Autonomic Neuropathic Changes in Diabetes: Early marker of Impending Complications

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Abstract

Background: Cardiac autonomic neuropathy (CAN) is a critical intricacy of diabetes mellitus. Autonomic neuropathy is postulated to be an indicator of impending demise. It is not very easy to detect the diabetic autonomic neuropathy at an earlier stage. The objective of this study was to weigh up the affiliation between autonomic neuropathy and the heart rate variability (HRV) in Type 2 Diabetics. HRV can indicate early subclinical manifestation of autonomic dysfunction, and this could be of value from clinical perspective to understand the risk associated with the subject and further management. In other words, having HRV insight may influence the aggressiveness of the intervention and the choice of therapy when dealing with hyperglycaemia and the complications and also for identifying potential risks, which are not obvious (e.g., CAN). Methods: The present study was conducted on 50 type 2 Diabetics attending the diabetic clinic and 25 healthy attendants served as controls. The patients were divided into two major groups, i.e. (<5 years of duration, >5 years of duration). Autonomic nervous system activity was evaluated. HRV was measured by Standing to lying ratio (S/L ratio), 30/15 ratio, Valsalva ratio and Deep breathing test (DBT). The results were statistically analysed. Results: Significant changes in parasympathetic activity (30:15 ratio, DBT, S/L ratio) were observed in diabetics as compared to normal which progressed with duration of disease (<5 years vs >5 years, p<0.05). Conclusion: With early detection of autonomic neuropathy, use of aggressive approach in management of Diabetes Mellitus would reduce mortality and morbidity in these patients. Keywords: Cardiac autonomic neuropathy(CAN), Diabetes Mellitus, Heart Rate Variability (HRV)

I. Introduction

The progression of chronic disease is triggered by multiple risk factors related to the lifestyle and the environment (physical inactivity, obesity, alcohol, tobacco, chronic stress, insomnia, etc.) resulting in changes in pathophysiology. Specifically, the journey towards any chronic disease begins with signs of autonomic dysfunction, metabolic syndrome (MetS), insulin resistance (e.g. diabetes) and the chronic disease itself followed by the complications (e.g., neuropathy for diabetes). T2D is a multifactorial disease and may be associated with Metabolic syndrome characterised by altered glucose metabolism that can affect organ function either directly or indirectly through oxidative stress and inflammatory mechanisms linked to hyperglycaemia, increase in free fatty acids, triglycerides and methylglyoxal with a deficiency of endogenous antioxidants; superoxide dismutase, catalase, ceruloplasmin and antioxidant nutrients. Free radical stress and inflammation are considered as the main causative factors of diabetes and its complications including renal, retinal, vascular and neurological impairments. However, the mechanisms for the development of complications due to diabetes are multifactorial. Apart from diet and lifestyle factors causing oxidative stress and inflammation, environmental factors and genetic predisposition may also contribute in the development of complications. Specifically, the complications of T2D mellitus (T2DM) do not always occur in isolation but are often found as a group in patients, particularly among those with uncontrolled blood glucose and most often involve autonomic dysfunction.

The sympathetic and parasympathetic components of the ANS are both affected by increased blood glucose levels, oxidative stress and inflammation, leading to multiple organ dysfunction and cardiac autonomic neuropathy (CAN). CAN is characterised by an altered cardiac rhythm due to the initial changes in the parasympathetic system, followed by sympathetic modulation of the cardiac rhythm as well as blood pressure and blood glucose variations. Cardiovascular autonomic neuropathy is defined as the impairment of autonomic control of the cardiovascular system. Subclinically, the disease is defined by cardiovascular reflex testing, which may have
prognostic implications. Clinically, the impairment in autonomic function is associated with resting tachycardia, exercise intolerance, orthostatic hypotension, syncope, intraoperative cardiovascular instability, silent myocardial infarction and ischemia, and increased mortality. Autonomic neuropathies impinging cardiovascular system cause resting tachycardia and orthostatic hypotension. Reports of sudden death have also been ascribed to autonomic neuropathy.

The evaluation of cardiovascular autonomic function is the cornerstone of the clinical investigation of autonomic function. The anatomic situation of the cardiovascular autonomic nervous system renders it inconvenient for simple direct physiological testing. Consequently, autonomic tests based on cardiovascular reflexes to various physiological agitations (e.g., heart rate response to deep breathing, postural change, and the Valsalva manoeuvre and blood pressure response to sustained hand grip and postural change) are usually employed.

II. Material And Methods

The study was conducted on 50 Type 2 diabetics which were further divided into two groups according to the duration of disease, less than 5 years of disease and more than 5 years of disease. Detailed history of the patients were taken and enquired about their lifestyle and the various battery of tests were done assessing their pulse rate, blood pressure and ECG with posture variations i.e., sympathetic and parasympathetic parameters were completely evaluated. ECG for autonomic function testing was done with RMS ECG machine, using standard limb lead II. Blood pressure was recorded using sphygmomanometer. Sympathetic activity was measured by cold pressor test, hand grip test, and blood pressure response to standing. Parasympathetic activity was measured by S/L ratio, 30/15 ratio, valsalva ratio and I/E ratio.

Observations were recorded and interpreted. Data were analysed using SPSS-10. The statistical difference in mean values was tested using ANOVA with post hoc turkey, and p<0.05 was taken as significant.

III. Results

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>GROUP</th>
<th>DURATION OF DISEASE</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDDM Ia</td>
<td>&lt;5 years</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>NIDDM Ib</td>
<td>&gt;5 years</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CONTROL II</td>
<td></td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

<p>| TABLE 2: Pre-test mean values of pulse rate and blood pressure in all the groups |
|-----|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Pulse rate (per min) (range)</th>
<th>Pulse rate Mean±SD</th>
<th>SBP (mm Hg) (range)</th>
<th>SBP Mean±SD</th>
<th>DBP (mm Hg) (range)</th>
<th>DBP Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>25</td>
<td>66–107</td>
<td>86.84±11.49</td>
<td>120–160</td>
<td>136.08±9.44</td>
<td>70–92</td>
<td>84.64±4.78</td>
</tr>
<tr>
<td>Ib</td>
<td>25</td>
<td>60–130</td>
<td>82.52±16.48</td>
<td>110–154</td>
<td>138.40±9.52</td>
<td>68–100</td>
<td>86.40±6.21</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>70–80</td>
<td>76.84±5.46</td>
<td>104–134</td>
<td>120.16±9.39</td>
<td>60–88</td>
<td>76.96±7.83</td>
</tr>
</tbody>
</table>

<p>| TABLE 3 Mean values of parasympathetic function tests |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>30:15 ratio Mean±SD</th>
<th>Valsalva ratio Mean±SD</th>
<th>DRT Mean±SD</th>
<th>S/L ratio Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>0.9±1.12</td>
<td>1.01±0.05</td>
<td>0.8–1.93</td>
<td>1.15±0.28</td>
</tr>
<tr>
<td>Ib</td>
<td>0.93–1.08</td>
<td>1.00±0.05</td>
<td>0.9–1.85</td>
<td>1.19±0.25</td>
</tr>
<tr>
<td>II</td>
<td>1.0–1.14</td>
<td>1.05±0.04</td>
<td>1.04–1.25</td>
<td>1.15±0.08</td>
</tr>
</tbody>
</table>

Data analysis showed that:
1. Out of 50 diabetics only 8 had active life style while 42 had sedentary mode of living adding on to the disease status.
2. Increase in mean pulse rate, Systolic blood pressure and diastolic blood pressure in the two groups. Increase in pulse rate is statistically significant p<0.05 as compared to the control group and loss of variability of heart rate with duration of disease is seen. Pre test mean value for DBP is highly significant when compared between the two groups p<0.01.
3. Sympathetic impairment evident by postural fall in BP, occurred in Group Ib and is statistically significant. But the cold pressor test and Hand grip test did not show significant change.
4. Parasympathetic parameters showed deterioration with the duration of the disease. The statistical comparison for 30:15 ratio, Valsalva ratio and Deep breathing were highly significant and progressed with the duration of the disease.

IV. Discussion

Autonomic neuropathy is a frequently observed intricacy of diabetes that has a noteworthy distressing influence on the survival and quality of life of the patients. Generally, diabetic autonomic neuropathy may be clinically evident long after the onset of diabetes. Sub-clinical autonomic dysfunctions can occur within a year of Type 2 diabetes diagnosis. Early awareness of autonomic dysfunctions can encourage patients and physicians to improve metabolic control and use the treatments that may be effective in patients with autonomic dysfunctions, particularly cardiac autonomic dysfunction (CAN).

Cardiac marker heart rate variability (HRV) is an eloquent, sensitive and early prognosticator which can be used for early diminution of complications among diabetics. It was observed that there is resting tachycardia in diabetics. These findings are consistent with the study done by Shuldiner et al in which the authors observed resting tachycardia in diabetics suffering from cardiovascular autonomic neuropathy. Similar were the observations of other authors. The involvement of the vagal parasympathetic component of autonomic nervous system is obvious in Diabetic patients. This is evidenced by increased resting heart rate and decreased Valsalva ratio; E/I index and standing ratio in diabetics relative to controls. These findings are in line with those of Freccero et al who reported a high frequency of parasympathetic and sympathetic neuropathy in both type 1 and type 2 diabetic patients. They suggested that severe damage to large myelinated nerve fibres in addition to the widespread neurological degeneration which usually affects the small nerve fibres of the autonomic nervous system was culpable for profound parasympathetic neuropathy in patients with T2DM.

Other researchers also found appreciable degree of autonomic neuropathy in patients with T2DM. In fact significantly reduced HRV measures in DM patients compared to controls have been previously verified in large-population-based studies. The same results had also been documented in the Framingham Heart Study and in the Atherosclerosis Risk in Communities (ARIC) cohort.

V. Conclusion

Autonomic signs and symptoms are common in diabetes and with early detection of autonomic neuropathy, use of aggressive approach in management of Diabetes Mellitus, would reduce mortality and morbidity in these patients.

Bibliography


