

# Prevalence of autonomic dysfunction among pre-dialysis chronic kidney disease patients in a tertiary hospital, South East Nigeria

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## Abstract

**Background:** Autonomic dysfunction (AD) has been recognized as an important contributor to the poor outcome in chronic kidney disease (CKD) patients. Several studies have reported abnormalities in heart rate variability (HRV) among these patients.

**Objectives:** To determine the prevalence of Autonomic Dysfunction (AD) in pre-dialysis Chronic Kidney Disease (CKD) patients in a tertiary hospital in South East Nigeria.

**Methods:** A cross sectional study of eighty chronic kidney disease patients attending the renal unit out-patient in the University of Nigeria Teaching Hospital (UNTH) Enugu was carried out. Forty subjects, drawn randomly, who had no kidney disease served as control. Autonomic function was assessed with non – invasive cardiovascular tests including, measurement of resting tachycardia, orthostatic hypotension, heart rate response (HRR) to standing test, heart rate response to Valsalva manoeuvre and heart rate response to respiration.

**Results:** With the battery of 5 tests used to assess AD, the frequency of autonomic dysfunction in pre-dialysis chronic kidney disease patients was 51.3% compared to 7.5% in the control group. Heart rate response to standing was the most sensitive test to detect AD in this group of subjects.

**Conclusion:** AD is a common problem among pre-dialysis CKD patients in Nigeria.

**Keywords:** Prevalence, autonomic dysfunction, pre-dialysis.

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## Introduction

In Nigeria and other parts of Africa, CKD is a common disease accounting for a significant proportion of patients dying in a typical hospital medical ward<sup>1</sup>. It is a major cause of cardiovascular morbidity and mortality in Nigeria, and most parts of Africa<sup>2</sup>. CKD is an important indirect cause of congestive cardiac failure, and other

cardiovascular diseases particularly myocardial infarction, sudden cardiac death, hypertension and stroke. Systolic and diastolic dysfunctions are common in CKD<sup>3</sup>.

The pathophysiology of cardiovascular disease (CVD) in patients with CKD remains undetermined. Risk factors such as hypertension, diabetes and hyperlipidemia are well recognized as important mechanisms<sup>3</sup>. Other risk factors, including autonomic dysfunction, have now been identified as contributors to the increased CVD in patients with CKD<sup>4</sup>. Several studies have reported a reduction in heart rate variability (HRV) and the development of complex arrhythmias in CKD<sup>5</sup>. Autonomic neuropathy as part of uraemic neuropathy has been studied in both pre-dialysis CKD patients and maintenance haemodialysis patients. In pre-dialysis CKD patients, according to earlier reports, autonomic neuropathy is in the order

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of 40-63%<sup>6</sup>. It is also said to be much more frequent in males than females<sup>7</sup>, more related to severity and duration of CKD<sup>8</sup> than the cause of the renal failure. We set out in this study to determine the actual prevalence of autonomic dysfunction in pre-dialysis CKD patients, in a tertiary hospital located in the South Eastern part of Nigeria.

## Methods

We evaluated 80 consenting pre-dialysis CKD patients (stages 3–5), drawn consecutively from the medical out-patient department and medical wards of University of Nigeria Teaching Hospital (UNTH) over a one year period. Patients with severe cardiac disease, cancer, diabetes, collagen and demyelinating diseases, left ventricular systolic dysfunction, or a history of stroke were excluded. All medications with autonomic neuropathy-like symptoms were excluded except the following anti-hypertensive medications: calcium channel blockers, centrally acting anti-hypertensive drugs, diuretics and hydralazine as they are very important components of the patients' medication and we could not afford to withdraw them. This is a limitation to the study. Forty sex and age matched consenting individuals were drawn from amongst medical students, doctors, nurses, hospital staff, patients and patient's relations from the general out-patients dept, without symptoms and signs suggestive of renal failure, diabetes mellitus, or heart disease. The study was approved by the Ethics Committee of the University of Nigeria Teaching Hospital, Enugu, and all subjects signed an informed consent before being included in the protocol.

## Study design

This was a cross-sectional study in which we evaluated autonomic nervous function in patients with CKD on conservative treatment and compared the results to a control group. Autonomic neuropathy was assessed using a modified Ewing and Clarke's method used by Demir et al<sup>9</sup> which consisted of five tests: Resting tachycardia, Heart rate response (HRR) to Valsalva manoeuvre, HRR to deep breathing, HRR to standing, blood pressure response to standing. The parasympathetic function was assessed using resting tachycardia, HRR to Valsalva manoeuvre, HRR to deep breathing and HRR to standing. Sympathetic function was assessed with blood pressure response to standing (orthostatic hypotension). The su-

pine blood pressure was taken after 10 minutes of rest, with the cuff of the mercury sphygmomanometer (Accosson model, with standard cuff size 15cm x 55cm) applied to the right upper arm of the subject. The approximate systolic blood pressure was obtained by palpation. The cuff was then deflated and re-inflated to about 10mmHg above the approximate systolic value. Phases I and V Korotkoff's sounds were used for systolic and diastolic blood pressure reading respectively. Electrocardiography (ECG) was done to assess resting heart rate, using a triple lead rhythm strip (Cardiette Autoruler, with facilities for 12 lead electrocardiography). ECG monitoring was done while the patient was lying supine and forcibly exhaling for 10 seconds against a fixed resistance with an open glottis. The patient blew into an improvised sterile mouth piece (Empty 20ml syringe) attached to a mercury sphygmomanometer maintaining a pressure of 40 mmHg for 10 seconds<sup>9</sup>. The longest and shortest R-R intervals were measured with a ruler. The Valsalva Ratio (VR) was calculated;  $VR = \frac{\text{Longest RR (after the Valsalva manoeuvre)}}{\text{Shortest RR (During the Valsalva manoeuvre)}}$ .

The patient was then asked to breathe deeply and regularly at a rate of 6 breaths per minute while sitting up. The electrocardiogram was recorded over three breathing cycles. The average heart rate during deep expiration was subtracted from that during deep inspiration. The average difference found for 6 consecutive inspiration-expiration cycle was taken as the final result<sup>9</sup>. The subject was then asked to stand up from the lying position while the electrocardiogram was recorded. The point of standing was marked on the recording paper. ECG monitoring at a paper speed of 25mm/sec was performed after a rest period in the supine position of 10 minutes, starting from 1 minute before until 30 seconds after the subject started to stand. The ratio of the R-R interval of the 30<sup>th</sup> beat after standing (in millimetres) to that of the 15<sup>th</sup> beat was recorded<sup>9</sup>.

Blood pressure of the subject, obtained as already described above, was recorded after 10 minutes of supine rest and after 2 minutes in the standing position. If standing was followed by a reduction in systolic blood pressure of at least 20mmHg or in diastolic blood pressure of at least 10mmHg within 3 minutes, orthostatic hypotension was accepted to be present<sup>9</sup>.

Other values obtained during the procedure were inter-

preted as follows<sup>9</sup>: Heart rate response to Valsalva manoeuvre; Normal  $\geq 1.21$ , borderline =1.11-1.20, abnormal  $\leq 1.10$  Heart rate response to deep breathing: Normal  $\geq 15$ bpm, borderline =11-14bpm, abnormal  $\leq 10$ bpm. Heart rate response to standing: Normal  $\geq 1.04$ , borderline =1.01-1.03, abnormal  $\leq 1.01$ . Resting tachycardia: Heart rate  $\geq 100$ /minute, at rest.

The values for the autonomic function tests are as shown in table 1. Each normal test was scored 0, a borderline test was scored ½ and an abnormal test was scored 1. The 5 test results were summed up with a maximum total score of 5. A total score of 3 and above was considered evidence of autonomic neuropathy<sup>10</sup>.

**Table 1: Values of Autonomic Function Test (Adapted from Demir et al (9)).**

Test	Normal(0)	Borderline(1/2)	Abnormal (1)
HRR to standing (30/15 ratio)	$\geq 1.04$	1.01 – 1.03	$\leq 1.0$
HRR to deep breathing (Max.-Min. beats/min)	$\geq 15$	11 – 14	$\leq 10$
HRR to Valsalva manoeuvre (Valsalva ratio)	$\geq 1.21$	1.11 – 1.20	$\leq 1.10$
Resting Tachycardia	$<100$		$\geq 100$
Orthostatic hypotension	$<20$ systolic and $<10$ diastolic		$\geq 20$ systolic or $\geq 10$ diastolic or both

### Laboratory evaluation

Venous blood was collected from the subjects without using a tourniquet. The results of the following tests were obtained from the patients: Serum electrolytes – sodium, potassium, chloride, bicarbonate, calcium, phosphate, serum urea and creatinine, fasting blood glucose and 2 hours post- prandial glucose estimations, packed cell volume. For serum calcium and phosphate estimation, serum calcium – phosphate product above 55mg/dl was taken as abnormal and reflective of CKD<sup>11</sup>. An auto analyzer was used to analyze the blood for serum electrolytes, urea and creatinine. The GFR was estimated using the Cock-

croft/Gault formula<sup>12</sup>:  $GFR = [140 - \text{Age (years)}] \times \text{weight (kg)} / 0.8 \times \text{serum creatinine } (\mu\text{mol/l})$ . For women, this was multiplied by a factor 0.85 to get the GFR.

Abdominal ultrasound for kidney sizes and echo texture was also done.

The diagnosis of CKD was based on the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (KDOQI/ NKF);  $eGFR < 60 \text{ ml/min/1.73 m}^2$  and/or at least one marker of renal parenchymal damage (e.g., proteinuria), present for a period of  $\geq 3$  months<sup>4</sup>.

## Data analysis

The SPSS version 11.5 statistical software was used for data analysis. For continuous variables, mean value and standard deviation were calculated and the mean compared using independent t- test. Categorical variables were compared using the non-parametric tests – chi-square. All tests were two tailed with  $p < 0.05$  taken as statistically significant.

## Results

### Demographic data

The age and sex distribution was similar in both CKD and control groups (table 2). Most of the patients and control subjects were within the age range of 20-49 years, especially between 20-29 years. There were 39 male and 41 female patients giving a male to female ratio of 1: 1.05.

There were 21 male and 19 female control subjects giving a male to female ratio of 1.1:1. They were properly matched as there was no statistically significant difference among them.

In the CKD group, 30/80 patients were in stage 3 (37.5%; mean eGFR equal to  $44.3 \pm 7.6 \text{ ml/min/1.73 m}^2$ ), 32/80 patients were in stage 4 (40%; mean eGFR equal to  $22.5 \pm 4.2 \text{ ml/min/1.73 m}^2$ ), and 18/80 patients were in stage 5 (22.5%; mean eGFR equal to  $13.3 \pm 2.5 \text{ ml/min/1.73 m}^2$ ). In the control group, the mean eGFR was  $90.6 \pm 24.4 \text{ ml/min/1.73 m}^2$ .

Aetiologies of CKD were chronic glomerulonephritis 41 (51.25%), hypertensive nephropathy 21 (26.25%), obstructive uropathy 7 (8.75%), undetermined cause 6 (7.5%), autosomal dominant polycystic kidney disease 3 (3.75%), and chronic pyelonephritis 2 (2.5%).

**Table 2: Age and sex distribution of patients and control**

Age	Patient	Male N (%)	Female N (%)	X <sup>2</sup>	P	Control	Male N (%)	Female N (%)	X <sup>2</sup>	P
<19	2	0	2(2.5)			1	0	1(2.5)		
20-29	19	9(11.25)	10(12.5)			14	8(20)	6(15)		
30-39	17	6(7.5)	11(13.75)			11	6(15)	5(12.5)		
40-49	15	9(11.25)	6(7.5)	5.736	.333	4	2(5)	2(5)	.811	.368
50-59	17	8(10)	9(11.25)			7	3(7.5)	4(10)		
60-69	10	7(8.75)	3(3.75)			3	2(5)	1(2.5)		
Total	80	39(48.75)	41(51.25)			40	21(52.5)	19(47.5)		

\*N – Number of cases.

### Age and sex distribution of patients with autonomic neuropathy.

Table 3 demonstrates the age and sex distribution of patients with autonomic neuropathy. It shows that though more men 22(53.66%) than women 19(44.34%) had autonomic neuropathy among the patient population, this

was not statistically significant. Patients between the ages of 30-39 and 60-69 were the most affected by autonomic neuropathy, 11(26.8%). The least affected were patients within the age group 20-29.

Anthropometric and physiologic values for autonomic neuropathy present (AN+ve) and autonomic neuropathy absent (AN-ve) patients.

**Table 3: Age and sex distribution in autonomic neuropathy positive patients**

Age	M N (%)	F N (%)	Total N (%)	X <sup>2</sup>	P value
20 – 29	4(18.2)	1(5.3)	5(12.2)		
30 – 39	5(22.7)	6(31.6)	11(26.8)		
40 – 49	4(18.2)	3(15.8)	7(17.1)	3.939	.414
50 – 59	5(22.7)	2(10.5)	7(17.1)		
60 – 69	4(18.2)	7(36.8)	11(26.8)		
Total	22(53.66)	19(46.34)	41(100)		

Table 4 shows that there are no statistically significant differences in the mean age, weight, height, BMI, and blood pressure of the patients who had autonomic neuropathy and those who did not.

**Table 4: Anthropometric and physiologic values for AN +ve and AN-ve patients**

Variables	AN +ve Number (%) 41(51.3)		AN –ve Number (%) 39(48.8)		p value
	Mean	SD	Mean	SD	
Age	41.81	1.38	41.11	1.54	.643
Weight	65.45	11.08	65.52	12.61	.341
Height	1.67	0.10	1.69	0.09	.789
BMI	23.34	3.04	22.69	2.90	.721
Blood pressure					
Standing systolic	140.68	18.09	147.08	17.90	.968
Standing diastolic	82.84	12.41	89.44	10.94	.262
Supine systolic	146.77	17.61	146.94	16.53	.754
Supine diastolic	88.29	12.19	87.94	11.36	.440

AN +ve = Autonomic neuropathy present, AN –ve = Autonomic neuropathy absent

### Abnormal autonomic function test in patients and control

Table 5 shows that the frequency of abnormal HRR to standing, breathing, valsalva manoeuvre, and orthostatic hypotension were significantly commoner in the patients

compared with controls,  $p < 0.001$  for the first three, and 0.014 for orthostatic hypotension. Resting tachycardia did not demonstrate statistical significance,  $p = 0.34$ . It also showed that 41 (51.3%) of the patients had autonomic neuropathy, while 3 (7.5%) of the controls had it,  $p < 0.001$ .

**Table 5: Frequencies of abnormal autonomic function tests among patients and control.**

Autonomic function test	Patient n = 80 N (%)	Control n = 40 N (%)	X <sup>2</sup>	P value
Autonomic dysfunction	41(51.3)	3(7.5)	21.979	0.000
HRR to standing	64(80)	19(47.5)	17.592	0.000
HRR to breathing	63(78.8)	5(12.5)	55.767	0.000
HRR to Valsalva manoeuvre	49(61.3)	3(7.5)	43.757	0.000
Resting tachycardia	16(20.0)	2(5.1)	4.517	0.340
Orthostatic hypotension	11(13.8)	0	6.055	0.014

HRR: heart rate response

### Discussion

This study aimed at determining the prevalence of autonomic dysfunction in pre-dialysis CKD patients who are in stage 3 to stage 5, as dialysis has added autonomic dysfunction to the burden of CKD. The study revealed that autonomic dysfunction is common among predialysis CKD patients in Nigeria with a prevalence of 51.3%. This is similar to some other studies previously done. Sanya in Nigeria reported a prevalence rate of 65% among CKD patients<sup>10</sup> while other workers outside Nigeria reported prevalence rates of 40% – 63% in predialysis CKD patients.<sup>6</sup> Demir et al however reported a prevalence rate of 87.5% among 16 CKD patients already receiving HD.<sup>9</sup> The high prevalence value reported by Demir et al may be

because most of the patients they used in the study had been in stage 5 CKD for a long time, and already getting haemodialysis, a known cause of AD.

When patients with autonomic neuropathy were compared with those without, statistically significant differences were seen in four of the five tests used to assess presence of autonomic neuropathy, table 5. This contrasts to what Demir and colleagues reported. Apart from resting tachycardia which did not demonstrate statistical difference between the patients and the controls, all the other tests used to assess for autonomic dysfunction showed significant differences. In their study however, resting tachycardia was defined as resting heart rate above

100 beats/min, while resting heart rate of 100 beats/min was included as resting tachycardia in our study. Infact 3 out of 9 of their patients with parasympathetic dysfunction had heart rates of 100 beats per min.<sup>9</sup>

Most of the patients with autonomic neuropathy (95%) had abnormal heart rate response (HRR) to standing. This was found to be the most sensitive test in detecting autonomic neuropathy. This corresponds to earlier reports by Demir, et al and Sanya. Demir et al recorded abnormal HRR to standing in 87.5% of their patients with autonomic neuropathy<sup>9</sup> while Sanya recorded abnormal HRR to standing in 87% of his patients. However, unlike Demir et al who recorded abnormal HRR to respiration and Vasalva among patients with autonomic neuropathy in the order of 62.5% and 18.7% respectively, our study recorded 92.7% and 85.4% respectively, while Sanya recorded 61.5% and 81.8% respectively. Some of these differences may be explained in part by the fact that the patients used in our study were pre-dialysis patients while Demir et al only used patients on dialysis.<sup>9</sup> Our work showed that the significance of the HRR tests in descending order is: HRR to standing, HRR to respiration and then HRR to Vasalva. This matched the pattern found in the study by Demir et al, but does not correspond with the findings of Sanya.<sup>9,10</sup> Sanya found HRR to Vasalva more significant than HRR to respiration.

In our study, resting tachycardia was not found to be significant as a test for autonomic neuropathy. Autonomic dysfunction in CKD patients was not significantly affected by all the anthropologic and physiologic values tested.

The study revealed that CKD commonly involved the young adults, with peak prevalence between the ages of 20-29 years. This is in keeping with the previous observations of relative youth of CKD patients in tropical West Africa. The youths are often in their second and third decades of life, with bilaterally shrunken kidneys and in end stage renal failure.<sup>13</sup> We noted the slight female preponderance in this study unlike in previous studies.<sup>14,15</sup> This observation however was not statistically significant.

### Study limitation

The limitation of our study is the inclusion of patients on crucial anti-hypertensive medications that have autonomic neuropathy like side effects. This could be a basis for

further study in which these medications could be used as variables and controlled for. Severity of symptoms with medication could also be assessed.

### Conclusion

AD is a common problem among pre-dialysis CKD patients in Nigeria, with a frequency in pre-dialysis chronic kidney disease patients, of 51.3%. Heart rate response to standing was the most sensitive test to detect AD in this study.

### Conflict of interest

None.

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