Objective
To determine the frequency of cardiac autonomic neuropathy in type 2 diabetic patients attending diabetic clinic, GMC hospital, Sukkur.

Patients and Methods
This cross-sectional study was carried out at Diabetes Clinic, GMC Hospital, Sukkur from January 2011 to December 2011. A total of 100 type 2 diabetes patients as per criteria recommended by the WHO were included in the study. They were selected irrespective of the duration of disease and therapeutic status. Cardiac autonomic neuropathy (CAN) was detected by various cardiac autonomic function tests like valsalva ratio, heart rate response to standing, BP response to standing, hand grip and heart rate response to breathing. Dizziness on standing was the most commonly encountered symptom. Bladder symptoms and abnormal sweating were other symptoms commonly encountered in this study.

Results
CAN was found in 54% patients. Parasympathetic neuropathy was found in 52% cases and sympathetic neuropathy in 20% cases. 28% patients had two abnormal cardiovascular reflexes. Statistical evaluation revealed retinopathy and microalbuminuria were significantly associated with CAN.

Conclusion
Evaluation of cardiovascular reflexes constitutes an important feasible and reproducible beside clinical technique. Parasympathetic cardiac autonomic function tests are more sensitive for the detection of CAN than sympathetic cardiac autonomic function tests. (Rawal Med J 2012;37:356-359).

Keywords
Autonomic neuropathy, microalbuminuria, retinopathy, diabetes mellitus.

Original Article
Frequency of cardiac autonomic neuropathy in type 2 diabetic patients
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INTRODUCTION
Diabetes mellitus is well known for chronic complications particularly the triad of neuropathy, retinopathy, and nephropathy, which have a close correlation with the metabolic abnormalities characteristic of diabetes. One of the earliest manifestations of diabetic autonomic neuropathy is denervation of cardiovascular system.¹ Hence, assessment of cardiovascular reflexes affords a satisfactory evaluation. Presence of symptoms along with abnormal cardiovascular function tests suggest poor prognosis and increased incidence of silent myocardial infarction, cardiac arrest, sudden death, and adequate response to stressful events, e.g., anesthesia and surgery.¹ There are very few reports about the prevalence of cardiac autonomic neuropathy (CAN) along with correlation with other diabetic complications. To highlight the magnitude of the problem in Sindh the present study was undertaken to determine the frequency of cardiac autonomic neuropathy in type 2 DM and to correlate this with other complications of diabetes like retinopathy, microalbuminuria, and glycated hemoglobin (HbA1c).

PATIENTS AND METHODS
The study was conducted at the Diabetes Clinic, Ghulam Mohammad Mahar Medical College Hospital, Sukkur, Pakistan by selecting 100 documented type 2 diabetes patients as per criteria recommended by the WHO. Patients were selected irrespective of the duration of disease and therapeutic status. Patients with uncontrolled hypertension, heart failure, urinary tract infection, fever, cirrhosis of liver, prostatitis, all of which could have transient proteinuria were excluded from the study. Patients taking drugs such as calcium channel blockers and beta blockers, were stopped two weeks before the study, and they were switched to other drugs such as angiotensin converting...
enzyme inhibitors or angiotensin receptor blockers. Written informed consent was obtained from each patient prior to inclusion in the study.

Mercury sphygmomanometer, electrocardiography machine, and modified mouth piece were used for evaluation of cardiac reflexes. Quantitative estimation of microalbuminuria was done by ELISA. Patients with urine positive for protein were excluded from the study and those negative for protein were tested for microalbuminuria with timed urinary collection (24 hrs) by ELSIA method. The test for microalbuminuria was repeated for 2 times in the 3 months follow-up period. When at least 2 out of 3 test results were positive for microalbuminuria, patients were considered to have persistent microalbuminuria. HbA1c by using HPLC and values more than 7% were taken as elevated. Ophthalmoscopy was done for detection of retinopathy. The tests for autonomic cardiovascular function, performed as beside are described below:

A. Tests reflecting cardiac parasympathetic action:
   i. By the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40mmHg for 14 seconds while a continuous ECG was recorded. The maneuver was performed 3 times with an interval of one minute in-between. The result was expressed as the Valsalva ratio. The mean of three Valsalva ratios was taken as the final value (normal Valsalva ratio 1.21; borderline between 1.11 and 1.20; abnormal < 1.10).
   ii. Heart rate variation during deep breathing: The patient sat quietly and breathed deeply at 6 breaths a minute (5 seconds in, and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a mark used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals during each breathing cycle were measured and converted to beats/minute. The result was than expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute; (normal response > 15 beats/minute, borderline 11 - 14 beats/minute; abnormal response < 10 beats/minute).

iii. Immediate heart rate response to standing: The test was performed with the patient lying quietly on a couch while heart rate was recorded continuously on the ECG machine. The patient was asked to stand up unaided and the point at starting to stand was marked on the ECG. The shortest R-R interval at or around the 15th beat and largest R-R interval at or around the 30th beat after starting to stand was measured with a ruler. The characteristic heart rate response was expressed by 30-15 ratio (which is normal if > 1.04; borderline between 1.01 and 1.03; and abnormal if < 1.00).

B. Tests reflecting cardiac sympathetic action:
   i. BP response to standing: The test was performed by measuring the patient’s BP while he was lying down quietly and again when he stood up. The postural fall after 2 minutes in BP was taken as the difference between systolic BP lying and the systolic BP standing (normal response <10 mmHg; borderline 11-15 mmHg; abnormal >30 mmHg).
   ii. BP Response to sustained handgrip: After instructions in using hand grip of an inflated BP cuff, the subject gripped maximally with his dominant arm for a few seconds; this was repeated thrice. Highest of the 3 readings is called maximum voluntary contraction (MVC). Now the subject was instructed to maintain hand grip. The result was expressed as the difference between the highest DBP during hand grip exercise and mean of 3 DBP readings before hand grip began (normal response >16 mmHg; borderline 11-15 mmHg; abnormal <10 mmHg). All borderline tests were interpreted as normal in the present study.

RESULTS
A total 100 cases were included in the study. There was male (56%) predominating over females (44%). Maximum numbers of patients (32%) were in the age group 51-60 years, followed by age group 41-50 (24%). Younger patients (21-31 years ago group) constituted in insignificant portion (4%) of total patients in the study group. Clinical symptoms of autonomic neuropathy were
assessed on the basis of presence or absence of various symptoms like dizziness, bladder symptoms, abnormal sweating, impotence, diarrhea, and dysphagia.

Table 1. Distribution of type 2 DM cases (%) in various cardiovascular tests (n=100).

<table>
<thead>
<tr>
<th>Cardiovascular tests</th>
<th>Normal</th>
<th>Borderline</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural hypotension</td>
<td>64 (64%)</td>
<td>22 (22%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Effect of sustained hand grip on BP</td>
<td>60 (60%)</td>
<td>24 (24%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Effect of deep breathing on heart rate</td>
<td>52 (52%)</td>
<td>16 (16%)</td>
<td>32 (32%)</td>
</tr>
<tr>
<td>Effect of Valsalva maneuver on heart rate</td>
<td>38 (38%)</td>
<td>40 (40%)</td>
<td>22 (22%)</td>
</tr>
<tr>
<td>Heart rate response to standing (30:15 ratio)</td>
<td>62 (62%)</td>
<td>14 (14%)</td>
<td>24 (24%)</td>
</tr>
</tbody>
</table>

The dizziness on standing was the most frequently occurring symptom (36%), followed by bladder symptoms and abnormal sweating (16% each). Dizziness on standing was not always associated with documented postural hypotension on format test.

Table 2. Distribution of type 2 DM cases (%) in abnormal parasympathetic and sympathetic CV reflexes.

<table>
<thead>
<tr>
<th>Type of Automatic Neuropathy</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic neuropathy</td>
<td>52</td>
<td>52%</td>
</tr>
<tr>
<td>Sympathetic neuropathy</td>
<td>20</td>
<td>20%</td>
</tr>
</tbody>
</table>

Regarding various autonomic functions, heart rate response to deep breathing was the most sensitive test to determine autonomic neuropathy. It is abnormal in 32 (32%) patients, normal in 52 (52%) patients, and borderline in 16 (16%) patients. This was followed by abnormal heart rate response to standing (30:15 ratio), which was abnormal in 24 (24%) patients, normal and borderline response were found in 62 (62%) and 14 (14%) patients respectively. Abnormal hand grip test seen in 16 (16%) patients, normal in 60 (60%) cases, and borderline in 24 (24%) cases. Valsalva ratio was abnormal in 22 (22%) patients, borderline in 40 (40%) cases, and normal in 38 (38%) cases. The least sensitive test to detect autonomic neuropathy was postural hypotension. This was abnormal in 14 (14%) cases, normal and borderline in 64 (64%) cases and 22 (22%) cases respectively (Table 1).

The parasympathetic neuropathy (criterion: result of at least one of the 3 tests of parasympathetic function being abnormal) was seen in 52 (52%) cases while sympathetic neuropathy (criterion: abnormal result in one of the test of sympathetic function) was detected in 20 (20%) cases (Table 2). Majority of Patients (28 Patients, i.e., 28%) had two abnormal cardiovascular reflexes (Table 3).

Microalbuminuria was detected in 36 (36%) cases. Diabetic retinopathy was detected in 10 patients (10%). All of them had microalbuminuria and cardiac autonomic neuropathy (CAN). Statistical analysis revealed that retinopathy was significantly associated (p<0.05) with CAN. Of the 36 patients with microalbuminuria, 28 had cardiac neuropathy and microalbuminuria, the remaining eight patients had microalbuminuria without any abnormal autonomic cardiovascular functional testing. Out of 100 patients, 76 (76%) had raised HbA1C (>7%). Of these patients, 40 had cardiac neuropathy and the rest of the 36 patients had no neuropathy.

Table 3. Distribution of cases according to the number of abnormal cardiovascular reflex test.

<table>
<thead>
<tr>
<th>Abnormal reflex</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One abnormal CV reflex</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Two abnormal CV reflexes</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Three abnormal CV reflexes</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Total number of patients having abnormal CV reflexes</td>
<td>54 (54%)</td>
</tr>
</tbody>
</table>

DISCUSSION
In this study, CAN was found in 54% cases. Parasympathetic neuropathy was found in 52% cases, and sympathetic neuropathy in 20% cases. It is conformity with the finding of Ewing et al. A recent study from Jaipur revealed prevalence of CAN in 58% cases, all of them having parasympathetic neuropathy and sympathetic neuropathy in 20% cases. Heart rate response to deep breathing was the most sensitive test, 32% in this study. This is also in conformity with reports of Mehta et al. Symptoms of CAN were less commonly encountered in the present study. Dizziness on standing was most commonly encountered in 36% patients. Bladder symptoms and abnormal sweating were the other symptoms commonly encountered in this study.
These results are also in conformity with the previous study reports by Neil et al. Microalbuminuria was noted in 36% of patients in our study. It was also statistically significantly associated with CAN. A study from western India reported a higher incidence about 42%. None of the patient in the present study had overt proteinuria. Reports of Mehta et al study also showed a similar pattern of microalbuminuria, i.e., 35% of the patients in their study group. Retinopathy (both background and preproliferative) was detected in 10% of patients in the present study. Mehta et al reported a similar pattern, i.e., around 7.5% of type 2 DM patients had retinopathy. All of the patients with retinopathy had cardiac neuropathy and microalbuminuria in the present study. This is in conformity with previous reports of diabetes with cardiac autonomic neuropathy and microalbuminuria.

Raised HbA1c was found in 40 out of 52 patients with CAN and in 36 out of 46 patients without CAN. There is no statistical difference between these results. This suggests that poor short-term glucose control has no correlation with the prevalence of cardiac neuropathy. The probable explanation of this lack of correlation may be that HbA1c reflects glucose control over the past 2-3 months. Also, as diabetes, is a long duration metabolic disease, a single measurement of HbA1c fails to reveal the exact nature of glycaemic control over the past few years, which is important for the development of neuropathy, retinopathy, and nephropathy. Other metabolic parameters may play an important role in the genesis of long-term microvascular complications of diabetes mellitus. Hypertension is strongly associated with other microvascular complications and there is a strong genetic predisposition for the development of microvascular complications, which may be independent of glycaemic control.

CONCLUSION
We found a prevalence of cardiac autonomic neuropathy of 54%. Symptoms of autonomic neuropathy are not as sensitive as the autonomic function tests to detect cardiac neuropathy. Therefore, assessment of autonomic cardiovascular reflexes provides a satisfactory method for the evaluation of CAN. Parasympathetic cardiac autonomic function tests were more sensitive for the detection of CAN than sympathetic cardiac autonomic function tests. Heart rate response to deep breathing was the most sensitive parasympathetic cardiac autonomic function test which detects CAN, followed by heart rate response to standing and heart rate response to Valsalva maneuver. Cardiac autonomic neuropathy was strongly associated with other microvascular complications of diabetes, viz., microalbuminuria and retinopathy. There was no correlation between glycated hemoglobin and cardiac neuropathy.

REFERENCES