Original Article

Comparative Analysis of Fibroblast Growth Factor-23 as a Correlate of Cardiovascular Disease Among Individuals with Chronic Kidney Disease, Hypertensives, and Healthy Controls

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ABSTRACT

Background: Chronic kidney disease (CKD) is a global growing public health epidemic with attending morbidity and huge financial cost. Cardiovascular disease (CVD), a major complication of CKD, contributes to its excessive mortality rate. The aetio-pathogenesis of the excess burden of CVD in CKD is a feature yet to be unravelled. Fibroblast growth factor-23 (FGF-23) has been implicated as a risk factor for CVD among patients with CKD. However, most of these studies were predominantly among the Caucasian population. **Aim:** This study aims to determine the correlation between FGF-23 and CVD among Nigerians with CKD. **Patients and Methods:** A cross-sectional comparative study composed of three groups: participants with CKD, hypertensives without CKD, and healthy individuals, represented as group 1, 2, and 3, respectively. Information obtained included demographic data and occurrence of risk factors for CVD. Cardiovascular risks were assessed by echocardiography and all the participants had kidney function tests done with plasma FGF-23. **Results:** The study sample size consisted of 135 participants. The mean (SD) age for participants with CKD and controls were 50.2 (12.7), 54.3 (15.5), and 40.2 (14.1) years, respectively. The median [interquartile range (IQR)] of plasma FGF-23 for participants with CKD 210 (139–304) RU/ml, and controls 124 (86–170) RU/ml, and 71 (38 – 89) RU/ml $P < 0.001$. Most participants with CKD had left ventricular hypertrophy (LVH) (80.0%), compared to the controls; 28.9% and 6.7% $P < 0.001$. Similarly, majority of participants with CKD had elevated plasma FGF-23 with LVH (85.7%) compared to controls 55.6% and 11.5%, whereas for aortic valve calcification with elevated plasma FGF-23 among CKD and controls were 53.6% ($P = 0.29$), 37.0% ($P = 0.03$), and 19.2% ($P = 0.06$), respectively. **Conclusion:** Individuals with CKD had frequencies of elevated plasma FGF-23, LVH, and cardiac valve calcification, which are surrogates of cardiovascular events.

KEYWORDS: *Cardiovascular disease, chronic kidney disease, ESRD, fibroblast growth factor-23, Nigeria*

INTRODUCTION

Chronic kidney disease (CKD) is a global health burden with high economic cost to the affected individual, their families, and the healthcare system. It is an independent risk factor for cardiovascular disease (CVD). The epidemiology of CKD in sub-Saharan Africa (SSA) shows that it affects predominantly young people with an unacceptably high

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mortality rate.[1] CVD is prevalent among patients with CKD and End Stage Kidney Disease (ESRD).[2] Data from the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) revealed a 35-year-old dialysis patient sharing a cardiovascular prognosis with a 75-year-old subject from the general population.[3] All stages of CKD are associated with increased risks for cardiovascular morbidity, premature mortality, and decreased quality of life. The global prevalence of CKD is estimated to be 13.4%,[4] whereas SSA bears a higher estimate.[5]

In Nigeria, medical admission of patients with ESRD has increased from 6.1% to as high as 21%.[6] Furthermore, community-based studies have assessed CKD prevalence to be between 19% and 27%.[7,8] The complications associated with CKD/ESRD are the major contributors to morbidity, mortality, and poor quality of life. These common complications of CKD are anaemia, intractable fluid retention, chronic kidney disease–mineral bone disorder (CKD–MBD), vascular calcification, and left ventricular hypertrophy (LVH).[9] The latter has been shown to contribute to diastolic dysfunction, congestive heart failure, arrhythmia, and sudden cardiac death.[9]

In the past decade, fibroblast growth factor-23 (FGF-23), a phosphaturic hormone produced by osteoblasts and osteocytes, has emerged as a major regulator of mineral metabolism in health and disease. It has also been shown that serum FGF-23 levels rise before changes in calcium, phosphate, or parathyroid hormone levels and is now recognized as one of the earliest detectable biomarkers of CKD–MBD.[10]

Hyperphosphatemia is a known risk factor for CVD and mortality and serves as a potential target for interventions to improve clinical outcomes in patients with CKD.[11] Growing evidence suggests that hyperphosphatemia correlates with the calcification of coronary arteries, peripheral arteries, and cardiac valves in CKD patients.[12,13]

There is growing evidence in favour of serum FGF-23 as a novel risk factor for CVD among individuals with CKD, as against routine serum calcium, phosphorus, parathyroid hormone, and vitamin D that may be within normal limits even at an intermediate stage of the disease. Meanwhile, most of these studies that evaluated the relationship between FGF-23 and CVD in patients with CKD were predominantly among the Caucasian population. This study aimed to determine the correlation between FGF-23 and CVD among Nigerian patients with CKD.

Materials and Methods

A total of 135 participants were enrolled and they composed of 45 participants with established CKD defined as persistent estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 or those with ESRD with or without being on dialysis, 45 participants with hypertension but without CKD or diabetes mellitus (DM) and 45 apparently normal healthy participants. The study was approved by the Joint Institution Review Committee of the University College Hospital and The College of Medicine, University of Ibadan. All participants gave written informed consent. (IRB approval was obtained from the Joint University of Ibadan and University College Hospital, Ibadan with IRB Research Approval Number: NHREC/05/01/2008a. The approval was obtained on the 8th July 2018).

Data collection

A pre-tested questionnaire was administered to all participants. Information obtained from eligible participants included demographic data, duration and aetiology of CKD, history of hypertension, DM, past medical history of valvular heart disease, heart surgery, kidney transplant, bone pain or incidental fracture, malignancy, social history, lifestyle, prior history of stroke or coronary artery disease, hypertension or kidney disease, and patient's present medications. Body mass index (BMI) and blood pressure were measured and recorded with three readings taken 5 min apart; the average was obtained and recorded. Participants taking part in the study were instructed to avoid taking phosphorous-rich diet (ice cream, soda drinks, cheese, beef, liver, red meat, sardines, and beer) for at least 10 hours before samples were collected, to prevent osteoplastic FGF-23 secretion through oral phosphate loading. The plasma was separated into EDTA bottles and stored at –20°C using Bruhm deep freezer BCF-5D 200, China, until analyzed using Bioassay Technology Laboratory, Human Fibroblast Growth-23 ELISA Cat. No EOO59Hu, which detects both C terminal fragment and intact FGF-23. The ELISA kit containing 96 wells of which eight are standard, and the rest being sample wells. Both standard solution (50 µl) and anti-FGF23 antibody (40 µl) were added to both the standard wells and sample wells, respectively, whereas 50 µl streptavidin-HRA was also added to both wells. The kit was subsequently covered with a sealer to incubate for 60 min at 37°C after which the kit was taken to an automated washing machine and washed five times with wash buffer. Thereafter, 50 µl of solution A and B were added to all the wells and covered with a new seal for incubation at 37°C for 10 min. The last stage was the addition of a stop solution to all the wells with colour

developed and taken to a microplate reader to determine the optical density. A Roche Hitachi Cobas 6000 auto-analyzer machine (Bonney lake, WA, USA) was used to analyze serum calcium, phosphate, potassium, urea, creatinine, fasting lipid profile, and glucose (fasting and random).

The standard resting 12 leads Electrocardiogram (ECG) was performed on all participants using a commercially available machine (ECG Work station), Contec Medical System Co. Ltd, Republic of China (CONTEC 8000 G), at a paper speed of 25 mm/s and standardized at 0.1 mv/mm. Transthoracic echocardiography was carried out on all the participants in the three groups using a Toshiba Xario (Toshiba Medical Systems Corp, Japan) with a 3.5 MHz transducer. A two-dimensional guided M-mode echocardiography was performed on each subject in the left lateral decubitus position. Measurements were in accordance with the recommendation of the American Society of Echocardiography.[14]

Definition of terms

CKD was defined as pathological abnormalities, whether established via renal biopsy or imaging studies, or inferred from markers such as urinary sediment abnormalities or increased rate of urinary albumin excretion or decreased glomerular filtration rate (GFR) (with estimated GFR <60 ml/min/1.72 m^2 using MDRD formula) persisting for 3 months.[15] Albuminuria was defined as the presence of elevated protein in un-timed spot urine albumin to creatinine (ACR) of ≥30 mg/g or (3 mg/mmol).[15] LVH was defined as the enlargement and thickening of the walls of left ventricle. This study used LVMI ≥49.2 g/m^2 for men and ≥46.7 g/m^2 for women as LVH using echocardiography.[16] DM was defined as two fasting blood glucose values ≥126 mg/dl (7.0 mmol/l), HbA1C values ≥6.5%, and postprandial values more than 200 mg/dl (11.1 mmol/dl), one or two above with symptoms of diabetes or those on glucose-lowering medications.[17] Hypertension was defined as persistent elevation in systolic blood pressure (SBP) of ≥140 mmHg or more and a diastolic blood pressure (DBP) of ≥90 mmHg or more, or patients on antihypertensive medication.[18] Elevated FGF-23 was defined as plasma FGF-23 ≥100 RU/ml.[10] CVD was defined based on the presence of LVH and/or when valvular calcification around the heart valves was used.[19]

Data analysis

Data obtained were entered into Microsoft Excel for cleaning and afterwards transferred to the Statistical Package for Social Science (SPSS) version 22 for analysis. Baseline descriptions of socio-demographic and clinical variables were reported as proportions for categorical variables and mean (standard deviation) for continuous variables and median (interquartile range {IQR}) for non-parametric data. The 95% confidence intervals were appropriately reported. The Shapiro–Wilk test was used to assess normality. The difference between means (SD) across the three groups were determined using one-way ANOVA and the least significance difference determined to generate a post-hoc analysis. For continuous variables with non-parametric distribution, the Kruskal Wallis test was used. The association between categorical variables was tested using Chi-square analysis and Fisher's exact test where appropriate. The average FGF-23 was presented as values ≥100 RU/ml deemed elevated based on earlier studies carried out.[10] Spearman's correlation analysis was used to test the relationship between parameters. A logistic regression model was employed to determine variables that independently predict CVD (LVH and/or valvular calcification) among the groups. Statistical significance was deemed as P value < 0.05.

Results

The study enrolled a total number of 135 participants, with 45 in each arm; comprising of individuals with CKD, hypertension without CKD or DM, and apparently healthy controls, represented as group 1, 2, and 3, respectively. The mean age of participants in group 1, 2, and 3 were 50.2 (12.7), 54.3 (15.5), and 40.2 (14.1) years, respectively (P < 0.001). The proportion of male participants among group 1, 2, and 3 were 60.0%, 51.1%, and 55.6%, respectively. There was a significant difference in the median eGFR of group 1; 11.4 (2.2–53.4), group 2; 87.1 (61.0–213.1), and group 3; 117.1 (64.5–186.8) ml/min/1.73 m^2, P < 0.001. The mean packed cell volume among the participants in group 1 {27.61 (5.9%)}, group 2 {39.5 (3.9%)}, and group 3 {41.4 (3.1%)}, P < 0.001. The mean SBP was highest among group 1 {152.1 (25.2)} mmHg, compared to group 2 {147.4 (21.5)} mmHg and group 3: {114.5 (25.2)} mmHg P < 0.001 [Table 1].

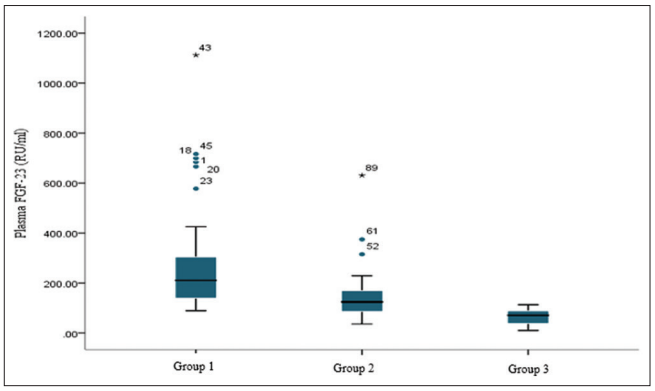

Figure 1: Box plot showing plasma FGF-23 level among study groups

Table 1: Socio-demography, blood indices, and baseline clinical characteristics among the participants

Blood indices	Group 1 *n*=45 Mean (SD)	Group 2 *n*=45 Mean (SD)	Group 3 *n*=45 Mean (SD)	*P*
Age, Mean (SD), year	50.2 (12.7)	54.3 (15.5)	40.2 (14.1)	<0.001
Gender, *n* (%)				
Male	27 (60.0)	23 (51.1)	25 (55.6)	0.698
Female	18 (40.0)	22 (48.9)	20 (44.4)	
PCV (%)	27.6 (5.9)[a]	39.5 (3.9)[b]	41.4 (3.1)[c]	<0.001
Urea (mg/dl)	112.8 (69.7)[a]	22.1 (10.4)[b]	17.5 (4.1)[c]	<0.001
Creatinine (mg/dl)	7.80 (6.43)[a]	1.0 (0.2)[b]	0.9 (0.2)[b]	<0.001
eGFR (ml/min/1.73 m)*	11.4 (2.2 - 53.4)[a]	87.1 (61.0-213.1)[b]	117.1 (64.5-186.8)[c]	<0.001
Serum calcium (mg/dl)	8.8 (8.3-9.6)[a]	9.4 (9.2-9.7)[b]	9.2 (8.9-9.6)[b]	<0.001
Serum Phosphate (mg/dl)	4.2 (3.5-5.9)[a]	3.5 (2.9-3.9)[b]	3.0 (2.8-3.6[b]	<0.001
Serum Albumin (g/dl)	3.5 (0.8)[a]	4.2 (0.4)[b]	4.2 (0.4)[b]	<0.001
RBG (mg/dl)	143.3 (33.9)[a]	129.9 (22.6)[b]	119.9 (19.6)[c]	<0.001
FBG (mg/dl)	99.6 (51.1)[a]	87.7 (9.5)[b]	83.1 (9.1)[b]	0.33
DBP	95.7 (16.3)[a]	92.3 (17.4)[a]	73.9 (9.6)[b]	<0.001
SBP	152.1 (25.2)[a]	147.4 (21.5)[a]	114.5 (10.4)[b]	<0.001
BMI	25.1 (5.1)[a]	26.7 (5.3)[a]	23.9 (4.3)[b]	0.029

BMI=Body mass index, DBP=Diastolic blood pressure, SBP=Systolic blood pressure, PCV=Packed cell volume, RBG=Random blood glucose, FBG=Fasting blood glucose, eGFR=estimated glomerular filtration rate, Group 1=CKD, Group 2=Hypertensives without CKD or DM, Group 3=apparently healthy participants, Values are means±standard deviation. Means with non-identical superscripts (a, b, c) within the same variable are significantly different from one another (P<0.05) according to least significance difference (LSD). *=median value

Table 2: Proportion of participant with elevated plasma FGF-23 and LVH

FGF-23 (RU/ml)	Group 1	Group 2	Group 3	*P*
≥100	41 (91.1%)	28 (68.2%)	6 (13.3%)	0.001
≤100	4 (8.9%)	17 (38.7%)	39 (86.7%)	
LVH				
Yes	36 (80.0%)	13 (28.9%)	3 (6.7%)	0.001
No	9 (20.0%)	32 (71.1%)	42 (93.3%)	

Group 1=CKD, Group 2=hypertensives without CKD or DM, Group 3=apparently healthy participants

The plasma FGF-23 levels were highest among the participants in group 1 with median values of 210 (IQR: 139 – 304) RU/ml, whereas group 2 and 3 had median values of 124 (IQR: 86–170) RU/ml and 71 (IQR: 38–89) RU/ml [Figure 1]. The proportion of participants with elevated plasma FGF-23 was significantly higher among group 1: 41 (91.1%) compared to group 2: 28 (62.2%) and 3: 6 (13.3%) $P < 0.001$. There was a significant inverse correlation between level of plasma FGF-23 and eGFR among the group 1 participants ($r = –0.485$, $P < 0.001$), whereas there was no relationship between plasma FGF-23 and eGFR among group 2 participants $P = 0.895$. The frequency of LVH was observed in 36 (80.0%), 13 (28.9%), and 3 (6.7%) among group 1, 2, and 3, respectively, $P < 0.001$ [Table 2].

Figure 2 shows a line graph, showing drop in median FGF-23 levels with increasing eGFR deciles among all the participants. Reduction in eGFR less than 70 ml/min/1.73 m^2 was correlated with increasing levels of plasma FGF-23. There was a significant inverse correlation between level of plasma FGF-23 and eGFR among the group 1 participants ($r = –0.485$, $P < 0.001$), whereas there was no relationship between plasma FGF-23 and eGFR among group 2 participants $P = 0.895$.

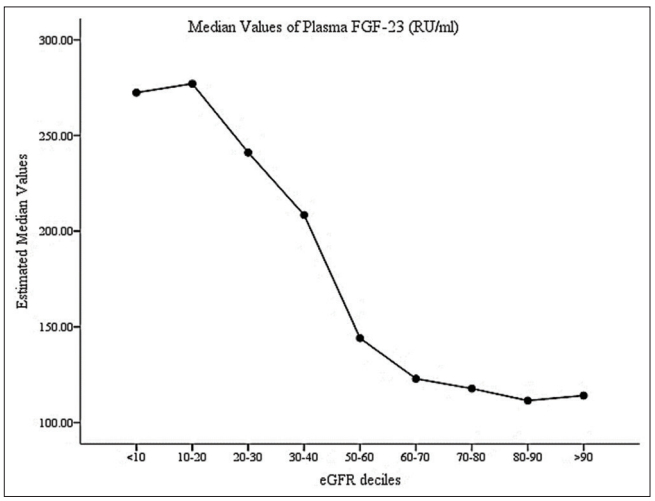

Figure 2: Line graph showing relationship between eGFR and FGF-23 among the group 1 and 2 participants

Among the group 1 participants with elevated FGF-23, 53.6% and 21.4% had aortic valve calcification (AVC) and mitral valve calcification (MVC), respectively. Similarly,

Table 3: Relationship between elevated plasma FGF-23 and cardiovascular disease (valve calcification and LVH) among studied population

CVD	Group 1			Group 2			Group 3		
	Elevated (≥100 RU/ml)	Normal (<100 RU/ml)	*P*	Elevated (≥100 RU/ml)	Normal (<100 RU/ml)	*P*	Elevated (≥100 RU/ml)	Normal (<100 RU/ml)	*P*
AVC									
Yes	15 (53.6%)	9 (52.9%)	0.29	10 (37.0%)	1 (5.6%)	*0.03	5 (19.2%)	0 (0.0%)	*0.06
No	13 (46.4%)	8 (47.1%)		17 (63.0%)	17 (94.4%)		21 (80.8%)	19 (100.0%)	
*MVC									
Yes	6 (21.4%)	3 (17.7%)	*1.00	2 (7.4%)	0 (0.0%)	*0.77	0 (0.0%)	0 (0.0%)	-
No	22 (78.6%)	14 (82.3%)		25 (92.6%)	18 (100.0%)		26 (100.0%)	19 (100.0%)	
LVH									
Yes	24 (85.7%)	13 (76.5%)	0.452	15 (55.6%)	12 (44.4%)	0.556	3 (11.5%)	23 (88.5%)	0.627
No	4 (14.3%)	4 (23.5%)		8 (44.4%)	10 (55.6%)		1 (5.3%)	18 (94.7%)	

*The significant value for MVC for Group I is 0.54, AVC=Aortic valve calcification, CVD=Cardiovascular disease, MVC=Mitral valve calcification, Group 1=CKD, Group 2=Hypertensives without CKD or DM, Group 3=apparently healthy participants, LVH=Left ventricular hypertrophy

Table 4: Multiple logistic regression cofounding variables and cardiovascular disease (LVH and or cardiac valves calcification) in study participants

Variable	Group 1		Group 2		Group 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	-	-	0.9 (0.9-1.1)	0.90	-	-
SBP	1.1 (1.0-1.2)	0.06	-	-	1.3 (1.0-1.6)	0.03*
eGFR	0.9 (0.8-1.0)	0.03*	1.0 (0.9-1.1)	0.14	1.0 (1.0-1.1)	0.44
Serum Phosphate	0.7 (0.2-1.8)	0.43	1.3 (0.210.5)	0.82	0.6 (0.7-1.4)	0.76
Calcium	-	-	0.4 (0.1-3.8)	0.45	-	-
LDL	-	-	1.0 (1.0-1.1)	0.07	-	-
FGF- 23	17.8 (0.3-1.5)	0.19	0.1 (0.0-4.5)	0.23	2.9 (2.3-3.0)	0.16

*=*P*<0.05, SBP=Systolic blood pressure, eGFR=estimated glomerular filtration, OR=Odds ratio, Group 1=CKD, Group 2=Hypertensives without CKD or DM, Group 3=apparently healthy participants. LDL=Low density lipoprotein

Table 5: Proportion of group 1 participants with elevated plasma FGF-23 and according to CKD stages

CKD Stage	Elevated FGF23 *n* (%)	LVH *n* (%)	C. Valve Calcification *n* (%)
Stage 3	7.0 (17.1)	5.0 (13.5)	2.0 (8.3)
Stage 4	8.0 (19.5)	6.0 (16.2)	4.0 (16.7)
Stage 5	27.0 (65.9)	26.0 (70.3)	18.0 (75.0)

CKD=Chronic Kidney Disease, FGF-23=Fibroblast growth factor, LVH=Left ventricular hypertrophy, C=cardiac

among the group 2 participants with elevated FGF-23, 37.0% and 7.4% had AVC and MVC, respectively, whereas in group 3, 19.2% of participants had AVC with elevated plasma FGF-23 but none had MVC. The proportion of participants with elevated plasma FGF-23 and LVH were 24 (85.7%), 15 (55.6%), and 3 (11.5%) in group 1, 2, and 3 participants, respectively $P > 0.05$. [Table 3]. The proportion of elevated plasma FGF-23 and LVH were 24 (85.7%), 15 (55.6%), and 3 (11.5%) in group 1, 2, and 3, respectively [Table 3].

Table 4 shows the multiple logistic regression of cofounding variables associated with CVD (LVH and or cardiac valves calcification) in study participants. The eGFR was the only significant independent variable that had relationship with CVD and drops in eGFR by 1 ml/min/1.73 m^2 increases the likelihood of CVD by 10%. No factor was found to be associated with CVD in group 2 participants on multiple logistic regression, whereas SBP was observed to be associated with CVD in the third group (Odd ratio 95% CI) with a 1 mmHg rise in SBP associated with a 30% increase in likelihood of CVD.

Table 5 shows the proportion of group 1 participants with elevated plasma FGF-23 and according to CKD stages. There was a progressive increase in the proportion of participants with elevated levels of plasma FGF-23 from 17.1% in CKD stage 3 to as high as 65.9% in stage 5 CKD. Similarly, the proportion of participants with LVH increases from 13.5% at stage 3 to 70.3% at stage 5 CKD. Cardiac valves calcification in group 1 participants increase from 8.3% at stage 3 to 75.0% at CKD stage 5.

Discussion

This study showed that a high proportion of patients with CKD had elevated plasma FGF-23, cardiac

valvular calcification, and LVH compared to hypertensives and healthy controls. Low eGFR and elevated SBP were independently associated with CVD among CKD and participants with elevated FGF-23, respectively.

In this study, the proportion of participants with elevated plasma FGF-23 levels (i.e., ≥100 RU/ml) among the participants with CKD were significantly more than the participants with hypertension and healthy controls. This finding is similar to what most of the previous studies have reported among the Africans and European populations.[10,20-22] Furthermore, the study reveals an exponential increase in the level of plasma FGF-23 in participants with CKD, and levels increase with worsening kidney function. Plasma level of FGF-23 has been shown to increase as the renal disease progresses even as high as 100–1000-fold above the normal range with ESRD.[14] Similarly, Orando *et al*.[23] gave more credence to the impact of renal impairment in their study, which demonstrated that plasma FGF-23 level rises by 3.4RU/ml for every 0.1 mg/dl increase in serum creatinine.

Isakova *et al*.,[10] in their study, found the plasma level of FGF-23 among CKD participants to be lower than what this study reported even though their study had a higher mean age, BMI, and a higher proportion of participants that smoked cigarettes. These factors have been implicated to increase the plasma level of FGF-23 in preserved renal function.[10] However, the inclusion of stage 2 to 4 CKD and those aged less than 70 years as in the study by Isakova *et al*.[10] may explain the low median plasma FGF-23 in their study compared to 58.7% observed in this study.

Orando *et al*.[23] and Negishi *et al*.,[24] in their different studies found significantly higher levels of plasma FGF-23 among participants with CKD compared to what was found in this study. The possible explanations for this high level of FGF-23 in the study by Orando *et al*.[23] could be because only a few of their participants (9%) were on phosphate binder compared to this study where about 71% were on phosphate binders. Similarly, Koiwa *et al*. and Negishi *et al*.[24] demonstrated the inhibitory role of phosphate binders on plasma FGF-23 and this may account for the lower level of plasma FGF-23 in this study, as most of the participants were on dietary phosphate binders.[25,26] Although, the samples of FGF-23 were collected for the participants in a faster state to minimise its effects on the laboratory assay.

This study demonstrates that eGFR is inversely correlated with elevated plasma FGF-23 among participants with CKD. Similarly, some studies have previously demonstrated this inverse association between eGFR and plasma FGF-23.[27,28]

This study shows that the proportion of LVH among participants with CKD was significantly higher than the participants with hypertension and healthy controls. In addition, among the CKD participants, it reveals an increased level of participants with LVH as the CKD stages progress from 3 to 5. This observation is similar to reports by other workers who found that the proportion of LVH increases as the stages of kidney disease advances.[29,30] Similarly, a study done in Pakistan got a lower prevalence of LVH (56.3%), but there were few participants with ESRD unlike this study.[31]

This study demonstrated that low haemoglobin concentration, low eGFR, high SBP, and being on haemodialysis were the variables found to be associated with LVH among participants with CKD. These factors identified are documented risk factors for LVH. Furthermore, some authors in Nigeria also found similar variables, such as low level of haemoglobin concentration and eGFR to be associated with LVH among patients with CKD.[29,32] Similarly, Sushanath *et al*.[30] also found low eGFR, elevated SBP, advanced stage of CKD, and low haemoglobin concentration to be related with LVH in CKD.

LVH was observed in 28.9% of participants with hypertension and was similar to a study conducted among patients with hypertension in Ibadan a decade earlier,[33] but significantly different from what was reported in a similar study among Ethiopians with hypertension (52%).[34] The possible reason for this difference may be because two-thirds of the participants in the Ethiopian study were in their sixth decade, also a majority of their participants had a long-term history of hypertension. Furthermore, a 10-year longitudinal study found that the incidence of LVH increased progressively from normotensive to pre-hypertensive and hypertensive (9%, 23.2%, and 36.6%, respectively).[35]

The strength of their study is the use of an ambulatory blood pressure machine to eliminate masked hypertension among normotensives. LVH is known to contribute to diastolic dysfunction, heart failure, arrhythmia, and even sudden death[9] either among hypertensives or patients with CKD. However, it is a major contributor to the cardiovascular event especially among patients with CKD.[36]

This study observed that elevated plasma FGF-23 was not found to be a surrogate marker of LVH among the three groups. However, the highest proportion of elevated FGF-23 and LVH was found in participants with CKD and highest in CKD stage 5. This finding was

at variance with most studies that look at association between FGF-23 and LVH.[20,37] The relatively small sample size in each group may be responsible for this observation. The prevalence of cardiac valve calcification was observed to be high in this study. Both aortic and mitral valve calcifications were prevalent among participants with CKD compared to hypertensives and healthy controls. A similar study done in Yaoundé on the pattern of cardiac lesion among patients on maintenance haemodialysis found a closely similar prevalence of aortic and mitral valve calcification.[38] In addition, this study found a progressively increase in the proportion of participants with CKD who had cardiac valves calcification as the kidney function deteriorates towards stage 5 CKD. Also, the CKD participants with abnormally elevated plasma FGF-23 level also demonstrated the highest proportion of participants with cardiac valves calcification. Previous studies have reported high prevalence of cardiac calcifications and its occurrence was associated with increasing age, cigarette smoking, DM, comorbidity, and low eGFR.[39-41] Therefore, prompt identification and treatment of these factors are cost-effective approach to prevent CVD among patients with CKD.

Some studies have shown that vascular calcification inducers (hypercalcaemia, hyperphosphataemia, hyperparathyroidism, uraemic toxins, inflammatory cytokines, advanced glycation products, and hypertension) were observed to be significantly high in individuals with CKD, and with reduced active inhibitors thus resulting in the high prevalence of vascular intima, media, and cardiac valvular calcification.[42,43]

Furthermore, cardiac valvular calcification was found to be prevalent among the participants with CKD and these findings were associated with haemodialysis, elevated SBP, low eGFR, and low haemoglobin. Jose *et al*.[44] found that patients that are older and with long years on haemodialysis had calcific cardiac valves. Although, the participants with CKD in this study were younger with a lesser number of years on haemodialysis – this may explain the difference in prevalences between this study and theirs. Furthermore, some epidemiological reports have shown that besides age and the length of dialysis, hypercalcaemia and most importantly, plasma phosphate have proven to be related to cardiac valve calcification.[45-47] In this study, a higher proportion of participants with CKD had hyperphosphataemia compared to the hypertensives and healthy controls. Furthermore, most of the participants with CKD were on calcium-containing phosphate binders that could also contribute to hypercalcaemia. Growing evidence has shown that hyperphosphataemia correlates with the calcification of coronary arteries, peripheral arteries, and cardiac valves among CKD patients and have been identified as harbingers of CVD.[12,13]

The strength of this study includes the use of a novel biomarker FGF-23 as a correlate of CVD among the SSA population where there are few local studies on the role of FGF-23 in the excess burden of CVD among individuals with CKD. Second, the involvement of three different groups showed an increasing rise in the level of plasma FGF-23 from apparently normal individuals to hypertensives and finally to participants with CKD. Last, echocardiography instead of electrocardiogram was used for the identification of participants with LVH. This study is not without some limitations, among which are first, being an observational comparative study, the establishment of temporal relationship and causality between FGF-23 and CVD may be difficult. Besides, the use of calcium phosphate binder and vitamin D among most of the participants with CKD could have contributed to the low prevalence of elevated plasma level of FGF-23 among the CKD participants.

Conclusion

The study found a high prevalence of elevated plasma FGF-23 among participants with CKD when compared to the hypertensives and healthy controls, whereas plasma FGF-23 was observed to be inversely correlated with eGFR in participants with CKD. Cardiovascular risk measured using LVH and cardiac valves calcification were higher among CKD participants when compared to the other groups. The trend of FGF-23 values was similar to the proportion of CVD risk when compared across stages of CKD. The findings of this study have demonstrated the need to include plasma FGF-23 in the routine evaluation of CVD risk among the patients with CKD.

Data availability

Data that support the findings in this study are summarised in the article and will be provided if required.

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Conflicts of interest

There are no conflicts of interest.

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