

Cardiovascular Autonomic Neuropathy in Chronic Kidney Diseases

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ABSTRACT

Introduction: This study was conducted to explore cardiovascular autonomic neuropathy and its pattern in chronic kidney disease patients.

Methods: Autonomic function using five standard tests was examined in 20 diabetic patients with CKD, 20 age and sex matched diabetic patients without CKD and 20 age and sex matched controls. Analysis of difference between the autonomic function was done in the three groups using Chi-square test or Fischer's test.

Results: Total 20 (100%) diabetic CKD patients were found to have autonomic neuropathy. Of these, 2 (10%) patients had early parasympathetic damage, 8 (40%) patients had definite parasympathetic damage, and 10 (50%) patients had combined damage. Heart rate response to standing was statistically significant ($p=0.014$) among diabetic CKD patients when compared with diabetic patients without CKD. Combined form of autonomic dysfunction was more frequent in advanced stages of diabetic CKD. Three (42.85%) patients in stage 3 CKD, 4 (66.66%) patients in stage 4 CKD and 5 (71.42%) patients in stage 5 CKD, had combined autonomic failure.

Conclusions: Autonomic neuropathy is common in native Nepalese diabetic CKD patients. Heart rate response to standing is significantly abnormal in diabetic CKD patients in comparison with diabetes mellitus patient without CKD. Severity of autonomic dysfunction increases with severity of CKD.

Key Words: cardiovascular autonomic neuropathy, chronic kidney disease, diabetes mellitus

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. Diabetes is the major cause of CKD. Cardiovascular morbidity and mortality is common in chronic kidney disease patients and may be explained in part by abnormalities in cardiovascular autonomic regulation. Abnormalities may be amenable to intervention to prevent progression and premature cardiovascular morbidity and mortality.

Dysfunction of both the parasympathetic and sympathetic nervous system has been observed in chronic renal failure (CRF) patients. Cardiovascular autonomic neuropathy (CAN) may present with significant impairment in all the heart rate reflex tests and blood pressure response to handgrip tests in patients of CRF.¹ However, the pattern of autonomic dysfunction in CRF is still controversial. Some studies report normal sympathetic dysfunction in patients of CRF while others contradict the presence of such abnormality in this group of patients.² This study explores the autonomic nervous dysfunction in patients of chronic kidney disease.

METHODS

A prospective comparative study was conducted in patients visiting the outpatient and inpatient department of Internal medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal in between July 2005 to July 2006. This included a total of 60 persons that included 20 diabetic patients with CKD, 20 age and sex matched diabetic patients without CKD and 20 age and sex matched healthy controls.

Diabetes Mellitus (DM) was diagnosed as per WHO guidelines. Patients of diabetes irrespective of their duration and control with and without CKD who were 14 years of age or above were included in the study after informed consent. Patients were excluded if they were on drugs known to interfere with autonomic functions, like β -blockers, nitrates, diuretics, tricyclic antidepressants and alcohol, for last one week, or acute on chronic renal failure as suggested by presence of encephalopathy, acidosis or pulmonary edema. Patients with history of recent myocardial infarction and medically unstable patients were excluded.

The diagnosis of CKD was based on NKF/DOQI 2002 guidelines.³ It was supplemented by the following $^{3}d2$ ultrasonographic criteria suggestive of kidney damage wherever required: 1) Increased cortical echogenicity, 2) Cortical thickness $< 12\text{mm}$, 3) Impaired or loss of cortico-medullary junction and 4) Documented kidney size $< 8.5\text{ cm}$. (bilateral)

Creatinine Clearance was calculated by Cockcroft and Gault formula and the CKD patients were grouped from stage 1 to stage 5. Detailed history was taken, physical examination done, relevant laboratory parameters and ultrasound KUB were obtained in all the participants. All the participants underwent the following five standard autonomic function tests:

Tests reflecting parasympathetic damage

1. Heart rate response to Valsalva maneuver:

The patient was asked to sit quietly and then asked to blow into a mouthpiece attached to a manometer, holding it at a pressure of 40mmHg for 15 seconds while a continuous ECG was recorded. The maneuver was repeated three times with one minute interval and result was expressed as: Valsalva ratio = longest R-R interval after the maneuver / shortest R-R interval during the maneuver. The mean of the three Valsalva ratio was taken as the final value.

2. Heart rate (R-R interval) variation during deep breathing:

The patient was asked to breathe deeply at 6 breaths per minute for one minute. ECG was recorded throughout and the period of deep breathing and the onset of each inspiration and expiration were marked on ECG paper. The maximum and minimum R-R intervals during each breathing cycle was measured with a ruler and converted to beats per minute. The result of the test was expressed as the difference between maximum and minimum heart rates for the six measured cycles in beats per minute.

3. Immediate heart rate response to standing (30:15 ratio test):

The test was performed with the patient lying down quietly on a couch while the heart rate continuously recorded on an electrocardiograph. The patient was then asked to stand unaided and the point at starting to stand was marked on ECG paper. The shortest R-R interval at around the 15th beat and the longest R-R interval at around the 30th beat after starting to stand were marked on ECG paper. The shortest R-R interval at around the 15th beat and the longest R-R interval at around the 30th beat after starting to stand were measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratios.

Tests reflecting sympathetic damage

4. Blood pressure response to standing:

The patient's blood pressure was measured with sphygmomanometer while the patient lied quietly and one minute after the patient was made to stand up. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic blood

pressure standing. The test was repeated three times and the mean was calculated.

5. Blood pressure response to sustained hand grip:

The blood pressure of the patient was taken three times before the maneuver. A modified sphygmomanometer was used for sustained handgrip maneuver. The patient was asked to grip the inflatable rubber bag and apply maximum voluntary pressure possible. Reading from the attached mercury manometer was taken during the maximum voluntary contraction. Then the patient was asked to maintain the pressure to 30% of the initial

voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute interval during the handgrip. The result was then expressed as the difference between the highest diastolic pressure during the handgrip exercise and the mean of the three diastolic pressures before the handgrip began.

Interpretation of the tests was based on the work of Ewing and Clarke (Table 1).⁴ The participants in healthy control group were grouped into Group-1, patients with diabetes were grouped into Group-2 and patients with CKD were grouped into Group-3.

Table 1. Interpretation of autonomic function tests as normal, borderline or abnormal

Tests	Predominant autonomic function tested	Normal	Borderline	Abnormal
Valsalva ratio	Parasympathetic	> 1.21	1.11-1.20	< 1.10
Deep breathing test (max-min heart rate beats/min)	Parasympathetic	> 15	11-14	< 10
Heart rate response to standing (30:15 ratio)	Parasympathetic	> 1.04	1.01-1.03	< 1.00
Blood pressure response to standing (fall in BP in mmHg)	Sympathetic	< 10	11-29	> 30
Blood pressure response to sustained hand grip (increase in diastolic BP in mmHg)	Sympathetic	> 16	11-15	< 10

The patients were categorized as "Normal", if all the tests were normal; with "Early parasympathetic", if one of the three tests of parasympathetic function was abnormal; with "Definite parasympathetic", if two or more of the three tests of parasympathetic function were abnormal; and with "Combined damage", if one or both the tests of sympathetic function were abnormal in addition to parasympathetic damage. For the purpose of the above mentioned classification, the borderline tests were interpreted as normal.

A Scoring system as suggested by Bellavere et al⁵ was also utilized to assess the extent of autonomic nervous damage. For each test "0" score was given for normal, "1" for borderline, and "2" for abnormal value. By adding the score of each of the five standard tests of autonomic

function, total autonomic function score was determined for every subject.

Data were entered into the Excel sheet. All analyses were performed using SPSS 11.0 version. The significance of difference in categorical variables between groups was tested with a χ^2 test or Fischer's exact test wherever needed. A P value < 0.05 was considered statistically significant.

RESULTS

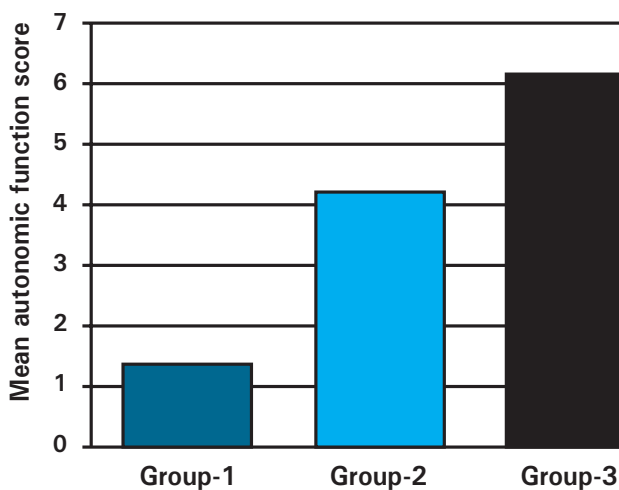
Mean age and sex distribution were similar in all the groups. Mean serum creatinine was higher (4.01 ± 3.10) in CKD patients (Table 2).

Table 2. Baseline Characteristics of the participants

Characteristics	Group-1 (20) (CONTROL)	Group-2 (20) (DM)	Group-3 (20) (DM + CKD)
Mean age in yr.(\pm SD)	55.40 (\pm 10.12)	57.15 (\pm 10.36)	58.35 (\pm 9.17)
Female sex no. - (%)	7 (35)	7 (35)	6 (30)
Smoking (current or past) no.(%)	10 (50)	10 (50)	10 (50)
Mean height – m. (\pm SD)	1.59 (\pm 0.07)	1.59 (\pm 0.07)	1.59 (\pm 0.08)
Mean weight – kg (\pm SD)	63.08 (\pm 8.28)	66.20 (\pm 10.55)	59.43 (\pm 6.48)
Mean BMI- kg/m ² (\pm SD)	24.88 (\pm 4.20)	26.18 (\pm 3.71)	23.34 (\pm 2.71)
Mean pulse- beats/m (\pm SD)	77.60 (\pm 5.09)	82.20 (\pm 12.3)	82 (\pm 12.82)
Mean SBP- mmHg (\pm SD)	127 (\pm 17.6)	139 (\pm 20.89)	131.4 (\pm 31.97)
Mean DBP- mmHg (\pm SD)	81.50 (\pm 12.21)	85.60 (\pm 9.85)	80.1 (\pm 11.9)
Mean urea- mg% (\pm SD)	18.50 (\pm 6.44)	24.50 (\pm 9.17)	68.80 (\pm 31.46)
Mean Creatinine- mg% (\pm SD)	0.66 (\pm 0.20)	0.79 (\pm 0.20)	4.01 (\pm 3.1)
Mean FBS- mg% (\pm SD)	94.10 (\pm 16.23)	114.50 (\pm 46.78)	141 (\pm 62.46)
Mean PPBS- mg % (\pm SD)	108 (\pm 18.03)	169.45(\pm 53.46)	241 (\pm 91.21)

SD = Standard deviation

Mean of the total autonomic function score was 1.35 (\pm 1.31) in Group-1 patients, 4.20 (\pm 1.47) in Group-2, and 6.15 (\pm 1.23) in Group-3 (patients with CKD). Mean of the autonomic function score was found to be higher in patients with CKD ($p < 0.0001$, when compared between groups) reflecting abnormality of increased number of bedside autonomic function tests (Figure 1).



When the three groups were compared with each other with respect to their individual autonomic function test, comparison between Group-1 (healthy controls) and Group-2 (diabetic patients) revealed that except for valsalva test and heart rate response to deep breathing test, all other bedside tests of autonomic function were not found to be significantly ($p = 0.006$ and 0.001 for valsalva test and heart rate response to deep breathing test respectively).

All tests of autonomic function were found to be significantly abnormal in patients with CKD when compared with controls except for Blood Pressure response to standing test ($p = 0.487$). Heart rate response to standing was significantly abnormal in patients with CKD when compared with patients with diabetes mellitus ($p = 0.014$). Other autonomic function tests were not significantly abnormal (Table 3).

Table 3. Number of patients with abnormal autonomic function tests in three groups

	Valsalva ratio	Deep breathing test	Heart rate response to standing	BP response to standing	BP response to sustained hand grip
Group 1	2 (10%)	4 (20%)	-	-	1 (5%)
Group 2	11 (55%)	15 (75%)	2 (10%)	-	3 (15%)
Group 3	10 (50%)	18 (90%)	10 (50%)	2 (10%)	9 (45%)
Group 1 Vs Group 2	P=0.006	P=0.001	P=0.487	-	P=0.065
Group 1 Vs Group 3	P=0.014	P= <0.0001	P= <0.0001	P=0.487	P=0.008
Group 2 Vs Group 3	P= 1.00	P=0.407	P=0.014	P=0.487	P=0.082

Out of 20 CKD patients, 6 had stage-4 CKD, 7 had stage-3 CKD and 7 had stage-5 CKD. None of the patients had stage-1 or stage-2 CKD. All CKD patients (100%) had some form of autonomic failure. The numbers of patients who had early parasympathetic, definite parasympathetic or combined form of autonomic failure were 2 (10%), 8 (40%) and 10 (50%) patients respectively.

Combined form of autonomic failure as assessed by above mentioned tests were seen in five (71.42%) patients of CKD stage 5, while two (28.57%) patients of CKD stage 5 demonstrated definite parasympathetic failure.

In CKD stage 4, two (33.33%) had combined autonomic dysfunction, two (33.33%) had definite and two (33.33%) had early parasympathetic failure. Similarly, in CKD stage 3, three (42.8%) patients had combined, four (57.1%) had definite and none had early parasympathetic failure (Table 4).

Table 4. Number of patients with different patterns of autonomic failure

CKD stage	1	2	3 (%)	4 (%)	5 (%)
Early	-	-	-	2 (33.3)	-
Definite	-	-	4 (57.1)	2 (33.3)	2 (28.5)
Combined	-	-	3 (42.8)	2 (33.3)	5 (71.4)
Total	-	-	7 (100)	6 (100)	7 (100)

In the present study, it is observed that combined form of autonomic failure as assessed by above mentioned tests were more evident at advanced stages of CKD.

None of the patients were found to have sympathetic dysfunction alone. Parasympathetic dysfunction was found to be present with sympathetic dysfunction.

The patients who reported the symptoms of autonomic failure were analyzed to see how many of them demonstrated the tests of autonomic failure. Seventeen patients reported erectile dysfunction, eleven patients reported fainting and two patients reported syncope. In patients reporting erectile dysfunction, eight (47.05%) patients had demonstrated abnormal Valsalva test (P=0.396). Fourteen patients (82.35%) had abnormal deep breathing test (P=0.04), seven (41.17%) patients had abnormal heart rate response to standing (P=0.02). Two (11.76%) patients had abnormal Blood Pressure response to standing (P=0.07) and five patients (29.41%) had abnormal sustained handgrip test (P=0.48).

Heart rate response to standing and heart rate response to deep breathing test were found to be significantly abnormal in patients reporting erectile dysfunction. In patients reporting faintness, six patients had demonstrated abnormal Valsalva test (P=0.306). Nine had abnormal deep breathing test (P=0.178), six patients had abnormal heart rate response to standing (P<0.005). Two patients had abnormal Blood Pressure response to standing test (P=0.03) and six had abnormal sustained handgrip test (P=0.009).

Out of eleven patients reporting syncope, 2 (18.18%) patients had abnormal deep breathing test (P=0.519). One (9.09%) patient had abnormal result in heart rate response to standing (P=0.363), and 1 (9.09%) patient had abnormal sustained handgrip test (P=0.389). None of them had abnormal Valsalva test (P=0.519) or abnormal Blood Pressure response to standing test (P=1.00) (Table 5).

Table 5. Number of patients with autonomic symptoms and abnormal autonomic function tests.

Autonomic symptoms	Valsalva ratio	Deep breathing test	30:15 ratio test	BP response to standing	Sustained hand grip test
Faintness (11*)	6	9	6	2	6
Syncope (2*)	-	2	1	-	1
Erectile dysfunction (17*)	8	14	7	2	5

* total number of the patients with autonomic symptoms

In present study, patients who did not report lightheadedness on standing also had abnormal autonomic function tests.

DISCUSSION

Diabetes Mellitus is a common cause of CKD and autonomic nervous dysfunction is a known complication of diabetes.⁴ An impairment of vagal function has been found associated with diabetic nephropathy.⁶ The presence of cardiovascular autonomic neuropathy (CAN) in patients with diabetes predicts a poor prognosis⁷ and the recognition of CAN is thus crucial. It has been stated that parasympathetic damage occurs more commonly than sympathetic damage.⁷⁻⁹

In our study 20 (100%) diabetic CKD patients were found to have an abnormal result in one or more autonomic function tests. However, Bhatia et al had found evidence of autonomic neuropathy in 29 out of 100 diabetic patients they studied.¹⁰ The frequency of autonomic neuropathy in diabetic patients is between 20 and 30%¹¹ the duration of the illness and metabolic condition play a modifying role which cannot be easily determined^{12,13} in the case of manifest renal insufficiency, the examination shows 100% manifestation. Our finding of 100% patients of CKD having autonomic neuropathy can be explained by kidney involvement playing a modifying role in diabetic autonomic neuropathy. Moreover, we had patients who were CKD stage 3 or more which could explain the higher frequency of autonomic neuropathy in CKD patients. Mean of the total autonomic function score was found to be higher in patients with CKD reflecting failure of relatively more autonomic functions in this group.

Our study did not show any statistically significant sympathetic failure as measured by five bedside autonomic function tests in patients with diabetes when compared with normal healthy people but Valsalva and deep breathing tests were significantly abnormal. Valensi et al had found 63% of diabetic patients to have parasympathetic dysfunction.¹⁴ We found 17 diabetic patients (85%) to have one or more abnormal

parasympathetic tests. Valensi et al had larger sample size (100 patients) and lesser age groups while we had all the patients of age 37 years or more. This could be the reason of us finding higher frequency of diabetic patients having parasympathetic dysfunction.

In our study, diabetic patients when compared to healthy controls had statistically significant value ($P=0.001$) for deep breathing test. This test did not reveal any additional information regarding CAN in patients with diabetic CKD as comparison between these two groups for the test was insignificant. In a study done by Ole May and Hanne Arildsen, deep breathing test was demonstrated to be the most informative test in the assessment of cardiovascular autonomic neuropathy in diabetes.¹⁵

Our patients of CKD demonstrated autonomic dysfunction by all the five standard bedside tests but it was only heart rate response to standing, which was significantly abnormal ($P=0.014$) when compared with diabetic patients without CKD. Hence, we feel that heart rate response to standing help us assessing severity of autonomic failure in diabetes as it may represents additional cause (CKD) for the abnormal response.

Interestingly, in our study both the tests for the sympathetic function did not differ significantly in patients with CKD when compared with patients with diabetes mellitus alone. This finding is consistent with the findings described by Ole May and Hanne Arildsen who demonstrated that no information is gained by adding the sympathetic function tests to the parasympathetic tests.¹⁵

Combined form of autonomic failure was observed in most of the patients of CKD. Combined form was predominant in the stage-5 CKD. This may be explained

by involvement of parasympathetic fibers first in the disease process which later involve the sympathetic fibers, which is also evident from our study that none of our patients were found to have sympathetic dysfunction alone. These findings were consistent with the previous studies demonstrating sympathetic dysfunction only in combination with parasympathetic dysfunction.

Analysis of symptoms of dysautonomia revealed that heart rate response to standing and deep breathing tests were significantly abnormal ($P=0.027$ and $P=0.045$ respectively) in patients reporting erectile dysfunction. Although our patients were having mean age of more than 55.4 year in the three groups, these symptoms couldn't be attributed to increased age alone. Heart rate response to standing, Blood Pressure response to standing and sustained handgrip tests were found to be significantly abnormal in patients reporting fainting.

Deep breathing test has been found to be the most informative test¹⁵ but we did not find it as the most frequently abnormal test in patients reporting faintness, syncope and erectile dysfunction. Our patients reporting syncope, had abnormal deep breathing test (2 patients; $P=0.519$), abnormal heart rate response to standing (1 patient; $P=0.363$), and abnormal sustained handgrip test (1 patient; $P=0.389$). It was interesting to note that none of them had abnormal Valsalva test ($P=0.519$) or abnormal Blood Pressure response to standing test ($P=1.00$). These observations need further study to find out the test, which could be correlated well with autonomic symptoms in patients with diabetic CKD.

Autonomic dysfunction may appear well before the symptoms as our patients who did not report lightheadedness on standing also had abnormal autonomic function tests.

Finally, considering the adverse prognostic implications of autonomic neuropathy reported in CKD patients, further prospective studies involving a larger number of patients are warranted to delineate the factors responsible for the derangement and find remedial measures if possible.

The gold standard in evaluating tests of autonomic neuropathy should ideally biopsies from the autonomic nervous system. But because such biopsies can not be achieved from healthy living persons, another reference must be sought. Although spectral analysis of the ambulatory ECG has been described as the best alternative, this facility is still not available in our set-up. Also diabetes patients with CKD were considered to be enrolled because of the availability of these patients and hence we did not get to compare the autonomic function tests in patients with CKD due to other causes. It must be pointed out that the high frequency of symptoms and signs of autonomic neuropathy seen in this study may not be extrapolated to the entire diabetic CKD, as the group studied was a selective ones and it is a hospital based study.

CONCLUSIONS

Our study shows that CAN is common in diabetic CKD. Heart rate response to standing is found to be frequently abnormal test in diabetic CKD. Combined autonomic failure is found to be predominantly involved and more in advanced stage of CKD. Parasympathetic dysfunction was present whenever sympathetic function was abnormal. Autonomic function tests did not correlate with the symptoms of dysautonomia. Information on autonomic neuropathy among patients with CKD in earlier stages may provide a mean to follow CKD progression.

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