ORIGINAL ARTICLE

Assessment of some cardiovascular risk factors in predialysis chronic kidney disease patients in Southern Nigeria

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ABSTRACT

Background: Cardiovascular risk factors are responsible for cardiovascular disease and rapid progression of chronic kidney disease (CKD) to end-stage renal disease. Prompt evaluation, modification, and treatment of these factors in predialysis patients will reduce morbidity and mortality. This study assessed some cardiovascular risk factors in predialysis CKD patients in a tertiary hospital in Southern Nigeria. **Patients and Methods:** This was a case–control study that involved 76 consecutive predialysis CKD patients and 38 age- and sex-matched controls without CKD over 1 year period. Both groups were assessed for cardiovascular risk factors, and comparisons were made. A *P* value of < 0.05 was taken as significant. **Results:** The mean ages of the CKD versus control group were 48.00 ± 15.28 versus 45.34 ± 15.35 years. The male:female ratio was 1.7:1 for both groups. The common etiologies of CKD in this study were hypertension 30 (39.5%), diabetes mellitus 23 (30.3%), and chronic glomerulonephritis 19 (25%). There were 38 (50%) in CKD stage 3, 31 (40.8%) in CKD stage 4, and 7 (9.2%) in CKD stage 5. The common cardiovascular risk factors found in the CKD versus control were hypertension (96.1% vs. 42.1%), anemia (96.1% vs. 23.7%), left ventricular hypertrophy (77.6% vs. 23.7%), dyslipidemia (67.1% vs. 39.5%), hypocalcemia (60.1% vs. 18.5%), hyperphosphatemia (63.2% vs. 0%), and hyperuricemia (57.9% vs. 15.8%). These risk factors were significantly higher in CKD group. Hyperphosphatemia and hypoalbuminemia significantly increased across CKD stages 3–5. Anemia was significantly more common in males whereas dyslipidemia was more common in female CKD patients. **Conclusion:** Cardiovascular risk factors were highly prevalent in predialysis CKD subjects even in early stages. Hypoalbuminemia and hyperphosphatemia significantly increased across the CKD stages 3–5 whereas anemia and dyslipidemia showed significant gender differences. Cardiovascular risk factors should be treated early in predialysis CKD patients.

Key words: Cardiovascular, chronic kidney disease, Nigeria, predialysis, risk factor

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of hospitalization and death in chronic kidney disease (CKD) patients at all stages.[1] The process of CVD is thought to commence early in CKD because it is common in patients commencing renal replacement therapy (RRT).[2] Foley *et al.* found that only 15% of end-stage renal disease (ESRD) patients commencing therapy were considered to have normal left ventricular structure and function by echocardiographic criteria.[3] In ESRD patients, CVD mortality rate is about 10–20 times higher than in the general population.[4]

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.171616

How to cite this article: Adejumo OA, Okaka EI, Madumezia G, Okwuonu CG, Ojogwu LI. Assessment of some cardiovascular risk factors in predialysis chronic kidney disease patients in Southern Nigeria. Niger Med J 2015;56:394-9.

The adverse cardiovascular event rates remain high in patients with CKD after adjustment for conventional CVD risk factors such as hypertension, diabetes mellitus, smoking, male gender, and dyslipidemia.[5] The progressive cardiovascular risk associated with worsening renal function may be explained by other factors referred to as nontraditional risk factors which include albuminuria, inflammation, anemia, malnutrition, homocysteinemia, and calcium and phosphate abnormalities.

Despite the established awareness of their high cardiovascular risk, CKD patients still have inadequate risk factor modification and intervention.[6] Prompt and comprehensive evaluation of CVD risk factors and modification will reduce morbidity and mortality in predialysis patients. This will slow the progression of CKD to ESRD and also reduce the huge financial burden on these patients, especially in developing countries such as Nigeria where RRT is not subsidized by the government and majority of patients cannot afford or sustain RRT.

The aims of this study were to determine the prevalence and pattern of some cardiovascular risk factors in relation to gender and CKD stage, and to compare these risk factors in the CKD patients and control subjects with normal renal function.

PATIENTS AND METHODS

The Renal Unit, Department of Internal Medicine, University of Benin Teaching Hospital, Benin, Edo State, receives referrals from within and outside the state of location. An average of 12 newly diagnosed CKD patients is seen in the Unit monthly while about same number commence maintenance hemodialysis monthly.

This was a case–control study spanning over 1 year period (January 2013 to December 2013). It involved 76 consecutive predialysis CKD patients and 38 age-matched controls who fulfilled inclusion criteria for this study. The sample size was derived with Fleiss formula for case–control study using prevalent rate of anemia as a cardiovascular risk factor in CKD.[7]

The following were used to determine the minimum sample size: Confidence interval = 95%, power of study = 80%, ratio of cases to control of 2:1, percentage of control exposed: 51.8, and percentage of cases exposed: 87.[8,9] This formula gave a minimum sample size of 38 for cases and 19 for control. Ethical approval was from obtained University of Benin Teaching Hospital's Ethics Committee on research, and informed consent was obtained from participants. Cardiovascular risk factors were assessed in the two groups, and comparisons were done.

Inclusion criteria for CKD subjects were adults aged ≥18 years, patients with CKD stages 3-5 yet to commence dialysis and those who gave informed consent to participate in the study. CKD patients already on dialysis therapy, those with HIV, hepatitis B or hepatitis C infection, those with chronic liver disease; those with cardiomyopathy; those with gout; and those on lipid or uric acid lowering medications were excluded from the study. Inclusion criteria for control subjects were adults aged ≥18 years with normal renal function, absence of chronic liver disease, absence of gout, negative hepatitis B, hepatitis C, and HIV status, and not being on lipid or uric acid lowering medications.

All subjects were interviewed using a structured questionnaire and then physically examined. Demographic information including age, sex, and history of renal symptoms was sought, and etiology of CKD was determined. Weight was measured using a bathroom weighing scale with subjects wearing light clothing. Height was measured using a stadiometer to the nearest centimeter with subjects not wearing shoes. The body mass index (BMI) was calculated using the formula: weight (kg)/height^2 (m^2), and blood pressure (BP) readings using standard protocols were taken and recorded

About 10 ml of venous blood was obtained from subjects after an overnight fast of 8 h to perform biochemical tests which included fasting serum lipids, serum albumin, calcium, phosphate, and uric acid. The packed cell volume (PCV) was determined by centrifugation method. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease which has been validated in Nigerians.[10]

Two-dimensional echocardiography was done using ALOKA 4000 ultrasound imaging system manufactured by ALOKA Co Ltd. The left ventricular mass was calculated using the American Society of Echocardiography formula modified by Lang *et al*.[11] Left ventricular mass was divided by the body surface area (BSA) to determine the left ventricular mass index (LVMI). The BSA was determined using the formula:

$$BSA = (0.001) \times (71.84) \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}.$$[12]

Definition of values

Hypertension was defined as BP greater or equal to 140/90 mmHg or previous established diagnosis of hypertension.[13]

Obesity was defined as BMI ≥30 kg/m^2.[14]

Dyslipidemia was defined as any or combination of the following: Total cholesterol >200 mg/dl, high-density lipoprotein cholesterol (HDL-C) <50 mg/dl in females, and <40 mg/dl in males low-density lipoprotein cholesterol (LDL-C) >130 mg/dl; triglyceride (TG) >150 mg/dl.[15]

Anemia was defined as PCV <36% in females and <39% in males using the WHO criteria.[16]

Hyperuricemia was defined as uric acid >7.0 mg/dl in males and >6.0 mg/dl in females.[17]

Hypocalcemia was defined as serum calcium <8.2 mg/dl.[18]

Hyperphosphatemia was defined as serum phosphate >4.8 mg/dl.[18]

Elevated serum calcium–phosphate product (CaxPP) was defined as CaxPP >55 mg^2/dl^2.[19]

Hypoalbuminemia was defined as serum albumin <35 g/L.[20]

Left ventricular hypertrophy (LVH) was defined in absolute terms as LVMI >134 g/m^2 in men and >110 g/m^2 in women.[12]

The estimated GFR (eGFR) was used in staging CKD as follows: Stage 3 - GFR of 30–59 ml/min, stage 4 - GFR of 15–29 ml/min, and stage 5 - GFR <15 ml/min.[21]

Data analysis

Data generated were analyzed using the Statistical Package for Social Sciences version 17.0. (SPSS Inc, Chicago). Results were presented in tabular forms. Univariate analysis was used in description of demographic characteristics of the study population. Continuous variables were presented as mean and standard deviation for unskewed data, median, and interquartile range for skewed data. Student's *t*-test was used to compare mean values of the sub-groups for those with unskewed data whereas Mann–Whitney U-test was used to compare skewed data. Discrete variables were presented as frequency and percentages. Chi-square test was used to determine the significance of the observed differences for categorical variables while Chi-square with trend was used where the categorical variable was ordinal. $P < 0.05$ was taken as significant.

RESULTS

This study involved 76 CKD patients and 38 age- and sex-matched controls without CKD. The male:female ratio was 1.7:1 for both CKD and control groups. Majority of the CKD subjects were ≤65 years, and this accounted for 66 (86.9%) of the CKD subjects. The common etiologies of CKD were diabetes mellitus, hypertension, and chronic glomerulonephritis in 23 (30.3%), 30 (39.5%), and 19 (25%), respectively. Thirty-eight (50%) were in CKD stage 3, 31 (39.5%) in stage 4, and 7 (9.2%) in stage 5 [Table 1].

There was no significant difference between the mean age and BMI of the CKD and control groups. The mean systolic BP, diastolic BP, serum uric acid, phosphate, and CaxPP were significantly higher in the CKD group compared to the control group ($P < 0.001$). The median value of TG, LDL-C, creatinine, and LVMI were significantly higher in the CKD group as compared to the control group with *P* values of < 0.001 except LDL-C that was 0.024. The mean serum calcium, median value of serum albumin, and eGFR were significantly lower in the CKD group compared to the control group ($P < 0.001$) [Table 2].

The prevalence of all the cardiovascular risk factors assessed in this study were significantly higher in the CKD group compared to the control group with *P* values of <0.001 except dyslipidemia that was 0.005 Although the prevalence of obesity was higher in the CKD group, it was not significant ($P = 0.737$) [Table 3].

Table 1: Characteristics of the study population

Parameters	CKD group (*n*=76) *n* (%)	Control group (*n*=38) *n* (%)	*P*
Gender			
Male	48 (63.2)	24 (63.2)	1.00
Female	28 (36.8)	14 (36.2)	
Age (years)			
≤65	66 (86.9)	33 (86.9)	1.00
>65	10 (13.1)	5 (13.1)	
CKD etiology			
Diabetic mellitus	23 (30.3)		
Hypertension	30 (39.5)		
Chronic glomerulonephritis	19 (25)		
Others	9 (7.2)		
CKD stage			
3	38 (50)		
4	31 (40.8)		
5	7 (9.2)		

CKD – Chronic kidney disease

Table 2: Comparison of parameters between CKD and control groups

Parameters	Mean (SD)/median (IQR)		*P*
	CKD (*n*=76)	Control (*n*=38)	
Age (years)	48.00 (15.28)	45.34 (15.35)	0.386
BMI (kg/m^2)	24.59 (4.27)	25.84 (3.89)	0.121
Systolic BP (mmHg)	163.95 (30.51)	126.68 (17.34)	<0.001*
Diastolic BP (mmHg)	98.68 (21.5)	80.55 (10.56)	<0.001*
Serum uric acid (mg/dl)	7.60 (3.38)	5.21 (2.56)	<0.001*
Serum albumin (mg/dl)	37.0 (6.40)	46.0 (7.40)	<0.001*
Serum calcium (mg/dl)	7.79 (1.01)	9.30 (0.98)	<0.001*
Serum phosphate (mg/dl)	5.09 (0.87)	4.04 (0.87)	<0.001*
CaxPP (mg^2/dl^2)	46.68 (10.16)	39.69 (7.68)	<0.001*
Serum TC† (mg/dl)	181 (50)	182.8 (59)	0.479
Serum TG† (mg/dl)	105 (68)	63.4 (55.4)	<0.001*
Serum HDL-C† (mg/dl)	50 (22)	77.8 (39.5)	<0.001*
Serum LDL-C† (mg/dl)	113 (46)	89.7 (73.4)	0.024*
Serum creatinine† (mg/dl)	2.5 (5.7)	0.92 (0.28)	<0.001*
eGFR† (ml/min/1.72 m^2)	29.42 (24.6)	93.32 (67.8)	<0.001*
LVMI† (g/m^2)	186.8 (98.5)	110.8 (37.8)	<0.001*

*Significant $P<0.05$; †Skewed data expressed in median (IQR) and Mann–Whitney U-test used: IQR – Interquartile range; HDL-C – High-density lipoprotein cholesterol; TG – Triglyceride; LDL-C – Low-density lipoprotein cholesterol; TC – Total cholesterol; SD – Standard deviation; BP – Blood pressure; CaxPP – Calcium phosphate product; CKD – Chronic kidney disease; LVMI – Left ventricular mass index; BMI – Body mass index; eGFR – Estimated glomerular filtration rate

The prevalence of obesity significantly decreased across CKD stages 3–5 ($P = 0.009$) while that of hypoalbuminemia and hyperphosphatemia increased significantly across CKD stages 3–5 with P values of 0.006 and 0.001, respectively [Table 4].

The prevalence of dyslipidemia was significantly higher in females ($P = 0.03$) while anemia was significantly higher in males ($P = 0.02$). There was no significant difference in the prevalence of other cardiovascular risk factors between the genders [Table 5].

Table 3: Comparison between prevalence of cardiovascular risk factors in CKD and control groups

Cardiovascular risk factor	CKD (*n*=76) *n* (%)	Control (*n*=38) *n* (%)	*P*
Dyslipidemia	51 (67.1)	15 (39.5)	0.005*
Hypertension	73 (96.1)	16 (42.1)	<0.001*
Hyperuricemia	44 (57.9)	6 (15.8)	<0.001*
Hypoalbuminemia	27 (35.5)	0 (0)	<0.001*
LVH	59 (77.6)	9 (23.7)	<0.001*
Obesity	14 (18.4)	8 (21.1)	0.737
Hypocalcemia	46 (60.1)	7 (18.5)	<0.001*
Hyperphosphatemia	48 (63.2)	0 (0)	<0.001*
Anemia	73 (96.1)	9 (23.7)	<0.001*
Elevated CaxPP	3 (3.9)	0 (0)	0.549

*Significant $P<0.05$. LVH – Left ventricular hypertrophy; CaxPP – Calcium phosphate product; CKD – Chronic kidney disease

Table 4: Prevalence of cardiovascular risk factor across CKD stages

Cardiovascular risk factor	Stage 3 (*n*=38) *n* (%)	Stage 4 (*n*=31) *n* (%)	Stage 5 (*n*=7) *n* (%)	*P*
Dyslipidemia	26 (68.4)	20 (64.5)	5 (71.4)	0.796
Hypertension	37 (97.4)	30 (96.8)	6 (85.7)	0.122
Hyperuricemia	12 (31.6)	17 (54.8)	3 (42.9)	0.209
Hypoalbuminemia	10 (26.3)	11 (35.5)	6 (85.7)	0.006*
LVH	28 (73.7)	25 (80.6)	6 (85.7)	0.512
Obesity	11 (28.9)	3 (9.7)	0 (0)	0.009*
Hypocalcemia	19 (50)	22 (71)	5 (71.4)	0.128
Hyperphosphatemia	17 (44.7)	25 (80.6)	6 (85.7)	0.001*
Anemia	37 (97.4)	29 (93.5)	7 (100)	0.516

*Significant $P<0.05$. LVH – Left ventricular hypertrophy; CKD – Chronic kidney disease

Table 5: Comparison of cardiovascular risk factors between male and female CKD patients

Cardiovascular risk factor	Female (*n*=28) *n* (%)	Male (*n*=48) *n* (%)	*P*
Dyslipidaemia	23(82.1)	28(58.3)	0.03*
Hypertension	26(92.3)	47(97.9)	0.28
Hyperuricaemia	15(53.6)	29(60.4)	0.56
Hypoalbuminaemia	12(42.9)	15(31.2)	0.31
LVH	19(67.9)	40(83.3)	0.12
Obesity	18(28.6)	6 (12.5)	0.08
Hypocalcaemia	14(50.0)	32(66.7)	0.15
Hyperphosphataemia	19(67.9)	29(60.4)	0.52
Anaemia	25(89.3)	48(100.0)	0.02*

*Significant $P<0.05$. LVH – Left ventricular hypertrophy

DISCUSSION

The burden of cardiovascular risk factors is enormous and is largely responsible for death among CKD patients because of inadequate risk assessment and management. This study showed a high prevalence of both traditional and nontraditional cardiovascular risk factors even in early stages of CKD.

The prevalence of hypertension in the CKD group was 96.1% which was significantly higher than 43.2% observed in the control group. This prevalence is higher than 85.2% reported by Ulasi *et al*.[22] The higher prevalence in this index may be related to exclusion of patients with HIV-associated nephropathy who do not commonly have hypertension who were included in the study by Ulasi *et al*. Optimal BP control had been established to slow CKD progression and reduce cardiovascular morbidity.[23]

The prevalence of obesity in the CKD group was 18.4% which was lower than 21.1% observed in the control group. The prevalence of obesity reduced significantly across CKD stages 3–5. The mean BMI was lower in the CKD group. The presence of malnutrition in CKD patients caused by anorexia, vomiting, and chronic inflammation may account for their lower BMI. Lower BMI has been reported to be associated with increased mortality in ESRD commencing RRT.[24]

The prevalence of anemia was 96.1% in the CKD group which is higher than 87% reported by Akinsola *et al*.[9] This higher prevalence may be due to the higher cutoff value used in defining anemia in the index study as compared to that used in the study by Akinsola *et al*.[9] The prevalence of anemia was significantly higher in male CKD patients. This could also be due to the higher PCV cut off value used in definition of anemia in male subjects. Anemia contributes significantly to development of CVD in CKD patients by causing LVH which could be reversed if correction of anemia is instituted early with erythropoietin.[25,26]

The prevalence of LVH in the CKD group was 77.6% which was significantly higher than 23.7% observed in the control group. The prevalence of LVH in earlier reports was between 27.6% and 95.5%.[3,22,27,28] Studies that used echocardiographic criteria for LVH as done in this present study had higher values than the study that used electrocardiography due to higher sensitivity of the former. LVH was observed to be more prevalent in male CKD patients. This may be related to the contribution of the male sex hormone; testosterone to development of LVH as reported in both experimental and human male subjects.[29,30] The prevalence of LVH increased across CKD stages 3–5. This study showed that LVH occurs early in CKD, which buttresses the fact that even CKD patients in early stages are at high risk of cardiovascular death since LVH is a predictor of mortality.[31] Optimal BP control in CKD patients

with use of drugs that block the renin–angiotensin system has been shown to reverse LVH and prevent associated CVD mortality.[32]

The prevalence of dyslipidemia in the CKD group was 67.1%, and this was significantly higher than 39.5% present in the control group. The prevalence of dyslipidemia was significantly higher in female CKD. The higher prevalence of dyslipidemia in female CKD patients may be explained by the higher cut off of <50 mg/dl used to diagnose low HDL-C in females compared to <40 mg/dl used in males. Furthermore, estrogen which is known to be protective against dyslipidemia by increasing the levels of HDL-C in premenopausal females is usually low in females CKD patients.[33] Treatment of dyslipidemia has been reported to reduce major atherosclerotic events and rate of progression in CKD.[34]

Hypocalcemia and hyperphosphatemia were present in 60.1% and 63.2% of the CKD group, respectively, which were significantly higher than that of the controls. These were lower than prevalence of 71% and 75% reported by Onyemekeiha *et al*.[35] The lower prevalence of both hypocalcemia and hyperphosphatemia may be due to the fact that the latter study was carried out in stage 5 CKD patients in whom calcium and phosphate abnormalities are more pronounced. Elevated CaxPP was present in only 4% of the CKD group which is lower than 12.5% reported in a previous study that involved only stage 5 CKD patients.[36] The prevalence of hyperphosphatemia increased significantly across the CKD stages 3–5. Hyperphosphatemia contributes to cardiovascular mortality in CKD patients.[37] There are established therapeutic agents that can reverse associated cardiovascular abnormalities when instituted early.[38]

Hypoalbuminemia was present in 35.5% of the CKD group while none of the controls had hypoalbuminemia. This prevalence is lower than 43.2% reported by Agaba and Agaba,[39] who studied only stage 5 predialysis CKD patients who are more likely to be malnourished, unlike this index study that involved stages 3–5 CKD patients. Hypoalbuminemia in CKD is associated with faster decline in GFR, poor cardiovascular outcome, and increased mortality after commencement of RRT.[40] The prevalence of hypoalbuminemia increased significantly from CKD stages 3–5 in this study, and this may be explained by progressive malnutrition that occurs from the effect of uremic toxins with declining renal function. The use of oral nutritional supplements may improve outcome in ESRD patients on dialysis.[41]

The prevalence of asymptomatic hyperuricemia was 57.9% in the CKD group which was significantly higher than 15.8% in the controls. Hyperuricemia is a risk factor for rapid progression of CKD, all-cause mortality, and cardiovascular events.[42,43] Treatment of asymptomatic hyperuricemia using allopurinol has been shown to reduce cardiovascular events and hospitalization, to achieve better BP control, and to reduce the progression of renal disease.[44]

The limitation of this study is the relatively small sample size of the study, and the ratio of cases to control used in this study was 2:1 due to limitation of funds because this study was self-sponsored.

Cardiovascular risk factors should be assessed, modified, and treated early in predialysis CKD patients in order to reduce disease progression, cardiovascular morbidity, and mortality.

CONCLUSION

Cardiovascular risk factors were highly prevalent in predialysis CKD subjects which were significantly higher compared to control subjects with normal renal function. Hypoalbuminemia and hyperphosphatemia significantly increased across the CKD stages 3–5 while anemia and dyslipidemia showed significant gender differences.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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