A Comparative Study of Autonomic Function Sensitivity Testing in Type 2 Diabetes

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Abstract: *Autonomic neuropathy is the most common complication of diabetes. Various studies showed that cardiac autonomic neuropathy (CAN) in diabetes is strongly associated with microvascular complications. Cardiac autonomic neuropathy in Type 2 diabetics is detected by various autonomic function tests. The scope of the present study is to compare the sensitivity of sympathetic and parasympathetic function tests in the early detection of autonomic dysfunction in Type 2 diabetics. The Autonomic function tests which are used to test the parasympathetic activity are deep breathing i.e., E: I ratio, valsalva ratio and Heart rate response to standing. The Sympathetic activity can be tested by using simple tests like blood pressure responses to standing, isometric handgrip test and cold pressure test. All the tests are capable for early detection of cardiovascular autonomic dysfunction. Results in our study showed that both Parasympathetic and sympathetic neuropathy was found in diabetics but parasympathetic cardiac autonomic function tests are more sensitive for the detection of cardiac autonomic neuropathy in type 2 diabetics than sympathetic cardiac autonomic function tests. Ultimately this study indicates that autonomic dysfunction occurs in diabetes Mellitus and Parasympathetic functional tests are highly sensitive in the early detection of Autonomic neuropathy.*

Keywords: Type II diabetes mellitus, Sympathetic & Parasympathetic Nervous System, Autonomic neuropathy.

1. Introduction

Type 2 Diabetes mellitus (formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is the most common metabolic and endocrine disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and shortage of insulin. The associated symptoms are polyuria, polyphagia, polydypsea and weight loss. Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity and lack of physical activity is thought to be the primary cause of type 2 diabetes and known to cause chronic complications particularly neuropathy, retinopathy, and nephropathy. Prevalence of type 2 diabetes have increased markedly since 1960 in parallel with obesity. According to WHO, there were approximately 285 million people diagnosed with the disease in 2010.

Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy. The most common neurological disturbance in diabetes is the involvement of autonomic nervous system. When autonomic nervous system is affected, it can lead to tachycardia, orthostatic hypotension, partial paralysis of GIT, Involuntary urination or defecation, bladder abnormalities and affects the quality of life of a diabetic patient. Thus the presence of Cardiovascular autonomic neuropathy is clinically important form of diabetic autonomic neuropathy which is associated with an increased risk of silent myocardial ischemia , cardiac arrest, sudden death.

The present study aims that the determination of presence of cardiovascular autonomic neuropathy is usually based on a variety of autonomic function tests. From the current study, we attempted to prove that both sympathetic and parasympathetic function tests in cases of type II diabetes mellitus by measuring the blood pressure response to standing from the supine position, blood pressure response to sustained handgrip, deep breathing test, valsalva menover test and cold pressor test and signifying their sensitivity in the early detection for diagnostic purposes.

2. Materials and Methods

Fifty subjects of Type II diabetes mellitus and Fifty non-diabetic age matched controls, including both males and females, were assessed for Autonomic functional status after acquiring oral and written consent. The study also got the approval from ethical committee. The following criteria were followed while selecting the patients as cases:

1. The individuals of type II diabetes mellitus attending Endocrinology O.P.D. for checkup (i.e. fasting blood sugar level ≤126 mg/dl and post prandial blood sugar level ≤180 mg/dl)
2. Age between 35-50 years.
3. No previous history of any other disease or complications.

All the healthy subjects (controls) and patients (subjects) were subjected to general and physical examination. Cardiovascular Autonomic function tests were carried out in the morning, after intimate testing procedures with the subjects .

The Autonomic function tests which were performed to assess the cardiovascular sympathetic functional status:

I. Cold Pressor test (cold pressure test): Subject was instructed regarding the test. Blood pressure was recorded under basal conditions. Cold water was taken in a container. Subject was asked to submerge one of his upper limbs in cold water for 60 seconds. Blood pressure was recorded at the end

of 60 seconds of submersion of the limb. Submersion of the limb in ice cold water increases systolic blood pressure by about 10-20 mm of Hg and diastolic blood pressure by about 10 mm of Hg.

II. Hand Grip Test: In the hand grip test, there is a rise in heart rate and blood pressure. The blood pressure rise is due to increased sympathetic activity and heart rate rise is due to decreased parasympathetic activity. Subject was made to lie down in semi recumbent position.
ECG electrodes were connected for lead II recording of ECG and sphygmomanometer for blood pressure measurement. Basal heart rate and blood pressure were recorded. Subject was asked to maintain a pressure of 30% of the maximum activity in the hand grip dynamometer for about 5 minutes. Heart rate and change in SBP, DBP were recorded.

III. Blood pressure response to standing: Patient is again allowed to assume a supine position, and a recording of blood pressure is done in the supine position. Patient is then asked to stand up and blood pressure is recorded at 0 and 1 minute intervals.

The Autonomic function tests which were performed to assess the cardiovascular parasympathetic functional status:
I. Deep breathing test - This test is used to assess the parasympathetic activity. Subject was instructed to maintain deep breathing at a rate of six breaths per minute and was made to lie down comfortably in supine position with head elevated to 30^0. ECG electrodes were connected for recording Lead II ECG. While subject was breathing deeply at a rate of 6 breaths per minute (allowing 5 seconds each for inspiration and expiration) maximum and minimum heart rates were recorded with each respiratory cycle. Expiration to inspiration ratio was determined by using the formula.

II. Valsalva Manoeuver - The valsalva ratio is a measure of parasympathetic and sympathetic functions. Subject was made to lie down in a semi recumbent or sitting position. Nostrils were closed manually. Mouth piece was put into the mouth of the subject and the Mercury manometer was connected to the mouth piece. ECG machine was switched on for continuous recording. Subject was asked to exhale forcefully into the mercury manometer and asked to maintain the expiratory pressure at 40 mm of Hg for 10 – 15 seconds. ECG changes were recorded throughout the procedure, 30 seconds before and after the procedure. Valsalva ratio were calculated by using the formula.

III. Heart rate response to standing: On changing the posture from supine to standing heart rate increases immediately by 10-20 beats per minute. This response is detected by recording ECG in supine and standing postures. Subject was made to lie down in supine posture. ECG electrodes were connected from the subject to the cardiowin system. Subject was asked to relax completely for a minimum period of 10 minutes. Basal heart rate was recorded by using cardiowin system. Subject was asked to stand up immediately and change in heart rate is noted from the monitoring screen of cardiowin. Heart rate response to standing was determined by using the formula heart rate in standing position – heart rate in supine position.

3. Results

Results were analyzed by ANOVA with SPSS version 17.0 using an unpaired 't' test. The results of the above tests were compared between the test group (type II diabetes mellitus) and healthy age matched controls.

Table 1: Statistical analysis of Parasympathetic function tests in Test and Controls

Variables	Controls	Diabetics	P value
Heart rate response to standing 30:15 Ratio	1.36 ± 0.19	1.17 ± 0.12	<0.01**
Valsalva ratio	1.62 ± 0.26	1.32 ± 0.22	<0.01**
Heart rate response to deep breathing	14.8 ± 7.5	10.2 ± 4.3	<0.05*

In our study 50 subjects of type 2 diabetes patients who were selected after using proper exclusion criteria.

Table -1 :- Heart rate response to standing 30:15 Ratio values were decreased in diabetics as compared to controls Valsalva ratio was decreased in diabetics as compared to controls Deep Breathing test i.e., E/I ratio in diabetics decreased in diabetics as compared to controls. All these Parasympathetic autonomic function tests shows significant P values.

Table 2:- All the sympathetic autonomic function tests like Blood pressure response to standing, Cold pressor test and Hand grip test shows decreased values in diabetics when compared to controls.

When compared all the autonomic function tests, it was proved that heart rate response to deep breathing was the most sensitive test to determine autonomic neuropathy. It is abnormal in 38 patients when compared with controls and normal in 12 patients. This was followed by abnormal heart rate response to standing (30.15 ratio), which was abnormal in 31 patients and normal response were found in 19 patients.

Valsalva ratio was abnormal in 31 patients and normal in 19 cases. Abnormal hand grip test seen in 24 patients and normal response were found in 26 cases. The least sensitive tests to detect autonomic neuropathy was Blood pressure response to standing and cold pressor test which were abnormal in 12 patients and normal in 38 cases. These results showed that Parasympathetic neuropathy i.e., abnormal parasympathetic function was seen in 38 cases while sympathetic neuropathy i.e., abnormal sympathetic function was detected in 24 cases

Table 2: Statistical analysis of sympathetic function tests in Test and Controls

Variables	Controls	Diabetics	P value
Isometric Handgrip SBP	19.55 ± 0.86	14.85 ± 1.20	<0.01**
Isometric Handgrip DBP	15.9 ± 0.83	11.5 ± 0.96	<0.01**
Cold Pressor Test SBP	12.2 ± 1.6	8.2 ± 1.4	<0.05
Cold Pressor Test DBP	13.1 ± 1.8	9.1 ± 1.4	<0.05
Bp Response to standing SBP change	-2.9 ± 0.41	-7.0 ± 1.22	<0.01**
Bp Response to standing DBP change	-2.20±0.43	-5.43±0.66	<0.01**

4. Discussion

Diabetes mellitus is one of the high risk factor for cardiovascular disease. Diabetic Autonomic Neuropathy (DAN) is associated with cardiovascular risk in people with diabetes mellitus. DAN is a progressive condition in which ANS dysfunction is not only more prevalent in diabetics but also worsens as the disease progresses.

As suggested in the previous studies and hypothesis, we found a significant decrease in E: I ratio values in Type 2 DM patients as comparison with the control in our study. This indicates that cardiac autonomic dysfunction is highly associated risk factor in DM patients. Deep breathing test is the simplest and most widely performed measure of autonomic control of the heart. This test produces a sensitive, specific, accurate and reproducible indirect measure of vagal cardiac function. This decreased E: I ratio values in diabetics indicates DAN. Our results in this study was almost matched with the studies conducted by Fareedabanu AB et al[6].

Statistically it was proved that heart rate response to deep breathing was the most sensitive test to determine autonomic neuropathy. During inspiration the heart rate increases and on expiration the heart rate decreases. The variation of heart rate with respiration often known as sinus arrhythmia is primarily mediated by the vagal innervation of the heart. The neuronal output from the respiratory center influences the gain of the afferent and efferent outputs at the nucleus tractus solitarius. Pulmonary stretch receptors as well as cardiac mechanoreceptors and possibly baroreceptors contribute to regulating the heart rate variation. But in diabetics due to the impairment of parasympathetic system the E: I ratio decreases.

This study also showed that Valsalva ratio is lower in diabetic patients than normal persons this reflects decreased parasympathetic function due to decreased vagal tone. The values of Valsalva ratio decreases and percentage of subjects who get abnormal results (<1.45) increases as the disease advances. Ultimately, heart rate response to deep breathing is decreased only in diabetics due to altered vagal tone as consequence of CAN and this Valsalva response decreases as duration of diabetes increases due to progressive nerve damage. The results in our study showed conformity with reports of Devika G. Rajput et al[5].

Heart rate response to standing up induces reflex tachycardia followed by bradycardia and is both vagal and baroreflex mediated. So in diabetics with autonomic neuropathy there is abnormal response due to damage to the reflex pathways, mediating the response. In our study we compared the heart rate response to standing values in diabetics and controls. These values were decreased in diabetic patients as compared to controls. The results in our study correlated with the study conducted by Prakash S B et al[7].

Hand grip test values were significantly lower in the diabetic group compared with the control group in control subjects during sustained hand grip, there is a sharp rise in blood pressure of more than 15mmHg. This rise in BP is due to heart rate dependent increase in cardiac output with unchanged peripheral vascular resistance, however in diabetics due to autonomic damage the rise in blood pressure is abnormally small. In controls the heart rate rise due to decreased parasympathetic activity and contraction of muscles that activate small fibres in the afferent arm of the reflex arc, however in diabetic patients the rise is very small. The results in our study correlated with the study conducted by Nazeema Khatoon et al[4].

The cold pressor test (CPT) is a potentially useful indicator of autonomic neuropathy in diabetes after deep Breathing test. The mechanism of the altered change of SBP in CPT in diabetic patients compared to the control could be due to impairment in either of afferent limb or the efferent sympathetic pathway mediating the vascular response of CPT. This study mainly suggest that attenuated change SBP in diabetic patients is due to impaired sympathetic response rather than due to impairment of the afferent limb of the CPT reflex. The results in our study correlated with the study conducted by Nazeema Khatoon et al[4].

In our study there is a fall in systolic and diastolic blood pressure responses to standing in diabetics as compared to the controls. This is mainly because of CAN in which there is damage to the efferent sympathetic vasomotor fibers particularly in the splanchnic vasculature. There is decrease in cutaneous, splanchnic, total vascular resistance and the baroreflex compensation is also impaired. The results in our study correlated with the study conducted by Langer et al.

5. Acknowledgment

6. Conclusion

Diabetic Autonomic Neuropathy (DAN) is associated with cardiovascular risk in people with diabetes mellitus. In this study, CAN was found in 76% cases. Parasympathetic neuropathy was found in 54% cases, and sympathetic neuropathy in 22% cases. The results in our study correlated with the finding of Ewing *et al*. Heart rate response to deep breathing was the most sensitive test to detect CAN followed by heart rate response to standing and heart rate response to Valsalva manoeuvre. Because in neuropathy first affected was the long nerve fibres as early as in the history of diabetes which impairs the parasympathetic function, followed by denervation of sympathetic trunk that affects from the apex to base of the heart and increases the propensity to dysrhythmias. Cold pressor test is slightly more sensitive to detect cardiac sympathetic neuropathy than that of postural hypotension and Blood pressure to sustained hand grip

The above study revealed that Cardiac autonomic neuropathy is detected by various cardiac autonomic function tests. The above mentioned symptoms of neuropathy will not detect cardiac neuropathy as sensitive as the autonomic function tests. These tests affords a satisfactory method for the quick detection of CAN. Parasympathetic autonomic function tests are more sensitive for the detection of CAN than sympathetic autonomic function tests. So this early detection of cardiac autonomic neuropathy will be of greatly helpful in recognition of those which are prone to risk of various cardiovascular complications.

7. Charts and Graphs
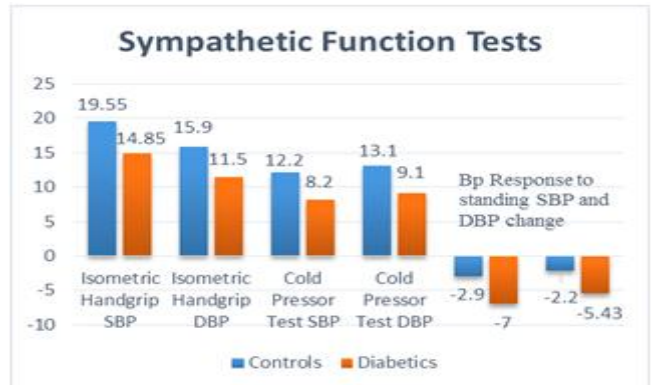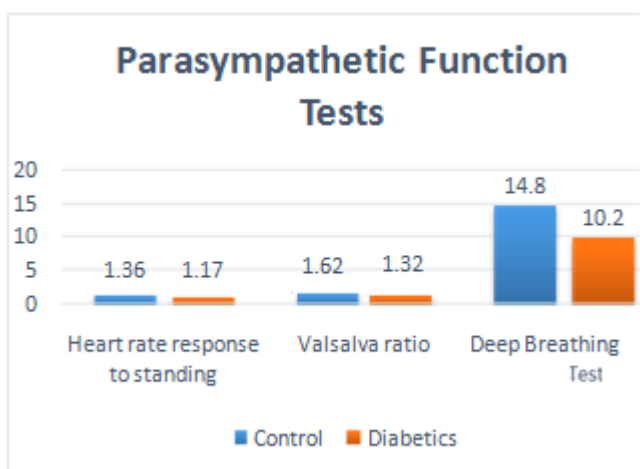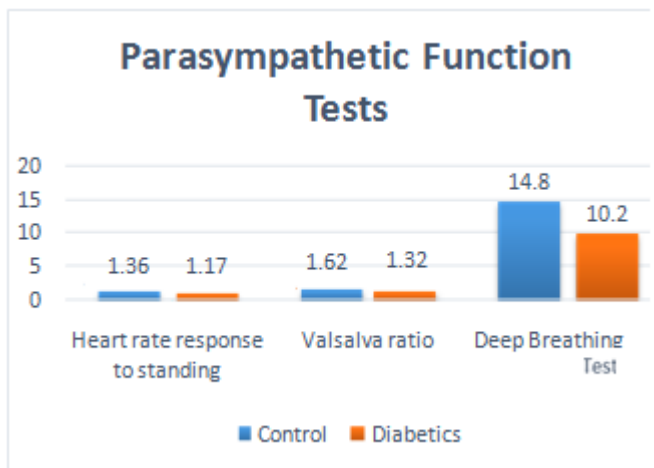
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