Original research article

Study of the functional status of cardiovascular autonomic neuropathy in type 1 diabetic mellitus as compared to healthy individuals

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Abstract

Background: In the presence of type 1 diabetes mellitus, the incidence of autonomic dysfunction has increased and various evaluation methods have been identified. Each of these is the classical autonomic control tests.

Aims and Objectives: The present study was conducted to evaluate and compare autonomic function tests in cases of type I diabetes mellitus and healthy individuals.

Material and Methods: In the study, 60 cases of diagnosed type I diabetes mellitus and 60 age and sex-matched healthy individuals both between the age group of 18-25 years were included. Autonomic function tests were carried out and these parameters were compared between these two groups using an unpaired t-test.

Results: Deep breathing difference in patients of type I diabetes mellitus was significantly decreased as compared to healthy individuals. Valsalva ratio in patients of type I diabetes was significantly decreased as compared to healthy individuals. Postural tachycardia index in patients of type I diabetes was significantly decreased as compared to healthy individuals. The decrease in systolic blood pressure in patients with type I diabetes was substantially higher than in healthy individuals. The increase in diastolic blood pressure with isometric handgrip monitoring in patients with type I diabetes was substantially lower relative to healthy individuals.

Conclusion: Deep breathing difference, Valsalva ratio, postural tachycardia index are a measure of parasympathetic function. Deranged autonomic function tests in type I diabetic patients may be due to sympathetic and parasympathetic dysfunction.

Keywords: Diabetes mellitus, Autonomic neuropathy, Autonomic function tests,Valsalva ratio, Postural tachycardia index.

Introduction

Diabetes is a major issue of concern and has been described as the biggest health care challenge in the twenty-first century. The prevalence of diabetes, along with complications, has increased exponentially. Type 2 diabetes mellitus (DM) is currently creating an epidemic worldwide. Data from the International Diabetes Federation (IDF) show that nearly 5 million people worldwide died of diabetes and its complications in 2015. There is a rapid rise in the prevalence of type 1 diabetes mellitus (T1DM) and an increase in type 2 diabetes mellitus (T2DM) in younger patients [1].Of all the serious complications of diabetes, cardiac autonomic neuropathy (CAN) is one of the most overlooked. It is a good predictor of the risk of death in diabetic patients, although silent at an early stage, and is a major concern for all doctors dealing with people suffering from diabetes. Owing to a high risk of cardiac arrhythmias, silent myocardial ischemia, and sudden death, patients with May have a fivefold rise in the risk of death. In addition to the increasing number of patients, the burden of DM is reflected in the increasing number of premature deaths due to diabetes [2,3,4].

Type 2 diabetes mellitus is a metabolic disorder in which high blood glucose levels are characterized by insulin resistance and relative insulin deficiency [5]. The incidence is rising and will double by 2030. Almost all organ systems are internalized by the Autonomous Nervous System (ANS) and are primarily involved in homeostatic regulatory mechanisms [3]. The main roles of ANS are the maintenance of the homeostatic conditions of the body; the control of visceral activities; the smoothing of the body's reaction to environmental changes, stress, and exercise; and the support of the endocrine system for the regulation of various functions. Diabetes mellitus (DM)-related nervous malfunction or neuropathy is called diabetic neuropathy. Different mechanisms, such as gastrointestinal, cardiovascular, sudomotor, genitourinary, and metabolic systems, include autonomic DM neuropathy. Cardiac autonomic neuropathy is the product of damage to the heart and blood vessels of autonomic nerve fibers, which in turn results in the control of altered heart rate (HR) and vascular dynamics [6].

As demonstrated by numerous clinical trials to determine baroreceptor reflex, cardiovascular autonomic function tests (CAFTs), a completely non-invasive method, have been clinically validated. With the aid of classical AFTs, subjects at risk of heart problems are established and early intervention can be performed to avoid DM-related morbidity and mortality.

HR and blood pressure (BP) responses to standing, deep breathing and isometric handgrip are used in non-invasive CAFTs. Given these specifics, this study aimed to compare AFTs in type 1 DM patients with healthy individuals.

Materials and Methods

This perspective cross sectional study was conducted to evaluate autonomic function tests in type 1 diabetes mellitus individuals and healthy individuals from November 2012 to June 2014.The study was conducted on 120 individuals of which 60 were cases of type 1 diabetes mellitus and 60 were healthy, both were age and sex-matched. Individuals between the age group of 18-25 years were included in both groups. Ethical committee approval was obtained from the local ethical committee for human research to perform this study.For this study, diabetic individuals who attended a diabetic clinic at a tertiary care center; and who were previously diagnosed with type 1 diabetes mellitus were selected. All the diabetic individuals were taking treatment regularly. Healthy individuals for this study were selected as controls from nursing students and the non-teaching working staff of Medical College.

Inclusion criteria for study group were Cases of diagnosed Type 1 diabetes mellitus of either sex (male as well as female) between the age group of 18-25 years, minimum duration of diabetes mellitus of 5 years.Participants having a history of smoking, alcoholism, having injury or disability to limbs, having any systemic diseases like renal diseases, hypertension, liver diseases, and those disorders which require drugs like reserpine, nitrofurantoin, and other drugs that may cause neuropathy or myopathy, any cardiovascular, respiratory diseases causing disabilities, diminished hearing or vision, color blindness, psychiatric disorder affecting their psychomotor abilities.

Inclusion criteria for controls was Healthy individuals of either sex (male as well as female) between the age group of 18-25 years.and exclusion criteria for controls were Having a history of smoking, alcoholism, diminished hearing or vision , having color blindness

Written informed consent was taken from every individual before enrolment in the study. The objectives and detailed procedures were explained to each individual before performing the tests. A detailed history was taken, the general and systemic examination of each subject was carried out as outlined in proforma. Following Autonomic function tests were performed:
1. Heart rate response to deep breathing
2. Heart rate variation to Valsalva maneuver
3. Heart rate response to standing (postural tachycardia index)
4. Systolic blood pressure response to standing (orthostatic test)
5. Diastolic blood pressure response to sustained handgrip

The data collected during the present study from Group I and Group II subjects were arranged in a tabular form and analyzed statistically by using categorical variables. These variables were compared by using an unpaired t-test to determine the significance of different parameters by using SPSS package data software. Data were presented as mean + standard deviation (SD). A p-value of <0.05 was considered significant.

Results

Table 1: Comparison of mean values of Heart Rate Response to Deep Breathing in controls and type 1 diabetics

Parameter	Group	Mean± SD	t- Value	p -Value	S/NS
DBD	I : Control	16.81 ±1.62	26.43	<0.001	S
	II: Type I DM	10.05 ±1.14			
Valsalva Ratio	I : Control	1.33 ±0.08	11.16	<0.001	S
	II: Type I DM	1.11 ±0.13			
Postural tachycardia Index	I : Control	1.08 ±0.05	9.11	<0.001	S
	II: Type I DM	1.02 ±0.01			
Fall in SBP	I : Control	8.57 ±2.13	24.38	<0.001	S
	II: Type I DM	18.60±2.37			
Rise in DBP	I : Control	19.43 ±2.37	22.58	<0.001	S
	II: Type I DM	10.18 ±2.11			

S: Significant, NS: Not significant

The above table 1 shows the mean and standard deviation of deep breathing difference, Valsalva ratio, Postural tachycardia Index, fall in systolic blood pressure on standing, and rise in diastolic blood pressure with isometric handgrip test among group I and group II subjects.
The deep breathing difference in group II subjects was significantly decreased as compared to group I subjects (p-value < 0.001) by unpaired t-test.
The Valsalva ratio in group II subjects was significantly decreased as compared to group I subjects (p- value < 0.001) by unpaired t-test.
By applying an unpaired t-test, it was found that the postural tachycardia index in group II subjects was significantly less as compared to group I subjects. (p- value < 0.001)
The fall in systolic blood pressure on standing in group II subjects was significantly higher as compared to group I individuals (p-value < 0.001), by unpaired t-test.

When unpaired t-test was applied, a statistically significant difference was found between the mean values of rise in diastolic blood pressure with isometric handgrip test in group I and group II subjects. (p- value < 0.001)

Discussion

As per Table 1, the mean of deep breathing difference in patients with type I diabetes mellitus was 10.5±1.14 beats per minute, and in healthy individual's mean of deep breathing, the difference was 16.81 ±1.62 beats per minute. (p- value < 0.001). Therefore deep breathing difference was significantly decreased in type I diabetic as compared to healthy individuals. This finding is similar to a study done by Sundkvist et al. (1982) [7], Krishna BH et al. (2014) [8] and Prasad HB et al. (2014)]9], Nagalaxmi V et al. (2016) [10].

As per Table 1, the mean Valsalva ratio in patients with type I diabetes was 1.11 ±0.13 while in healthy individuals mean Valsalva ratio was 1.33 ±0.08. (P-value < 0.001). Therefore Valsalva ratio was significantly decreased in type I diabetic as compared to healthy individuals. Our finding correlated with other studies Smith SA. (1984) [11], Pfeifer MA et al. (1982) [12], Nazeema K et al. (2010) [13].

As per Table 1, the mean of postural tachycardia index in patients of type I diabetes was 1.02 ±0.01 while in healthy individuals mean of postural tachycardia index was 1.08 ±0.05. (p-value < 0.001). Therefore, the postural tachycardia index was significantly decreased in type I diabetic as compared to healthy individuals.

As per Table 1, the mean of fall in systolic blood pressure on standing in patients of type I diabetes was 18.60 ±2.37 mm Hg while in healthy individuals mean of fall in systolic blood pressure on standing was 8.57±2.13 mm Hg. (p-value < 0.001). Therefore, fall in systolic blood pressure on standing in patients of type I diabetes was significantly greater as compared to healthy individuals. The results in our study correlated with the study conducted by Endukuru CK et al. (2015) [14], Datta S et al. (2005) [15].

As per Table 1, the mean of the rise in diastolic blood pressure with isometric handgrip test in patients of type I diabetes was 10.18 ± 2.11 mmHg while in healthy individuals mean of the rise in diastolic blood pressure with isometric handgrip test was 19.43 ± 2.37 mmHg. (P-value < 0.001). Therefore, the rise in diastolic blood pressure with isometric handgrip test in patients of type I diabetes was significantly less as compared to healthy individuals. This is similar to a study done by the consensus committee of the American Autonomic Society [16] and Hassan ZF et al. (2014) [17].

There was a statistically significant fall in systolic blood pressure on standing in patients of type I diabetes mellitus as compared to healthy individuals. Our results are supported by similar studies like Maser RE et al. (1990) [18], Bhatia SG et al. (1976) [19], Lakhotia M et al. (1997) [20], Ghosh A and Mukherjee SC. (1998) [21].

Diabetic neuropathy especially cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes having high morbidity and mortality. The etiopathology of diabetic autonomic neuropathy is multifactorial and involves several mechanisms that cause neuronal ischemia or dysfunction (death).

Hyperglycemia results in increased oxidative stress [22]. Increased oxidative stress results in the activation of poly-ADP ribose polymerase. This interacts with cell components like nerves and causes damage that leads to neuronal dysfunction and death when combined with other activated pathways such as the polyol pathway, hexosamine pathway, protein kinase C [23,24]. Neuronal axons are rich in mitochondrion which makes them particularly susceptible to direct and indirect effects of oxidative stress [25].

Polyol pathway leads to increased sorbitol accumulation which is neurotoxic to autonomic nerves as well as other nerves. Autoimmunity is observed in patients with type I diabetes mellitus. It is demonstrated that patients having complement-fixing antibodies against the sympathetic ganglion, vagus nerve cause a significant risk to develop cardiac autonomic dysfunction.

Both sympathetic and parasympathetic fibers may be affected in CAN. Because neuropathy is seen first in the longest fibers, the vagus nerve (longest nerve) is affected first leading to parasympathetic denervation. Sympathetic denervation follows later.

Cardiovascular autonomic neuropathy is associated with a fatal outcome like silent myocardial ischemia. Therefore, with the use of careful measurement of autonomic function, it is possible to identify the early stages of CAN. This helps in the early intervention of disease and prevents further complications.

Conclusion

Deep breathing difference, Valsalva ratio, postural tachycardia index is an indicator of parasympathetic activity. Deranged autonomic function tests in diabetic type I patients may be due to sympathetic and parasympathetic dysfunction. All these parameters are decreased in diabetes due to parasympathetic denervation associated with diabetes. Blood pressure response to standing and blood pressure response to isometric handgrip monitoring is a measure of sympathetic activity. Diabetes has a higher decrease in systolic blood pressure standing and a lower spike in diastolic blood pressure with an isometric handgrip exam relative to healthy individuals.

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