INTRODUCTION

The prevalence of Diabetes Mellitus (DM) for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of DM is projected to rise from 171 million in 2000 to 366 million in 2030. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to DM prevalence across the world appears to be the increase in the proportion of people >65 years of age.¹ DM affects approximately 2.7 million people in Pakistan. Higher prevalence in women is observed in both urban and rural areas of Pakistan. One in four urban obese, over 40 years of age, is diabetic.² The prevalence of diabetes in Pakistan is 8.6%, 11.1% and 13.9% in the provinces of Baluchistan, NWFP and Sindh respectively.³ The risk of cardiovascular events is at least 2-4 times higher in patients with diabetes. CAN is a result of damage to the vagal and sympathetic nerves. Clinical findings may include exercise intolerance, persistent sinus tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver by electrocardiogram (ECG). An R-R variation with respiration of >15 beats per minute was taken normal, while 10-15 beats and <10 beats per minute were taken as borderline and definitive CAN respectively. QTc intervals were measured. Patients with HbA1c levels <7% were considered as well-controlled. The associations between CAN, the duration of diabetes and the diabetic control were determined.

RESULTS: The mean age was 35.16±10.58 years with 32 males and 18 females. The mean values for the known duration of diabetes and HbA1c were 13±7.3 years and 9.36±2.5 mg/dl respectively. Definitive and borderline CAN were noted in 20% and 24% respectively. Variability of heart rate with respiration was significantly related to the duration but not to the control of the diabetes (p<0.05). QTc showed a significant correlation with the known duration of diabetes and heart rate variability with respiration (p<0.05). Most of the patients had uncontrolled glycemic status.

CONCLUSION: Cardiac autonomic neuropathy is common in long standing type-1 diabetics. CAN resulted in prolonged QTc interval that may result in cardiac arrhythmias and even death. Intensive glycemic control improves the cardiac autonomic nerve functions.

ABSTRACT

Objective: To determine the frequency of Cardiac Autonomic Neuropathy (CAN) in type-1 Diabetes mellitus patients and its association with the duration of disease and glycemic control.

Study Design: Descriptive study.

Place and Duration of Study: Department of Medicine, Liaquat University Hospital, Hyderabad/Jamshoro, from December, 2004 to April, 2005.

Methodology: Fifty patients of type-1 Diabetes Mellitus (DM) of ≥10 years duration were selected. CAN was evaluated in terms of presence of resting tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver by electrocardiogram (ECG). An R-R variation with respiration of >15 beats per minute was taken normal, while 10-15 beats and <10 beats per minute were taken as borderline and definitive CAN respectively. QTc intervals were measured. Patients with HbA1c levels <7% were considered as well-controlled. The associations between CAN, the duration of diabetes and the diabetic control were determined.

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Conclusion: Cardiac autonomic neuropathy is common in long standing type-1 diabetics. CAN resulted in prolonged QTc interval that may result in cardiac arrhythmias and even death. Intensive glycemic control improves the cardiac autonomic nerve functions.

Key words: Cardiac autonomic neuropathy. Resting tachycardia. Sinus arrhythmia. Valsalva maneuver.

INTRODUCTION

The prevalence of Diabetes Mellitus (DM) for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of DM is projected to rise from 171 million in 2000 to 366 million in 2030. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to DM prevalence across the world appears to be the increase in the proportion of people >65 years of age.¹ DM affects approximately 2.7 million people in Pakistan. Higher prevalence in women is observed in both urban and rural areas of Pakistan. One in four urban obese, over 40 years of age, is diabetic.² The prevalence of diabetes in Pakistan is 8.6%, 11.1% and 13.9% in the provinces of Baluchistan, NWFP and Sindh respectively.³ The risk of cardiovascular events is at least 2-4 times higher in patients with diabetes. CAN is a result of damage to the vagal and sympathetic nerves. Clinical findings may include exercise intolerance, persistent sinus tachycardia, bradycardia, and no variation in heart rate during daily activities. Baroreceptor disease contributes to the supine hypertension. In a patient with type-1 DM, an autonomic imbalance may result in a prolonged QT interval on the ECG, which may predispose the patients to the life-threatening cardiac arrhythmias and sudden death. CAN reduces appreciation of ischemic pain that may delay appropriate medical therapy and even death.⁴ CAN occurs in about 17% of type-1 diabetes.⁵ CAN can lead to resting tachycardia, silent myocardial ischemia, and arrhythmia etc.⁶ CAN may be detected by evaluating resting tachycardia, loss of sinus arrhythmia and heart rate response to Valsalva maneuver.

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If two of these are abnormal, the diagnosis of CAN is established.7 Intensive glycemic control substantially reduces the prevalence of CAN and slows the progression of R-R variation and Valsalva ratio.8,9 Many investigators have considered autonomic neuropathies to be irreversible, however, CAN has been shown to regress with good glycemic control.4 The objective of this study was to determine the frequency of Cardiac Autonomic Neuropathy (CAN) in type-1 diabetes mellitus patients and its association with the duration of disease and glycemic control.

**METHODOLOGY**

This study was conducted at the Department of Medicine, Liaquat University Hospital, Hyderabad/ Jamshoro, from December 2004 to April 2005, included 50 cases of type-1 DM of ≥ 10 years duration, selected through non-probability purposive sampling. A verbal consent was taken and data was collected on a structured proforma. Patients suffering from cardiac failure, renal failure, liver cirrhosis, receiving sympatholytic and vasodilator drugs, and those with diabetic retinopathy were excluded. Enquiry was made about the duration of diabetes mellitus and the insulin therapy. Resting heart rate was calculated for the evaluation of resting tachycardia under basal conditions; values of more than 100 beats per minute (bpm) were considered abnormal. Heart rate variation with respiration was observed for loss of sinus arrhythmia. Patients were asked to take 6 deep breaths per minute, while being monitored by ECG for one minute. Maximum and minimum R-R intervals were calculated and expressed in beats per minute. Normal R-R variation is more than 15 beats per minute, while 10-15 beats and <10 beats per minute were taken as borderline and definitive CAN respectively. Valsalva maneuver was performed in which the person was asked to blow against an aneroid or mercury manometer upto 40 mmHg for 15 seconds, simultaneously monitored by the ECG. Valsalva ratio was calculated as the ratio of longest R-R interval (during bradycardia) to the shortest R-R interval (during tachycardia). Normal Valsalva ratio is 1:2 or more; values less or equal to 1 were taken as evidence of CAN. Values between 1 to 1.2 were taken as borderline.10 The symptoms of Diabetic Autonomic Neuropathy (DAN) like postural hypotension, bladder dysfunction, gastroparesis, and impotence were sought after other causes were excluded. Postural hypotension was measured, when the patient was lying down and 2 minutes after the patient assumed upright posture. A fall of >30 mmHg was considered abnormal, and a fall between 10-29 mmHg was borderline. The ethics committee of the institute approved the study. The data was analyzed using student’s t-test and Chi-square tests as relevant on SPSS version 10.0.

**RESULTS**

The mean age of patients noted was 35.16±10.58 years (ranging from 25 to 47 years). Out of 50 patients, 32 (64%) were males and 18 (36%) were females. Mean duration of diabetes was 13±7.3 years. Definitive and borderline CAN were noted in 10 (20%) and 12 (24%) patients respectively (p<0.005, Table I). The median QTc differences, postural hypotension, and changes of heart rate by respiration were 0.62, 20 mmHg, and 6 beats/minute respectively (p<0.005). There was no difference in QTc values with respect to diabetic control but QTc values were significantly different with regard to the known duration of diabetes (p<0.005). BP variation with standing was significantly related to the control as well as to the known duration of diabetes (p<0.005). The variability of the heart rate with respiration was significantly related to the duration but not to the control of the diabetes (p<0.005). QTc showed a significant correlation with the known duration of diabetes, postural BP changes, and Heart Rate Variation (HRV) with respiration (p<0.005). Other signs and symptoms related to the autonomic neuropathy were resting tachycardia in 10 (20%), borderline postural hypotension in 12 (24%), hyperhidrosis in 18 (36%), constipation in 7 (14%), diarrhea in 3 (6%), gastroparesis in 5 (10%) and hypertension in 10 (20%) [Table II]. The mean value of HbA1c noted was 9.36±2.5 mg/dl, with only 3 patients (6%) having HbA1c values <7%, while 36 (72%) patients having <9%, 6 (12%) having values between 9-12%, and 5 (10%) patients were having values >12%.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Borderline</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R variation</td>
<td>28 (56%)</td>
<td>12 (24%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Normal heart rate</td>
<td>Resting tachycardia</td>
<td></td>
</tr>
<tr>
<td>HbA1c values</td>
<td>Number of patients</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>&lt; 7%</td>
<td>2</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>&lt; 9%</td>
<td>10</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>9-12%</td>
<td>23</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>&gt;12%</td>
<td>15</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

**Table II: Miscellaneous diabetic autonomic neuropathy signs and symptoms (n=50).**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural hypotension</td>
<td>12</td>
<td>24%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>14%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>20%</td>
</tr>
<tr>
<td>Paresthesiae</td>
<td>16</td>
<td>32%</td>
</tr>
</tbody>
</table>
Cardiac autonomic neuropathy not only causes decline in life comfort but may also be the direct cause of death in diabetic patients. The reported prevalence of diabetic CAN varies, with community-based studies lower rates than clinic-based and hospital-based studies, in which the prevalence may be as high as 100%. Prevalence of CAN, based on assessment of abnormal cardiovascular autonomic tests is variable (5-90%). A Hungarian study revealed definite and early CAN in 44% and 30% of patients respectively. Chanudet et al. found Valsalva ratio and abnormal R-R variation with respiration in 16% and 57% of patients respectively. Zeigler et al. and Hasslacher et al. showed CAN in 17% and 26% of type-1 diabetic patients respectively. In this study, definitive and borderline CAN was present in 20% and 24% of type-1 diabetics respectively as evidenced by abnormal reflex tests. In other words, some form of CAN was present in 44% of the diabetics. These results are comparable with those mentioned in the literature.

Intensive glycemic control is critical in preventing the onset and slowing the progression of CAN. The Diabetes Control and Complication Trial (DCCT) showed that intensive glycemic control reduced the prevalence of autonomic dysfunction by 53%. In an Indian study, CAN was present in 60% of insulin dependent patients. According to a Polish study significant CAN is present in type-1 diabetic patients with short duration of diabetes of upto 10 years illness. Definite CAN, as one of the late complications of diabetes mellitus, suggests poor prognosis. It specifically causes myocardial ischemia, decreased heart rate, and prolongation of QTc interval, abnormal ejection fraction, poor exercise tolerance, unexplained sudden death, and increased mortality.

CAN in long-standing diabetics is caused by parasympathetic (vagal) impairment. Resting tachycardia is an early sign, as is loss of heart rate variation during deep breathing. In this study, other autonomic symptoms were present in 8 (16%) of patients. The DCCT has demonstrated that the tight glycemic control may result in a 60% reduction in the risk of developing clinical neuropathy. According to the DCCT standards, these complications can be reduced by tight glycemic control with mean blood glucose level of 155 mg/dl and HbA1c value of 7.2%.

Most of the patients in this study had very bad glycemic status as evidenced by the HbA1c value. The public sector must carry campaigns in this regard to make public awareness about diabetes mellitus and its complications. The behaviour of the public needs to be modified with an emphasis on compliance with therapy.

**CONCLUSION**

Cardiac autonomic neuropathy is common in long-standing type-1 diabetics. CAN results in prolonged QTc interval that may result in cardiac arrhythmias and even death. Intensive glycemic control improves the cardiac autonomic nerve functions. A public awareness campaign needs to be launched to make diabetics realize the importance of diabetes control and prevent complications related to the cardiovascular system.

**REFERENCES**


Haji Khan Khoharo, Shuaib Ansari, Imran Ali Shaikh and Fatima Qureshi
Cardiac autonomic neuropathy in type-1 diabetes mellitus patients and its association with the duration of disease and glycemic control


