Short Communication

Cardiovascular autonomic neuropathy (CAN) in patients of type 2 diabetes mellitus: A tertiary care hospital based study

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency. Cardiovascular autonomic neuropathy invokes potentially life threatening outcomes especially in poorly controlled diabetic patients. However, there is scarcity of epidemiological data for CAN in poorly controlled type 2 diabetic patients in Pakistan.

Objective: The objective of this study is to assess the frequency of cardiovascular autonomic neuropathy (CAN) in patients with poorly controlled type 2 diabetes mellitus in Pakistan.

Study design: Descriptive cross-sectional.

Setting: Department of Medicine, Liqueat University Hospital, Hyderabad/Jamshoro, Sindh, Pakistan.

Duration: February to November 2012.

Sampling technique: Non-probability purposive.

Material and method: This study included 207 patients, who all met the inclusion criteria and gave an informed consent for inclusion in the study. All the patients in the study were evaluated for CAN using four different clinical tests- Resting heart rate, test for orthostatic hypotension, hand gripping test and QTc interval on ECG. Resting Heart Rate of more than 100 beats per minute was taken as abnormal. Orthostatic hypotension was defined as a fall of systolic blood pressure >20 mmHg and/or diastolic blood pressure >10 mmHg on change of posture. The patients were asked to squeeze a small ball in hand gripping test and an increase in diastolic blood pressure <15 mmHg was considered abnormal. ECG recording with QTc interval >440 ms was considered abnormal or prolonged. Patients were labeled as CAN +ve if any two or more than two of the above listed tests were found positive/abnormal.

Results: In our study, 76 out of 207 (36.7%) of the patients with poorly controlled type 2 diabetes mellitus were found to have cardiovascular autonomic neuropathy (CAN).

Conclusion: Cardiac autonomic dysfunctions are common in poorly controlled type 2 diabetes.

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1. **Introduction**

Cardiovascular autonomic neuropathy (CAN) is one of the more often overlooked, but serious complications of diabetes. This is largely owing to the fact that very little information on epidemiology of CAN in diabetic populations from Pakistan is available. Furthermore, heterogeneous methodology of available epidemiological studies from this region makes it difficult to compare date from the available studies.

Available studies have highlighted a variety of factors to be associated with CAN and indicate that its prevalence increases with age of diabetic patient, duration of diabetes, and poor glycemic control. CAN also co-exists with distal symmetric polyneuropathy and microangiopathy of diabetes. Age of the patient, duration of diabetes, obesity and smoking are independent risk factors for reduced heart rate variability (HRV) in type 2 diabetes. Another study concluded that abnormal HbA1c levels, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycemia were risk factors for developing CAN in type 1 diabetes.

Resting tachycardia and fixed heart rate are characteristic late findings in diabetic patients with vagal impairment due to CAN. Therefore, diabetic patients who are likely to have CAN should be tested for cardiac stress test before undertaking an exercise program. The autonomic dysfunction impairs exercise tolerance, reduces response to heart rate, blood pressure and blunts the increased cardiac output in response to exercise.

Diabetic patients also run a 2–3 folds higher risk of cardiovascular morbidity and mortality during surgery. There is an association between CAN and intraoperative hypothermia and orthostatic hypotension, although the fall in blood pressure may also be asymptomatic. The mechanisms by which CAN causes increased mortality remains obscure and it is often difficult to determine the independent effects of CAN on intraoperative mortality because of the coexisting cardiovascular disease (CVD). Two prospective studies have studied the relationship between CAN and major intraoperative cardiovascular events. One potential cause of higher mortality during surgery in such patients could be severe but asymptomatic ischemia, which can induce lethal arrhythmias. Patients with severe autonomic dysfunction also have a higher risk of BP instability. Thus, intraoperative inotropic support is often needed in patients with greater autonomic impairment. American Diabetes Association recommends yearly screening for autonomic neuropathy in type 2 diabetes mellitus from the time of diagnosis.

Patients meeting the following exclusion criteria were excluded from the study:

1. Patients with hypotension, Congestive cardiac failure, Ischemic heart Disease, Hyperthyroidism, Chronic renal failure
2. Patients on medications such as Vasodilators, Diuretics, Anti-arrhythmic, Beta-blockers, Alpha-agonist or Alpha-blockers

An informed consent for inclusion in this study was obtained from all the patients. We used non-probability purposive sampling technique for this study. All patients were fully explained about the different maneuvers like hand grip, standing and squeeze of ball. The recruited patients were tested for

1. Resting heart rate- A resting heart rate of more than 100 beats per minute considered abnormal.
2. Orthostatic hypotension – Blood pressure was first measured (using the aneroid sphygmomanometer) in supine position and then the patient was instructed to stand up. Blood pressure was again measured after 2 min of standing. A fall in systolic blood pressure of >20 mmHg and/or in diastolic blood pressure >10 mmHg was considered abnormal.
3. Hand gripping test – The blood pressure of the patient was first measured in supine position. The patient was instructed to squeeze a small ball in his/her hand for about 5 min while lying in the bed and then his/her blood pressure was measured (using the aneroid sphygmomanometer) again. An increase in diastolic blood pressure <15 mmHg was considered abnormal.
4. ECG recording-QTc interval >440 or prolonged ms was considered abnormal.

If the findings on any two or more of the above tests in a patient were abnormal, the patient was diagnosed as positive for CAN.

Data was entered and analyzed by SPSS version 16. The frequencies and percentages were calculated for qualitative variables such as gender and age group and chi-square test was used to compare the proportions. Mean ± SD was calculated for numerical variables like age in years, pulse rate (lying/supine, standing), blood pressure (lying/supine, standing and after hand gripping), QTc interval, random blood sugar level (RBS) and HbA1c. All the data was analyzed for a 94% confidence interval. A p-value ≤0.05 was considered as statistically significant.

2. **Materials and methods**

This study included two hundred and seven (207) type 2 diabetes patients who attended medical wards and/or OPDs at Liaquat University of Medical & Health Sciences Hospital (LUMHS) Jamshoro/Hyderabad, Sindh, Pakistan. All the patients from either sex who met the following inclusion criteria were considered for inclusion in this study.

1. Age above 30 years
2. S. HbA1c 7 % –11.5%

A total of 207 type 2 diabetic patients fulfilling the inclusion criteria were included in this study. The mean age of these patients was 54.6 ± 7.8 years. Out of 207 patients, 80 (38.6%) aged between 41 and 50 years, 75 (36.2%) were between 31 and 40 years old and 50 (24.2%) were between 51 and 60 years old. Please see Table 1 below for full age-wise distribution of the study population.
There were 107 (51.7%) male and 100 (48.3%) female patients in the study group with an average weight of 75.0 ± 15.1 kg and mean HbA1c level of 7.9 ± 4.2%. The mean blood pressure in the studied patients was found to be 133.3 ± 26.4 mmHg and the mean random blood sugar level was 170.1 ± 62.5 mg/dl. A total of 76 (36.7%) patients were found to have cardiovascular autonomic neuropathy (CAN) based on the diagnostic protocol described above. The mean QTc interval was 490.8 ± 22.3 (m sec), as given in Table 2 below.

There was no statistically significant difference in incidence of CAN among patients belonging to two genders (p > 0.17). However, a statistically significant difference in incidence of CAN was observed when comparing occurrence of CAN in different age groups (p < 0.04), as given in Table 3 below.

### Table 1 – Distribution of age (n = 207).

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>107</td>
<td>51.7</td>
</tr>
<tr>
<td>Female</td>
<td>100</td>
<td>48.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group (Yrs)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>31–40</td>
<td>75</td>
<td>36.2</td>
</tr>
<tr>
<td>41–50</td>
<td>80</td>
<td>38.6</td>
</tr>
<tr>
<td>51–60</td>
<td>50</td>
<td>24.2</td>
</tr>
<tr>
<td>&gt;61</td>
<td>2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Mean ± SD 54.6 ± 7.8

4. Discussion

Our analysis revealed that a total of 76 (36.7%) patients with type 2 diabetes mellitus had cardiovascular autonomic neuropathy (CAN). It further revealed that there were no significant differences between incidences of CAN between two sexes, but the difference in incidence between different age groups was significant.

In another descriptive study from Hyderabad, Pakistan, researchers found the incidence of CAN to be 60%. Univariate analysis showed a significant association between CAN and higher age (odds ratio (OR) 15.75), prolongation of QTc (OR 5.55), duration of disease over 10 years (OR 2) and peripheral neuropathy (< 0.001) in patients with type 1 diabetes. Significant risks factors for CAN among patients with type 2 diabetes included coexistent peripheral neuropathy (OR 14), prolonged QTc (OR 9.75), higher age (OR 7.2) and disease duration over 10 years (OR 1.92) in univariate analysis, but none of these factors showed independent risk in multivariate analysis. The Disease duration over 10 years resulted in QTc prolongation in a significant numbers of cases with type 1 and type 2 diabetes.

In our study, we found a strong correlation between occurrence of CAN and widening of QTc interval and age at diagnosis. However, we found no significant correlation between gender and incidence of CAN.

Other researchers have studies to detect other useful indicators for diagnosing CAN. Another study described the usefulness of heart rate variability (HRV) and complexity analyses from short term ECG recordings as a screening tool for CAN. A total of 17 sets of ECG recordings taken from diabetic subjects with and without CAN performed in resting supine position were evaluated. The study demonstrated the potential utility of SampEn (a complexity based estimator) of HRV in identifying asymptomatic CAN. Another study evaluated the impact of parental type 2 diabetes on the autonomic nervous system of non-diabetic offspring. The study attempted to determine if the evaluated non-diabetic subjects with parents having type 2 diabetes had, autonomic neuropathy and if autonomic neuropathy in these subjects was associated with changes in 24-h ambulatory blood pressure (AMBP) and urinary albumin excretion rate (UAER). The study examined 223 non-diabetic offspring of type 2 diabetic subjects and a control group of 258 offspring of non-diabetic subjects. The prevalence of autonomic neuropathy in the non-diabetic offspring with parental type 2 diabetes (6.7%) was significantly higher compared with the control group (1.6%). Autonomic neuropathy in such subjects was also found to be associated with a higher fasting insulin level, higher UAER, higher 24-h mean AMBP and reduced diurnal blood pressure variation after adjustment for age, sex, and BMI. In conclusion, parental type 2 diabetes was found to be associated with alterations in the autonomic nervous system in non-diabetic subjects.
A study from India attempted to determine the prevalence of CAN in type 2 diabetes mellitus and to correlate CAN with retinopathy, microalbuminuria and glycated haemoglobin levels. The results of this study revealed that 54% of studied patients had CAN. Furthermore, the researchers found that 52% patients had parasympathetic neuropathy, 20% had sympathetic neuropathy and 28% had two abnormal cardiovascular reflexes. The researchers also observed microalbuminuria and retinopathy in 36% and 10% of these patients respectively. The percentage of CAN in our study was comparatively lesser than the above study. This difference in results may be due to operational definitions and further classification of CAN into different groups. Autonomic neuropathy is a serious complication of diabetes mellitus. Another study found the prevalence of CAN among diabetic patients to be 51.9%. The prevalence of sympathetic and parasympathetic CAN was 28.9% and 44% respectively. These researchers also noted a significant different in the incidence of CAN between type 1 and type 2 diabetic patients. The postural drop in blood pressure caused by autonomic neuropathy in diabetes mellitus is regarded as a risk factor for cardiovascular disease. A study was conducted in a tertiary care hospital of Peshawar to assess the prevalence of orthostatic hypotension in diabetic patients and to find its correlation with hypertension in patients with diabetes mellitus. Two hundred indoor diabetic patients were assessed; of which 26% were found to have orthostatic hypotension.

5. Conclusion

The cardiac autonomic neuropathy is common in diabetic patients in Pakistan. The clinician should identify early CAN by doing simple tests. This study also demands for large scale population based studies in future.

Conflicts of interest

All authors have none to declare.

REFERENCES


