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ORIGINAL ARTICLE

Hyperuricemia in predialysis chronic kidney disease patients in Southern Nigeria

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of hospitalization and death in chronic kidney disease (CKD) patients. Hyperuricemia has emerged as one of the nontraditional cardiovascular risk factors. Studies have shown that hyperuricemia plays a major role in the development of CVD and rapid progression of CKD to end-stage renal disease. **Objective:** The aim was to determine the prevalence and pattern of hyperuricemia in predialysis CKD patients attending a teaching hospital in Southern Nigeria. **Methodology:** One hundred and twenty consecutive predialysis CKD patients and 40 control subjects with normal renal function were recruited over 2 years. Data obtained from participants included demographics, body mass index, blood pressure reading, and etiology of CKD. Blood sampling was done for the determination of serum uric acid, creatinine, and fasting serum lipids. $P < 0.05$ were taken as significant. **Results:** The mean age of the CKD subjects was 48.8 ± 16.6 years with a male:female ratio of 1.7:1. The prevalence of hyperuricemia in the CKD subjects was 47.5% and this was significantly higher than 15% observed in the control group ($P \leq 0.001$). The prevalence of hyperuricemia was highest in CKD stage 3b. Hyperuricemia was more prevalent in younger predialysis CKD subjects and those with hypertensive nephropathy. There was no significant association between hyperuricemia, obesity, gender and dyslipidemia in this study. **Conclusion:** Hyperuricemia is highly prevalent in young predialysis CKD patients even in the early stages. Measures to reduce hyperuricemia should be put in place especially lifestyle and dietary modification.

Keywords: Chronic kidney disease, hyperuricemia, Nigeria, predialysis

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of hospitalization and death in chronic kidney disease (CKD) patients at all stages[1] and accounts for about 50% mortality in this group of patients.[2] The prevalence of CVD among patients commencing renal replacement therapy (RRT) is high, indicating that the process of CVD commenced during the earlier stages of CKD.[3] Individuals with CKD encounter the problems of inadequate risk factor modification and intervention, despite established awareness of their high cardiovascular risk.[4]

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Hyperuricemia has emerged as one of the nontraditional cardiovascular risk factors.[5] Uric acid was thought before now to cause gouty nephropathy by causing deposition of urate crystals in the kidney, but recent studies have now shown that uric acid can induce renal injury or even cause rapid deterioration in renal disease through crystal independent mechanisms.[6-8]

Uric acid is the end product of purine metabolism in humans due to loss of uricase enzyme activity during evolution.[9] It is produced primarily by the liver and intestine, but also by other peripheral tissues such as muscles, endothelium and the kidneys. About two-thirds of uric acid is excreted by the kidney and the remaining one-third by the biliary system, hence uric acid accumulates in the presence of renal impairment. Hyperuricemia can result from overproduction, under-excretion of uric acid, or by both processes.[10] Genetic factors also influence serum uric acid level in different racial groups.[11]

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Early diagnosis and treatment of hyperuricemia in predialysis CKD patients will slow the progression of CKD to end-stage renal disease, reduce cardiovascular morbidity and mortality. These will reduce the huge financial burden on these patients especially in developing countries like Nigeria where RRT is not subsidized by the government and majority of patients cannot afford nor sustain RRT.

The aim of this study was to determine the prevalence and pattern of asymptomatic hyperuricemia in predialysis CKD patients attending a teaching hospital in Southern Nigeria.

METHODOLOGY

This was a cross-sectional descriptive study that involved one hundred and twenty consecutive predialysis CKD patients attending University of Benin Teaching Hospital, Benin City, Nigeria. The study was carried out over a 2 year period (between September 2011 and August 2013). Forty control subjects who had normal renal function without gouty arthritis were also recruited. Informed consent was obtained from the participants in this study and ethical approval was obtained from University of Benin Teaching Hospital Ethical Committee on Research.

Inclusion criteria

(a) Subjects with CKD stages 1–5. (b) CKD patients yet to commence dialysis. (c) Those consenting to participate in the study.

Exclusion criteria

(a) CKD patients on dialysis, (b) HIV positive patients (c) Nonconsenting predialysis CKD patients (d) patients with gouty arthritis (e) patients already on allopurinol therapy.

Demographic information including age and sex of patients were obtained. History of renal symptoms, hypertension, diabetes mellitus, joint pains, joints swelling, and allopurinol use were obtained. The etiology of CKD was determined for each patient.

Weight was measured using a bathroom weighing scale made by U-MEC (model 98114) with subjects wearing light clothing. Height was measured to the nearest centimeter, using a stadiometer with subjects neither wearing shoes nor head gear. Body mass index (BMI) (kg/m^2) was calculated using the formula: Weight (kg)/height (m^2).

About 10 ml of fasting venous blood was obtained from patients to perform biochemical tests which included uric acid, creatinine, and fasting serum lipids. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease formula, which has been previously validated in Nigerian subjects for predicting GFR.[12]

Definition of variables

Hyperuricemia was defined as uric acid level >7.0 mg/dl in males and 6.0 mg/dl in females.[13] Obesity was defined as BMI >29.9 kg/m^2.[14] Estimated GFR was used to stage CKD as stage 1 (GFR of ≥90 ml/min), stage 2 (GFR of 60–89 ml/min), stage 3a (GFR of 59–45 ml/min), stage 3b (GFR of 30–44 ml/min), stage 4 (GFR of 15–29 ml/min) and stage 5 (GFR <15 ml/min).[15] Dyslipidemia was defined as any or a combination of the following: Total cholesterol >200 mg/dl, high-density lipoprotein cholesterol <50 mg/dl in females and <40 mg/dl in males, low-density lipoprotein cholesterol >135 mg/dl and triglyceride >150 mg/dl.[16]

Data analysis

Data generated were analyzed using the statistical package for social sciences (SPSS) version 17.0 (Chicago, SPSS Inc). Results were presented in tabular and graphical forms. Univariate analysis was used in description of demographic characteristics of the study population. Continuous variables were presented as means and standard deviation. 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. Student's *t*-test was used to compare mean values of sub-groups. $P < 0.05$ were considered as significant.

RESULTS

One hundred and twenty predialysis CKD patients were recruited during the study period consisting of 76 (63.3%) males and 44 (36.7%) females. Forty adults consisting of 25 males and 15 females without CKD were recruited as control subjects. Sixty-eight (56.7%) of the CKD patients were above 45 years. Twenty-three (19.2%) of the CKD patients were obese while dyslipidemia was present in 72 (60%). The common etiologies of CKD in this study were hypertensive nephropathy in 49 (36.6%), diabetic nephropathy in 36 (30%) and chronic glomerulonephritis in 33 (27.5%). Majority of the CKD patients were in stages 4 and 5, accounting for 40.8% and 21.7%, respectively. Hyperuricemia was present in 57 (47.5%) of the CKD subjects [Table 1].

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The mean age of the CKD patients was 48.8 ± 16.6 years while that of the control was 45.00 ± 14.09 years with a *P* value of 0.205. The mean BMI of the CKD patients was 24.8 ± 4.9 kg/m^2 and was not significantly different from the BMI of the control group. The mean systolic blood pressure (SBP), diastolic BP, serum uric acid, serum creatinine, and EGFR were significantly different between the CKD and control groups [Table 2].

The prevalence of hyperuricemia in the CKD subjects was 47.5% and this was significantly higher than 15% observed in the control group with a $P < 0.001$ [Figure 1]. The prevalence of hyperuricemia was 60% in stage 2, 50% in stage 3b, 61.5% in stage 3b, 42.8% in stage 4, and 38.5% in stage 5 [Figure 2]. Hyperuricemia was most prevalent among patients with hypertensive nephropathy, followed by those with chronic glomerulonephritis [Figure 3].

There was a significant association between age and uric acid levels such that CKD patients aged 45 years or younger tended to have higher uric acid levels compared to those above 45 years of age. There was no significant association between hyperuricemia, gender, and dyslipidemia among the CKD subjects [Table 3].

Table 1: Characteristics of the CKD patients (*n*=120)

Parameters	Frequency (%)
Gender	
Male	76 (62.5)
Female	44 (37.5)
Age (years)	
≤45	52 (43.3)
>45	68 (56.7)
Obese	
Yes	23 (19.2)
No	97 (80.8)
Dyslipidemic	
Yes	72 (60.0)
No	48 (40.0)
Diagnosis	
Hypertensive nephropathy	44 (36.7)
Diabetic nephropathy	36 (30.0)
Chronic glomerulonephritis	33 (27.5)
Others	7 (5.8)
CKD stages	
2	5 (4.2)
3a	14 (11.7)
3b	26 (21.7)
4	49 (40.8)
5	26 (21.7)
Serum UA	
Normal	63 (52.5)
Elevated	57 (47.5)

CKD: Chronic kidney disease; UA: Uric acid

Table 2: Comparison of mean parameters of CKD patients and controls

Parameters	CKD (*n*=120)	Controls (*n*=40)	*P*
Age (years)	48.77±16.60	45.00±14.90	0.205
Systolic BP (mmHg)	163.45±28.57	125.95±17.27	<0.001
Diastolic BP (mmHg)	97.09±19.70	80.28±10.91	<0.001
BMI (kg/m^2)	24.75±4.86	26.10±3.82	0.113
Serum UA (mg/dl)	6.91±3.78	5.22±2.54	0.003
Serum creatinine (mg/dl)	3.06±1.58	0.92±0.23	<0.001
Estimated GFR (ml/min)	31.03±16.04	105.89±42.71	<0.001

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; UA: Uric acid; BP: Blood pressure; BMI: Body mass index

DISCUSSION

The mean age of the CKD patients in this study was 48.8 ± 16.6 years which was comparable to a previous study on CKD patients in Nigeria.[17] This showed that CKD affects the economically productive group in Nigeria with attendant huge economic loss to the nation. The common causes of CKD in this study were hypertension, chronic glomerulonephritis, and diabetic nephropathy, this is similar to an earlier report.[18] Majority of the patients were in CKD stages 4 and 5 which was not surprising because most patients present late due to poor health seeking attitude and lack of funds.

The prevalence of hyperuricemia in this study was 47.5% which was significantly higher than 15% in the control subjects. This prevalence was higher than 19.6% reported by Siu *et al*.[19] The higher prevalence in our study may be due to the fact that it involved CKD patients in both early and late stages unlike the latter study that involved only stages 3 and 4.

Hyperuricemia was significantly higher in the patients who were <45 years old compared to older patients. This finding was similar to reports by Fujimori *et al*. who found that the highest prevalence of hyperuricemia was in the 4th and 5th decades of life.[20] This may be due to lifestyle practised by persons in this age group such as consumption of alcohol and diets rich in purines and fructose. However, Kuzuya *et al*. reported an age related increase in the prevalence of hyperuricemia in their study population.[21]

There was no significant difference in the prevalence of hyperuricaemia in both gender similar to the finding by Ogbera and Azenabor in Nigerian type 2 diabetic patients without nephropathy.[22] This finding could be explained by the fact that the low estrogen levels that occur in female CKD patients obviates the expected effect of estrogen in reducing uric acid levels by promoting its renal clearance.[23,24]

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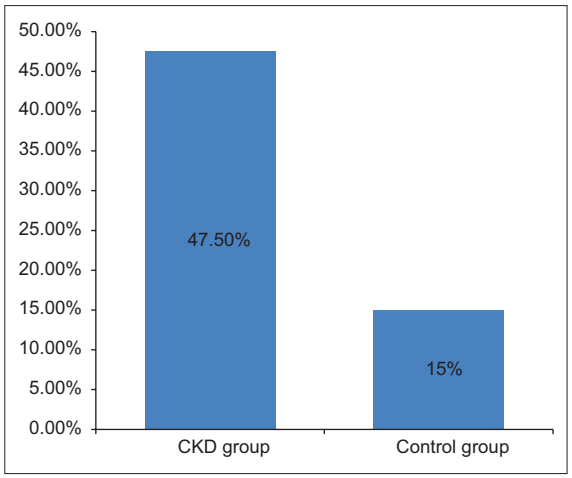

Figure 1: Prevalence of hyperuricemia in the chronic kidney disease and control subjects

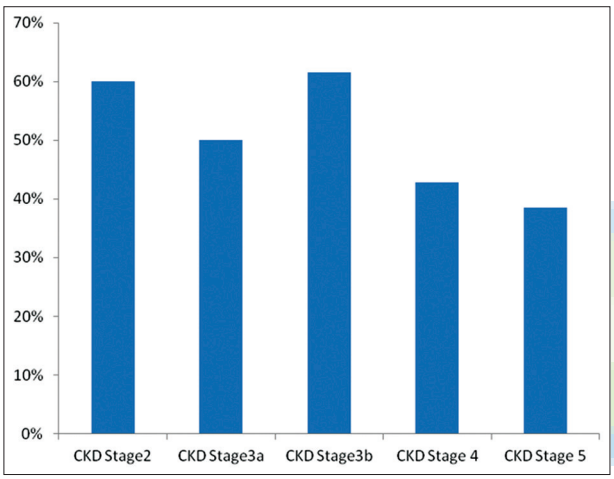

Figure 2: Prevalence of hyperuricemia across the chronic kidney disease stages

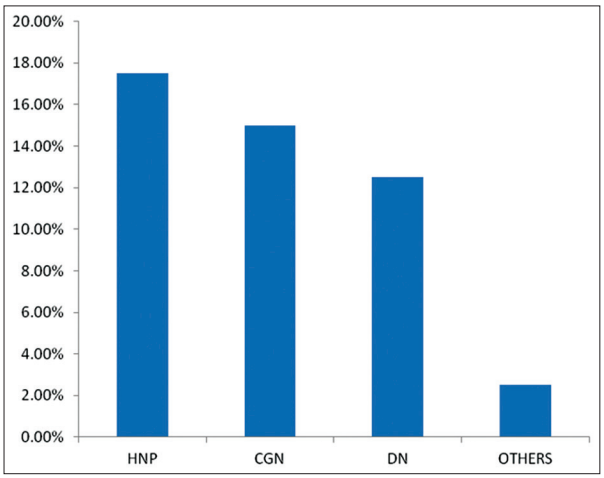

Figure 3: Prevalence of hyperuricemia across etiologies of chronic kidney disease. HNP: Hypertensive nephropathy; CGN: Chronic glomerulonephritis; DN: Diabetic nephropathy

The prevalence of hyperuricemia was higher in CKD patients in early stages compared to those in stages 4 and 5 though this was not statistically significant. Genetic factors, gender and etiology of renal disease may also contribute to prevalence of hyperuricemia across the CKD stages apart from the GFR.

Table 3: Association between serum UA levels and other parameters in the CKD group

	High UA group (*n*=57) (%)	Normal UA group (63) (%)	*P*
Gender			
Male	39 (51.3)	37 (48.7)	0.343
Female	18 (40.9)	26 (59.1)	
Age (years)			
≤45	31 (59.6)	21 (40.4)	0.020
>45	26 (38.2)	42 (61.8)	
Obese			
Yes	13 (56.5)	10 (43.5)	0.362
No	44 (45.4)	53 (54.6)	
Dyslipidemic			
Yes	36 (50.0)	36 (50.0)	0.577
No	21 (43.8)	27 (56.3)	

UA: Uric acid; CKD: Chronic kidney disease

There was no significant association between etiology of CKD and hyperuricemia in this study, however, patients with hypertensive nephropathy had the highest contribution to the prevalence of hyperuricemia in this study compared to other etiologies. This may be explained by the high prevalence of hyperuricemia in hypertensives with normal renal function as well as the postulation that uric acid has a causal role in hypertension.[25,26]

There was no significant association between hyperuricemia, obesity, and dyslipidemia in this study as opposed to the report by Ogbera and Azenabor who studied type 2 diabetics with normal renal function.[22] Future study involving a large CKD population is recommended to validate the findings in our study.

Purine rich diet and alcohol consumption have been reported to be significant risk factors for hyperuricemia.[27,28] This present study did not however include dietary association with hyperuricemia in CKD patients. Lifestyle and dietary restriction that include weight reduction, avoidance of beer, moderate reduction in consumption of shrimps, consumption of food rich in fiber, folate, vitamin C such as vegetables and fruits have been reported to be protective against hyperuricemia.[28,29]

The use of allopurinol, a uric acid lowering drug has been reported to lower uric acid levels and retard progression in CKD patients.[19,30]. Kanbay *et al*. also

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reported improved GFR, BP control, and reduction in inflammation in hyperuricemic patients with allopurinol treatment.[31] A meta-analysis of randomized control trials on the effect of uric acid lowering treatment in hyperuricemic CKD patients reported a delay in the decline of GFR and an improvement in SBP control in these patients. It also indirectly proved that hyperuricemia is a risk factor for CKD progression.[32]

There is still reluctance by nephrologists to treat hyperuricemia in CKD in spite of convincing reports that showed the deleterious effects of hyperuricemia on the cardiovascular system and CKD progression. A major concern of physicians is the safety profile of allopurinol use in CKD patients, however Siu *et al*. reported that allopurinol is relatively safe in CKD having found only one out of 54 patients who had to discontinue allopurinol on account of severe skin rash.[19]

The limitations of this study include inability to study the effect of hyperuricemia on CKD progression due to the cross sectional nature of this study and nonexclusion of patients on diuretics and angiotensin receptor blocker, this is because most CKD patients are on these medications.

RECOMMENDATION

Serum uric acid should be routinely assessed in all CKD patients and those with hyperuricemia should be placed on dietary and lifestyle modification. There should also be a multicenter prospective study to determine the effects of hyperuricemia in Nigerian CKD patients as well as the safety profile of allopurinol in these patients.

CONCLUSION

Hyperuricemia is highly prevalent in young predialysis Nigerian CKD patients even in the early stages. Measures to reduce hyperuricemia should be put in place especially life style and dietary modification while the safety profile of allopurinol is being evaluated.

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