

Autonomic Neuropathy in Young Asymptomatic Type 2 Diabetics - A Rural Based Indian Study

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Abstract: *Aims:* To evaluate autonomic functions in young diabetics without any symptoms and signs of autonomic neuropathy and compare the same with young non diabetics. *Materials Method:* It is a prospective observational study, done at Sree Sidhi Vinayaka Diabetic Center, during July to December 2017. Autonomic function tests were done on young diabetics without symptoms or signs of autonomic dysfunction [Group A] and compared same with young age matched non diabetics [Group B]. *Result:* A total of 84 participants were included in the study having 48 patients [Group 'A'], and 36 subjects [Group 'B']. The mean age of the patient in Group A 35.33 ± 3.76 and Group B 34.61 ± 3.68 [p-value 0.90] with male to female ratio of 2.81: 1 [male preponderance]. A statistically significant variation was found in Resting Heart Rate, Heart Rate Variation to deep breathing, Valsalva Ratio, Postural Fall of SBP, Rise in DBP on Sustained Hand Grip [p<0.01]. *Conclusion:* Impaired autonomic neuropathy is associated with development of diabetes and autonomic denervation is evident even before diagnosis of diabetes.

Keywords: Cardiac Autonomic Neuropathy, Young Diabetics, Rural Indian Population.

Introduction

Diabetes mellitus is one among the leading cause of morbidity and mortality [1]. The scenario of diabetes is changing in the last decade where in younger generation has been affected very often [2]. There are various predisposing factors that are either the cause or the effect the disease. One among the pathophysiology of development of diabetes is autonomic denervation. Impaired autonomic nervous system function is associated with development of diabetes, hyper insulinaemia and hyper triglyceridemia [3]. Functional disturbance of peripheral and autonomic nervous system are often present at the time of diagnosis and autonomic neuropathy carries higher mortality in diabetics [4]. With this background we have evaluated cardiac autonomic function test in young type 2 diabetics without the symptoms and signs of autonomic neuropathy and compared the same with age matched non diabetics.

Material and Methods

After informed consent and ethical committee permission study was carried out at Sree Sidhi Vinayaka Diabetic Center during July to December 2017. The study group was divided into Group 'A' [cases - N=48] consisted of young type 2 diabetics within the age of 40 years, diagnosed as per ADA guidelines [5], having no apparent symptoms and signs of autonomic dysfunction. Group 'B' [controls- N=36] consisted of subjects having no diabetic history and were non diabetic on evaluation.

They were included in the study after a thorough history and clinical examination. Subjects with history of ischemic heart disease, valvular heart disease, left ventricular failure, fever and on any medication that influence the autonomic functions were excluded. The subjects were advised to come

after overnight fast and abstain from alcohol and smoking 12 hours prior to and during evaluation.

Methods:

The autonomic battery of test [6-7] evaluating cardiovascular functions were performed as bed side procedure and are described below;

I. Tests Reflecting Cardiac Parasympathetic Function:

1. *Resting Heart Rate (RHR):* This is obtained by recording a resting ECG in lead II at a paper speed of 50 mm/sec. From which the heart rate is calculated.
2. *Heart Rate Variation during deep breathing:* The subjects sit quietly and breathe deeply at 6 breaths a minute (5 sec in and 5 sec out) for one minute. An ECG was recorded throughout the period of deep breathing with a marker used to indicate the onset of each inspiration and expiration, the maximum and minimum R-R intervals during each breathing cycles were measured and converted into beats/min. The result is then expressed as the mean of the response
3. *Heart Rate Response to Valsalva Maneuver:* The test was performed by subject blowing into a mouth piece connected to sphygmomanometer with closed nostrils and holding at pressure of 40 mm Hg, for 15 seconds while a continuous ECG was recorded. The maneuver was performed 3 times with an interval of one minute in between. The results were expressed as the valsalva ratio which is the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver. The mean of three valsalva ratio was taken as final value.

II. Test Reflecting Sympathetic Function:

1. *Postural fall in Systolic Blood Pressure:* The test was performed by measuring the subjects BP while he is lying down quietly and again when he stood up. The postural fall in BP was taken as the difference between systolic BP while lying and the systolic BP on standing up.
2. *Rise of Diastolic Blood Pressure Response to Sustained Handrip:* After instructing the procedure to use the grip dynamometer the participant grips maximally with his

dominant hand, for a few seconds [this is maximum voluntary contraction (MVC)]. Now he/she is instructed to maintain handgrip steadily at 30% of MVC for about 5 minutes. BP was measured on non exercising arm and Diastolic BP was taken at muffling of sound. BP was recorded 3 times at intervals of one minute, during the handgrip. The result was expressed as difference between highest DBP during handgrip to mean of the 3 DBP readings before handgrip began.

Results

The results were analyzed with SPSS version 23 statistical software operating on windows. The results were presented as Mean ± SD and the difference between the mean was analyzed by student t-test with two sided confidence interval of 95%. The level of significance was set at p ≤ 0.05. Group ‘A’ [cases - N=48] consisted of patients with type 2 diabetes within the age of 40 years. Group ‘B’ [controls-N=36] consisted of subjects having no diabetic history and were non diabetic on evaluation. The results of Cardiac autonomic function tests were compared between the two groups for statistical significance.

The mean age of the patient in Group A 35.33 ± 3.76 and Group B 34.61 ± 3.68 (p-value 0.90) with male to female ratio of 2.81: 1 [table 1].

| Table-1: Showing Demographic details of study participants. | | | | |
|---|--------|----------------|----------------|---------|
| | | Group A (n=48) | Group B (n=36) | P-value |
| | | Mean ± SD | Mean ± SD | |
| Age in Years | | 35.33 ± 3.76 | 34.61 ± 3.68 | 0.90 |
| Gender | Male | 34 | 28 | |
| | Female | 14 | 08 | |
| *p-value <0.05 statistically insignificant. | | | | |

Among the Parasympathetic function tests, Resting heart rate of Group ‘A’ was 80.33 [SD± 14.87] and of Group ‘B’ was 71 [SD± 6.92], Heart Rate Variation to Deep Breathing

of Group ‘A’ was 15.45[SD± 10.37] and of Group ‘B’ was 25.36 [SD± 0.51] and Valsalva ratio of Group ‘A’ was 1.393 [SD± 0.34] and of Group ‘B’ was 1.59 [SD± 0.09] which were statistically significant [p<0.01] [table 2].

Among the sympathetic function tests, Postural fall of SBP of Group ‘A’ was 1.79 [SD± 8.29] and of Group ‘B’ was 7.16 [SD± 0.6] and Rise in DBP on sustained Hand Grip of Group ‘A’ was 17.125 [SD± 13.94] and of Group ‘B’ was 18.61 [SD± 1.83] which were statistically significant [p<0.01] [table 2].

| Table 2: Showing the Mean ± SD of Resting Heart Rate, Heart Rate Variation, Valsalva Ratio, Postural Fall of SBP, Rise in DBP on Sustained Hand Grip in two groups | | | |
|---|---|---|---------------------|
| | Group A (n=48) Mean ± SD | Group B (n=36) Mean ± SD | p- value |
| Resting Heart Rate | 80.33 ± 14.87 | 71 ± 6.92 | <0.01* |
| Heart Rate Variation | 15.45 ± 10.37 | 25.36 ± 0.51 | <0.01* |
| Valsalva Ratio | 1.393 ± 0.34 | 1.59 ± 0.09 | <0.01* |
| Postural fall of SBP | 1.79 ± 8.29 | 7.16 ± 0.6 | <0.01* |
| Rise in DBP on sustained Hand Grip | 17.125 ± 13.94 | 18.61 ± 1.83 | <0.01* |
| *p-value <0.05 is statistically significant. | | | |

Discussion

Last few decades has seen the emergence of diabetes as a new epidemic and has been diagnosed at an early age. Impaired autonomic nervous system function is associated with development of diabetes, hyperinsulinaemia and hyper triglyceridemia [3].

In the present study, we have evaluated 48 young type 2 diabetics having no symptoms or signs of autonomic neuropathy and compared with age matched non diabetics. The autonomic function tests evaluating parasympathetic functions, viz. Resting Heart Rate (RHR), Heart Rate Variation (HRV) to Deep Breathing, Valsalva Ratio showed a statistically significant variation. Postural fall of

Systolic Blood Pressure (SBP) and a rise in Diastolic Blood Pressure (DBP) on sustained Isometric Hand Grip among young diabetics even without the signs and symptoms of autonomic dysfunction which evaluate the sympathetic functions showed a statistically significant variation similar to previous studies [8-12].

Hyperglycemia is considered the principle cause of diabetic complications. As long as the average blood glucose level is normal it leads to normal glucose metabolism. In conditions of sustained hyperglycemia, the proportion of glycated hemoglobin is increased and studies have shown that HbA1c is the index of mean blood glucose, which includes both fasting and post prandial blood glucose levels, over the preceding weeks to months [13-14]. Persistent elevated glucose levels leads to formation of glucotoxins by various biochemical pathways, which produce end organ damage such as neuropathy, nephropathy, retinopathy and cardiovascular complications [14].

Its deleterious effects are attributable to the formation of glucose derived substances called Advanced Glycated End Products (AGEp). In diabetic vascular tissue the concentration of AGEp is four times than the normal, more so when blood sugar levels are chronically elevated [14]. Autonomic neuropathy is one among the microvascular complications. Early detection and treatment of which postpones these complications. It is to remember that the parasympathetic pre-ganglionic fibres are long and are prone to damage very early in diabetes due to prolonged hyperglycemia even before the development of diabetic complications [14].

As pancreatic beta cells are also innervated by parasympathetic nerves, hyperglycemia stimulates pancreas to augment insulin secretion and hyperinsulinaemia [15] and insulin resistance. Studies have shown that when glucose levels are lowered towards the normal range, microvascular complications of type 2 diabetes are reduced [16-17].

The study results suggest that cardiac autonomic denervation do occur even without

the symptoms or signs of autonomic neuropathy. This study where in we have applied simple bedside tests to detect autonomic dysfunction, can help in long way in detecting and preventing the complication of diabetes.

Conclusion:

Autonomic denervation occurs way before the development of overt diabetes and autonomic dysfunction is proved to be associated with macro

and micro vascular complication of diabetes and end-organ dysfunction. Hence simple bedside tests to detect the autonomic dysfunction may help in long way to identify the population at risk and apply proper therapeutic measures. Therefore, autonomic function testing should be advocated as important tool in the battery of investigations for diabetics to identify & postpone complication of diabetes mellitus.

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