic damage. These tests when performed individually, provide a useful framework to assess autonomic neuropathy simply, quickly and non – invasively and may also be applied to detect asymptomatic autonomic neuropathy.

Conclusion

Autonomic dysfunction is a prevalent and serious complication of T2DM. The patients' history and physical examination are ineffective for early indications of autonomic nerve dysfunction. Given the clinical and economic impact of this complication, the present study emphasizes the testing of T2DM individuals for cardiovascular autonomic dysfunction as a part of their standard of care.

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