Carotid Intima-Media Thickness: A Surrogate Marker for Cardiovascular Disease in Chronic Kidney Disease Patients

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ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is the leading cause of mortality in patients with chronic kidney disease (CKD). Carotid intima-media thickness (CIMT) is a measure of atherosclerotic vascular disease and considered a comprehensive picture of all alterations caused by multiple cardiovascular risk factors over time on the arterial walls. We therefore sought to determine the CIMT of the common carotid artery in patients with CKD and to evaluate the clinical pattern and prevalence of CVD in CKD patients.

METHODS: A case-control study involving 100 subjects made of 50 patients with CKD stages 2 to 4 and 50 age and sex matched apparently normal individuals. Carotid intima-media thickness of the common carotid artery was considered thickened if it measured greater than 0.8 mm. All subjects had laboratory investigations, 12-lead electrocardiogram, transthoracic echocardiography, and ankle-brachial index.

RESULTS: The mean CIMT was higher in CKD population compared with controls ($P < .001$). Eighty-four percent of the study population was found to have thickened CIMT compared with 18% of controls ($P < .001$). Patients with CKD had significantly higher blood pressure and heart rate than controls. Cardiovascular disease was also more prevalent among patients with CKD as compared with controls. Carotid intima-media thickness positively correlated with age, blood pressure, and random blood sugar.

CONCLUSIONS: As CIMT was well correlated with many cardiovascular risk factors among CKD patients, it may serve as a surrogate marker for CVD and its early assessment may target patients who may need more aggressive therapy to retard the progression of kidney disease and improve outcome.

KEYWORDS: carotid intima-media thickness, chronic kidney disease, cardiovascular disease

Introduction

Chronic kidney disease (CKD) is a major problem worldwide and constitutes an enormous burden to health care resources and patient care.[1,2] The prevalence of CKD is on the increase and approaching epidemic proportions.[1–4] In spite of the improvement in the management of cardiovascular diseases (CVD) over 4 decades, CVD mortality is approximately 15 times higher in patients undergoing dialysis than in the general population.[5–11] The increased prevalence of CVD among patients who got dialysis incidentally indicates that CVD begins in the preceding stages of CKD and do occur across the stages of CKD.[5,7,8,10,11] The high prevalence of CVD among patients with CKD still holds regardless of the cause of CKD.[11] As a result, CKD has been regarded as a cardiovascular risk equivalent.[6]

Hence, the need to identify useful markers that may precede the occurrence of CVD among patients with CKD. Instituting risk factor reduction strategies early in the course of CKD may also provide an opportunity to prevent CVD among patients with CKD. It is hoped that the complete appraisal of cardiovascular burden in CKD patients will inform the strategies and policies for the prevention and control of this condition.

We therefore aim to assess the utility of carotid intima-media thickness (CIMT) as a surrogate marker for CVD among patients with CKD.

Methodology

This was a case-control study that involved 50 patients with stages 2 to 4 CKD as cases, and 50 age and sex matched apparently

normal individuals without any known medical illness as controls. Subjects who fulfilled the inclusion criteria and gave informed consent were serially recruited from the nephrology outpatient clinic while age and sex matched apparently healthy adults without hypertension and diabetes were recruited from the community. All the patient population studied were blacks from Nigeria.

This study was conducted at Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC). Ethical approval was obtained from the Institutions' Ethical Review Board before the commencement of the study. Informed written consent was obtained from all participants in this study.

Patients (aged $\geqslant 18$ years) with CKD and estimated glomerular filtration rate (eGFR) between 15 and 90 mL/min per 1.73 m² (stages 2 -4 CKD) were included in the study while CKD patients with calculated eGFR < 15 mL/min (stage 5 CKD), dialysis dependent CKD patients, and patients with primary cardiovascular or valvular heart disease were excluded. (Primary CVD/valvular disease were excluded with history, examination, and ultimately with echocardiography, which all studied participants underwent.)

CKD was defined in this study as abnormalities of kidney structure or function, present for >3 months, with implications for health.[12] CKD was also staged based on eGFR determined using the Cockcroft and Gault formula.[13] Cockcroft and gault was validated in the study population and was found to be adequate for determining eGFR in them.[13–15]

Clinical CVD was defined in this study based on the Kidney Disease Outcome Quality Initiative (KDOQI) definition as cardiovascular events comprising of stroke, arrhythmias, peripheral arterial disease, ischemic heart disease, and congestive cardiac failure.[12,16] Congestive cardiac failure was defined based on the Framingham criteria. (Congestive heart failure was diagnosed if at least 2 major criteria or 1 major and 2 minor criteria were met),[17,18] while ischemic heart disease was defined according to World Health Organization criteria (diagnosed if 2 of typical chest pain, new ST changes on electrocardiogram and elevated cardiac enzymes were present).[19] In this study, peripheral arterial disease was defined based on history of intermittent claudication/rest pain on lower limb as well as hand held Doppler derived ankle brachial index less than 0.9.[20] Stroke or transient ischemic attack (TIA) was recorded if there was a history of stroke or TIA symptoms, diagnosis of stroke or TIA in a hospital or finding of classical presentation, or of such documentation in patients' clinical notes confirmed by cranial neuroimaging. Arrhythmia was defined based on electrocardiographic evidence such as sinus bradycardia, sinus tachycardia, premature atrial complexes, first and second-degree heart block, right bundle branch block, and left anterior fascicular block.[21,22]

The sociodemographic and clinical parameters were assessed using a clinical proforma. Blood investigations were performed to establish baseline renal function and to assess risk factors for CVD. All the participants in this study had 12 lead electrocardiogram to evaluate arrhythmias and to establish the presence of left ventricular hypertrophy. Echocardiography was performed using 2-dimensional, M-mode, conventional Doppler as well as tissue Doppler imaging to assess cardiac structure and function. Ankle brachial index[23–25] was assessed using the hand held Doppler machine.

Carotid intima-media thickness was assessed using the carotid ultrasound machine. (Mind ray Real time ultrasound scanner DC-6 with Doppler facilities: transducer probe frequency of 7.5 MHz.) With the subject in supine position, neck extended and head turned 45° away from the side being scanned, the intima-media thickness of both common carotid arteries on longitudinal views were measured at 3 different sites about 1 cm proximal to the bulb and the average of the 3 measurements taken. The intima-media thickness (IMT) was defined as the distance between the leading edge of the luminal echo to the leading edge of the adventitia of the media. Carotid intima-media thickness is a well-validated research tool.[26] In this study, CIMT was considered thickened if its thickness was greater than 0.8 mm.[27] Examiner was blinded to both subjects and controls in performing the procedures.

Statistics

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA). Data that were normally distributed were analyzed using parametric tests, while data not normally distributed were evaluated with the nonparametric tests. Continuous variables were described as means and standard deviation (SD) while categorical variables were expressed as proportions. Means of continuous variables for cases and controls were compared using the Student t test while categorical variables were analyzed with chi-square. Correlation was used to define the relationship between the means of 2 continuous variables while regression analysis was performed to describe the relationship between a set of independent variables and the dependent variable. The level of significance was P-value of $\leqslant .05$ and confidence interval of 95%.

Results

One hundred subjects participated in the study, comprising 50 stages 2 to 4 KDOQI CKD subjects, and 50 apparently healthy age and sex matched individuals that served as normal controls. The proportion of CKD patients with eGFR between 60 and 89 mL/min/1.73 m² (stage 2 CKD), 30 to 59 mL/min/1.73 m² (stage 3 CKD), and 15 to 29 mL/min/1.73 m² (stage 4 CKD) was 38%, 46%, and 16%, respectively.

The age range of the participants was between 23 and 65 years. As shown in Table 1, there was no difference in the mean ages of both subjects and controls (51.06 ± 11.09 vs 51.65 ± 13.80; P = .906). Each group comprised 33 men and 17 women. The anthropometry measures (weight, height, and body mass index [BMI]) were not statistically different in both subjects and control, whereas the cardiovascular parameters such as heart rate and the mean arterial pressure were

Table 1. Anthropometric and cardiovascular features of the study population.

PARAMETERS	MEAN ± SD (SUBJECTS)	MEAN ± SD (CONTROLS)	*P*-VALUE
Gender (male), No.	33	33	
Gender (female), No.	17	17	
Age, y	51.06 ± 11.90	51.65 ± 13.80	.906
Weight, kg	68.05 ± 12.14	68.15 ± 12.93	.968
Height, m	1.67 ± 0.10	1.66 ± 0.09	.836
BMI, kg/m²	24.67 ± 4.61	25.12 ± 5.09	.644
HR, beats/min	78.40 ± 0.61	73.08 ± 0.49	.007*
SBP, mm Hg	149.21 ± 26.01	111.64 ± 0.91	<.001**
DBP, mm Hg	86.29 ± 14.8	71.00 ± 11.11	<.001**
MAP, mm Hg	106.99 ± 18.46	84.55 ± 10.73	<.001**

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; No., number of male and female subjects and controls; SBP, systolic blood pressure.
*Significant *P*-value < .05; **Significant *P*-value < .001.

significantly higher in CKD subjects compared with controls (1.67 ± .10 vs 1.66 ± 0.09, *P*=.007 and 106.99 ± 18.46 vs 84.55 ± 10.73, *P*<.05) respectively.

Laboratory parameters of study subjects. As shown in Table 2, serum chemistry in the cases showed worse renal function indices compared with the controls as evidenced by higher serum urea and creatinine (8.70 ± 6.14 vs 3.81 ± 0.91, *P*<.001; 159.19 ± 80.74 vs 86.06 ± 14.23, *P*<.001) and lower eGFR values (52.11 ± 18.57 vs 85.95 ± 22.30, *P*<.001). Chronic kidney disease populations also had impaired lipid profile parameters compared with controls. Serum hemoglobin concentration (11.85 ± 1.79 vs 14.65 ± 1.12, *P*<.001) is lower in the study populations, whereas erythrocyte sedimentation rate (ESR) was found to be higher in them (50.84 ± 35.18 vs 10.46 ± 9.28, *P*<.001) The mean CIMT results for both right and left common carotid arteries were significantly increased in the subjects compared with the controls (1.1 ± 0.38 vs 0.70 ± 0.10 and 1.1 ± 0.43 vs 1.0 ± 0.11; *P*<.001 for both right and left, respectively).

Table 3 details gender difference between various parameters, with BMI and packed cell volume (PCV) showing significant difference between men and women (*P*-values .027 and .013), respectively (Figure 1).

There was a negative correlation between the mean arterial pressure (mm Hg) and the eGFR (mL/min) (*r*=−0.285; *P*<.001) as shown in Figure 2.

Correlation between the mean arterial pressure and the eGFR. Tables 4 to 6 reveal positive correlation between CIMT and age, hypertension, mean arterial blood pressure, random blood sugar, and ESR, while negative correlation was recorded with eGFR, Plasma albumin level, and high-density lipoprotein (HDL; Figure 3).

Correlation between carotid intima–media thickness (CIMT) and various echocardiographic parameters. Right CIMT positively correlated with left atrial diameter (LAD): *r*=0.570, *P*=<.001; left ventricular posterior wall in diastole (LVPWD): *r*=0.369, *P*<.001; interventricular septal diameter in diastole (IVSD): *r*=0.480, *P*<.001. Left CIMT correlated positively with LAD: *r*=0.862, *P*=<.001; LVPWD: *r*=0.257, *P*=.010; IVSD: *r*=0.344, *P*<.001.

While negative correlation occurred between CIMT and fractional shortening (FS), LVEF, estimated glomerular filtration rate (eGFR), and the result is as stated below:

Right CIMT and FS: *r*=−0.293, *P*=.003; LVEF: *r*=−0.334, *P*<.001; eGFR: *r*=−0.402, *P*<.001.

Left CIMT and FS: *r*=−0.250, *P*=.012; LVEF: *r*=−0.303, *P*=.002; eGFR: *r*=−0.346, *P*<.001.

Correlation analysis was performed to evaluate relationship between CIMT and various parameters. The factors with significant correlation were further analyzed using the multiple linear regression analysis with resultant factors: low LVEF and increased LAD and erythrocyte sedimentation rate (ESR) as the predictors of CIMT in the studied population.

Tables 7 and 8 showed LVEF, LAD, and ESR as the positive predictors of CIMT in CKD patients. eGFR, though showed negative association on correlation, was no longer significant on further multivariate analysis.

A significantly higher proportion of patients with CKD had increased CIMT as compared with the controls (84% vs 18%; *P*<.001) as shown in Table 9.

A total of 17 (34%) of the CKD patients had one form of the CVD studied with arrhythmias being the most prevalent

Table 2. Laboratory characteristics of the study population.

PARAMETERS	MEAN ± SD (SUBJECTS)	MEAN ± SD (CONTROL)	P-VALUE
Sodium, mmol/L	134.06 ± 3.63	133.90 ± 3.93	.833
Potassium, mmol/L	3.68 ± 0.60	3.61 ± 0.43	.512
Urea, mmol/L	8.70 ± 6.14	3.81 ± 0.91	<.001**
Creatinine, μmol/L	159.19 ± 80.74	86.06 ± 14.23	<.001**
HCO_3, mmol/L	22.30 ± 2.14	23.00 ± 2.40	.127
Uric acid, mmol/L	0.38 ± 0.13	0.27 ± 0.11	.001*
Calcium, mmol/L	2.10 ± 0.25	2.31 ± 0.14	<.001**
Phosphate, mmol/L	1.52 ± 0.81	1.04 ± 0.26	<.001**
eGFR, mL/min	52.11 ± 18.57	85.95 ± 22.30	<.001**
FPG, mmol/L	5.30 ± 1.90	4.49 ± 0.51	.006*
Total cholesterol, mmol/L	6.28 ± 3.32	4.67 ± 1.06	.002*
HDL cholesterol, mmol/L	1.24 ± 0.26	1.41 ± 0.24	.001*
LDL cholesterol, mmol/L	3.96 ± 2.95	2.8 ± 0.82	.009*
TG cholesterol, mmol/L	1.13 ± 0.72	0.90 ± 0.29	.049*
PCV, %	35.54 ± 5.38	42.94 ± 3.35	<.001**
Hb conc., g/dL	11.85 ± 1.79	14.65 ± 1.12	<.001**
Total WBC count × 10^3 (cell/mm³)	5.90 ± 1.90	5.13 ± 1.51	.039*
ESR, mm/h	50.84 ± 35.18	10.46 ± 9.28	<.001**
Right CIMT	1.1 ± 0.38	0.70 ± 0.10	<.001**
Left CIMT	1.1 ± 0.43	0.70 ± 0.11	<.001**

Abbreviations: CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; Hb conc., hemoglobin concentration; HCO_3, serum bicarbonate; HDL, high-density lipoprotein; LDL, low density lipoprotein; PCV, packed cell volume; TG, serum triglycerides; WBC, white blood cell.
*Significant P-value < .05; **Significant P-value < .001.

followed by stroke. Ischemic heart disease/heart failure was the least pattern of CVD found in CKD patient population.

Characteristic findings in CKD patients with CVD and those without. There was no significant difference observed in the laboratory parameters between CKD patients with CVD and those without as illustrated in Table 10.

Discussion

This study targeted predialytic CKD patients with reduced eGFR. Various studies have established a high burden of CVD in dialytic CKD patients and this has been less well studied in predialytic CKD patients.[28,29]

In this study, the mean age of patients with CKD indicates that a large proportion are in their economically productive years, that is, less than 60 years of age, unlike what is observed in industrialized countries where the peak age of presentation is 65 to 74 years[30–33] Various reports of CKD in different parts of sub-Saharan Africa suggested that it occurs commonly in young adults between the ages of 20 and 50 years, unlike the comparatively older age groups affected in developed countries.[30–33] This definitely has a negative implication on the country's economy.[34–36] Some of the justifications for the younger age of patients with CKD in the developing world include high preponderance of infections/infestations, especially in childhood leading to chronic glomerulonephritis, which is one of the prevailing causes of CKD in Africa[32,33,36]

Carotid intima-media thickness is a measure of atherosclerotic vascular disease, and it is considered a comprehensive picture of all alterations caused by multiple cardiovascular risk factors over time on the arterial walls.[20,26,37] Carotid intima-media thickness is a noninvasive and reproducible method of

Table 3. Student *t* test showing gender difference between various cardiovascular parameters.

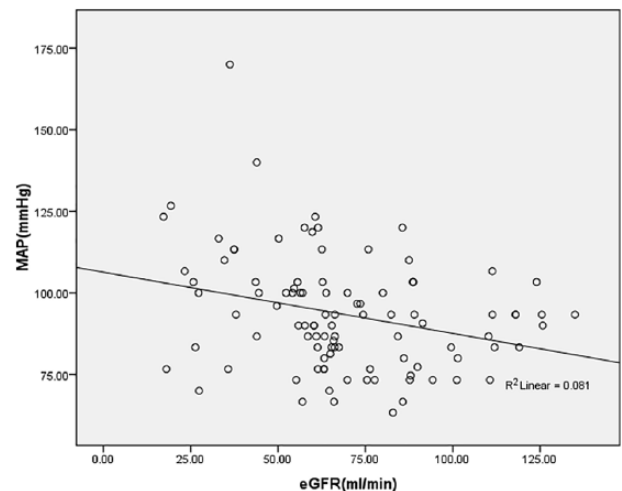| PARAMETERS	MALE	FEMALE	*P*-VALUE
Age	48.3 ± 16.60	51.06 ± 14.94	.568
BMI	23.46 ± 3.5	27.01 ± 5.62	.027**
Systolic BP	143.21 ± 30.85	134.71 ± 26.01	.336
Diastolic BP	84.55 ± 18.04	83.65 ± 11.12	.85
EF	67.57 ± 11.05	72.79 ± 5.46	.073
FS	38.43 ± 8.8	41.56 ± 5.4	.188
LAD	3.87 ± 0.06	3.82 ± 0.46	.78
Rt CIMT	0.11 ± 0.44	0.10 ± 0.02	.1
Lt CIMT	0.11 ± 0.05	0.10 ± 0.02	.26
PCV	36.88 ± 5.35	32.94 ± 4.53	.013**
ESR	53.43 ± 35.63	41.33 ± 34.82	.466
Urea	9.56 ± 6.72	7.02 ± 4.55	.168
Creatinine	172.28 ± 85.97	133.76 ± 64.35	.11
eGFR	50.60 ± 17.99	55.05 ± 19.86	.427
LVMI	117.65 ± 41.86	103.99 ± 16.82	.109

Abbreviations: BMI, body mass index; BP, blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FS, fractional shortening; LAD, left atrial diameter; Lt CIMT, left carotid intima-media thickness; LVMI, left ventricular mass index; PCV, packed cell volume; Rt CIMT, right carotid intima-media thickness.
*P-value significant at $< .05$.
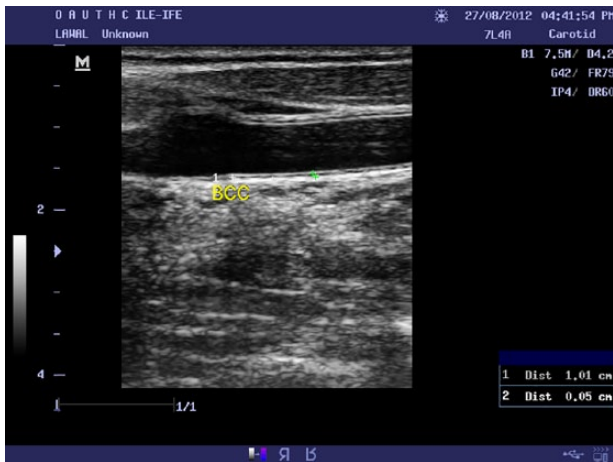
Figure 1. Ultrasound imaging of the common carotid artery showing a soft lucent atheroma at the point of bifurcation. BCC indicates bifurcation of the common carotid artery.

Figure 2. Correlation between eGFR and mean arterial pressure. MAP indicates mean arterial pressure; eGFR, estimated glomerular filtration rate.

identifying and quantifying subclinical CVD and for evaluating cardiovascular risk. Individuals with subclinical atherosclerosis are likely to experience future cardiovascular events, thus identifying such individuals and providing evidence-based medical intervention reduce cardiovascular risk, which likely decreases future morbidity and mortality from CVD.[20,38]

The CIMT was increased in patients with CKD compared with age-matched controls. This suggests that prevalence of carotid atherosclerosis is significantly higher in the CKD patients compared with controls. This compares favorably with findings by Zoungas et al.,[39,40] who found significantly

Table 4. Correlation between the mean CIMT and various parameters.

PARAMETERS	*R* VALUE	*P*-VALUE
Age	0.264	<.05*
HT	0.49	<.01*
MAP	0.466	<.05*
RBG	0.394	<.05*
ESR	0.498	<.05*
eGFR	−0.32	<.05*
Alb	−0.34	<.05*
HDL	−0.239	<.05*

Abbreviations: Alb, plasma albumin level; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; HT, hypertension; MAP, mean arterial pressure; RBG, random blood glucose.
*Statistically significant with *P*-value <.05.

Table 5. Correlation between right CIMT and various parameters.

PARAMETERS	*R* VALUE	*P*-VALUE
Age	0.282	.004*
ESR	0.479	<.001**
eGFR	−0.402	<.001**
MAP	0.426	<.001**
Serum creatinine	−0.288	.004*
Uric acid	0.372	.002*
LVM	0.354	<.001**

Abbreviations: CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LVM, left ventricular mass; MAP, mean arterial pressure.
*Significant *P*-value <.05; **Significant *P*-value <.001.

Table 6. Correlation between the left CIMT and various parameters.

PARAMETERS	R VALUE	*P*-VALUE
Age	0.228	.022*
ESR	0.462	<.001**
eGFR	−0.346	<.001**
MAP	0.347	<.001**
Serum creatinine	−0.273	.006*
Uric acid	0.221	.071
LVM	0.333	.001*

Abbreviations: CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LVM, left ventricular mass; MAP, mean arterial pressure.
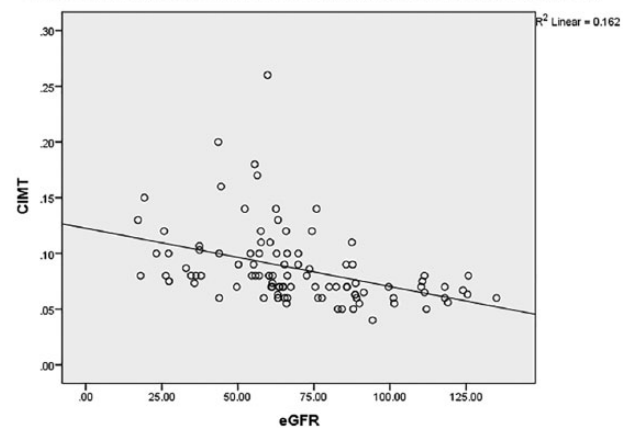*Significant *P*-value <.05; **Significant *P*-value <.001.

Figure 3 shows negative correlation between CIMT and the eGFR.

Figure 3. Correlation between eGFR and CIMT. eGFR indicates estimated glomerular filtration rate; CIMT, carotid intima-media thickness.

Table 7. Multiple linear regression for predictors of right carotid artery intimal thickness.

PARAMETERS	*B*	*β*	*P*-VALUE
LVEF	0.001	−2.743	.001*
LAD	0.025	0.414	<.001**
ESR	<0.001	0.204	.032*
eGFR	<0.001	0.14	.135

Adjusted R^2 = 0.502.
Abbreviations: eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LAD, left atria diameter; LVEF, left ventricular ejection fraction.
*Significant *P*-value <.05; **Significant *P*-value <.001.

Table 8. Multiple linear regression for predictors of left carotid artery intimal thickness.

PARAMETERS	*B*	*β*	*P*-VALUE
LVEF	−0.001	−0.213	.017**
LAD	0.033	0.465	<.0001**
ESR	<0.001	0.215	.033**
eGFR	<−0.001	−0.043	.659

Adjusted R^2 = 0.462.
Abbreviations: eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.
*Significant *P*-value <.05; **Significant *P*-value <.001.

thickened CIMT in CKD patients compared with controls (0.89 ± −0.17 vs 0.73 ± −0.13 mm, respectively). Some other authors also reported similar findings.[9,41]

In this study, clinical CVD was highly prevalent in the CKD population studied (8% had stroke, 20% had arrhythmias, 4% had peripheral arterial disease, and 2% had ischemic heart disease, congestive cardiac failure). Studies have shown

Table 9. Carotid intima media thickness in the study population using chi-square.

PARAMETERS	SUBJECTS, NO. (%)	CONTROLS, NO. (%)	X^2	*DF*	*P*-VALUE
Abnormal CIMT (thickened ≥ 0.8 mm)	42 (84)	9 (18)	43.58	1	<.001**
Normal CIMT (not thickened < 0.8 mm)	8 (16)	41 (82)			

Abbreviation: CIMT, carotid intima-media thickness.
**Statistically significant with a *P*-value of <.001.

Table 10. Comparison of physical, cardiac and laboratory parameters between CKD patients with CVD and CKD patients without CVD.

PARAMETER	CKD WITH CVD (MEAN ± SD) n = 17	CKD WITHOUT CVD (MEAN ± SD) n = 33	*P*-VALUE
Height, cm	166.41 ± 11.36	166.61 ± 8.65	.946
Weight, kg	66.73 ± 11.63	70.62 ± 13.05	.288
BMI, kg/m²	24.13 ± 4.47	25.69 ± 4.83	.263
HRrest, b/min	80.59 ± 11.15	77.27 ± 10.31	.3
SBPrest, mm Hg	145.88 ± 17.41	140.42 ± 29.55	.406
DBPrest, mm Hg	85.29 ± 13.28	83.70 ± 17.28	.74
MAP, mm Hg	105.20 ± 13.83	102.61 ± 20.63	.842
Creatinine, µmol/L	166.42 ± 89.11	145.14 ± 59.11	.383
Hco_3, mmol/L	22.06 ± 2.22	23.42 ± 2.12	.573
TC, mmol/L	5.32 ± 1.22	6.29 ± 3.07	.129
TG, mmol/L	0.98 ± 0.48	1.22 ± 0.83	.277
HDL, mmol/L	1.33 ± 1.00	1.46 ± 1.61	.763
LDL, mmol/L	3.08 ± 1.49	3.54 ± 1.51	.116

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; Hco_3, serum bicarbonate; HDL, high-density lipoprotein; HR, heart rate; LDL, low density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, serum triglycerides.
P-value is significant at <.05.

that ischemic heart disease and heart failure may present atypically in CKD patients with majority of these patient population presenting with silent ischemia and hence do not present in the acute state.[42] Previous studies show changing prevalence of CVD burden in hemodialytic CKD patients across countries: A study in the United States found ischemic heart disease, heart failure, peripheral vascular disease, and cerebrovascular disease in 41%, 40%, 22%, and 13% in the end-stage renal disease patients studied and 17%,14%,16%, and 2%, respectively, in hemodialytic patients[43] in Spain. This is in support of studies which establish CVD as a continuum across the CKD stages, with majority of the CKD patients succumbing to CVD and hence a very high burden in the subgroup reaching end stage renal disease and on hemodialysis.[8,43–45]

Cardiovascular parameters like blood pressure, mean arterial pressure, and heart rates in subject were found to be much higher in CKD patients compared with controls; this is in spite of the fact that majority of the CKD subjects were on 2 or more antihypertensive medications. Studies have shown that blood pressure control is likely to be suboptimal when CKD is present in spite of regular guideline directed therapies.[4] Lipid profiles were also found to be significantly impaired in the CKD patients compared with controls. The prevalence of dyslipidemia is high in patients with CKD and the prevalence is said to vary according to renal function; this has been repeatedly shown in other studies.[46] Serum uric acid is commonly elevated in subjects with CKD, uric acid has been seen as a potential contributory risk factor in the development and progression of CKD. Most studies documented that an elevated serum uric acid level independently predicts the development of CKD. Pilot studies suggest that lowering plasma uric acid concentrations may slow the progression of renal disease in subjects with CKD. Uric acid is emerging as

a potentially modifiable risk factor for CKD.[47] BMI and PCV showed significant gender difference. Increased BMI in women and its association with CKD has been demonstrated in previous studies.[48] Gender difference in hemoglobin concentration and PCV is well established and it is attributable to hormonal effect on erythropoiesis. Correlation between CIMT and various parameters was found in this study and this has been buttressed by different studies, which show significant association between traditional cardiovascular risk factors and severity of kidney dysfunction. Nontraditional oxidant stress have also been found to increase in frequency as renal function decline.[45,49,50] Echocardiographic parameters showed significant association with CIMT in the study population; similar associations have been documented in previous studies. After regression analysis, elevated LAD, ESR, and low ejection fraction predicted carotid intima-media thickness; eGFR had significant negative correlation which was not significant on multivariate analysis; this implies that simple tests like ESR as well as LAD and EF are very useful, especially in areas with no access to ultrasound and technical abilities to perform CIMT. These cardiovascular risk factors are highly prevalent in CKD patients and they significantly contribute to the excessive CVD in them; however, these cardiovascular risk factors alone do not exclusively explain the CVD in CKD patients. No significant difference was found in CKD patients with CVD and CKD patients without CVD further supporting the fact that CKD itself is an independent cardiovascular risk.[45,50-52]

Management of CVD in CKD patients comprise of use of antiplatelets, statins, angiotensin converting enzyme–inhibitors (ACE-I), angiotensin-receptor blockers (ARBs), and B-blockers. Studies have shown that optimal drugs are not used sufficiently in CKD patients, though optimal drug use have been shown to be of mortality benefit,[45,53] and combination therapy have been associated with favorable outcome.[4] Antiplatelet treatments constitute the basis of treatment for CVD with a clear advantage for low dose aspirin even in CKD patients in observational studies. No major bleeding episodes were found irrespective of CKD stage, although minor bleeding episodes could not be ruled out. Clopidogrel is advised in patients with acute coronary syndrome but less effective in CKD patients.[45] Molnar et al[54] revealed that the use of ACE-I/ARBs was linked with greater survival in nondialysis dependent CKD patients. B-blocker has mortality benefits in CKD patients with systolic heart failure[55]; KDOQI recommends statin use in CKD patients not on hemodialysis.[16] This is in tandem with another study which shows reduction in atherosclerotic events in CKD but indefinite mortality benefits suggesting that CKD may lead to cardiovascular mortality through pathways independent of statins.[56]

Other diagnostic modalities for CVD in CKD patients which may facilitate early and prompt diagnosis of CVD have been recorded in other studies, they include Cardiac SPECT (single photon emission computerized tomography), dobutamine stress echocardiography, stress CMR (cardiac magnetic resonance), and Coronary CT (computerized tomography) angiography.[45]

Elevation of fibroblast growth factor 23 (FGF 23), which studies have found to be the earliest detected serum abnormality of CKD-MBD (chronic kidney disease-mineral and bone disorder) have also been linked with CVD in CKD patients.[57] These tools are unavailable for the benefits of our patients. However, CIMT, which is a cheap, available and noninvasive investigation tool, is of importance in a developing nation like Nigeria with limited resources, the practicality of which has also been described by other studies[37] and hence its utility as substitute marker for CVD in CKD patients in this part of the world.

Limitations

The Cockcroft and Gault formula was used for eGFR instead of the more accurate Modification of Diet in Renal Disease (MDRD) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). (However, Cockcroft and gault was validated in the study population.)

Some biomarkers of poor cardiovascular outcomes regarded as nontraditional cardiovascular risk factor (inflammation, oxidative stress, sympathetic activation, hyperhomocysteinemia) cannot be measured due to resource limitation. Vitamin D and iPTH values could not be assessed in the study.

Conclusions

Increased CIMT, a measure of atherosclerotic vascular disease, was found to be higher in CKD patients compared with individuals without CKD. Cardiovascular disease was highly prevalent in CKD patients compared with controls. Carotid intima-media thickness was well correlated with many cardiovascular risk factors; hence, CIMT has the potential for evaluating CVD burden in CKD patients. Elevated LAD, ESR, and low EF predicted CIMT. Findings underscore the need for early assessment of these patients for CVD, as prompt treatment may prevent cardiovascular events and retard the progression of kidney disease. Surrogate measures such as CIMT are likely to improve risk assessment in CKD patients.

Author Contributions

Supervisors: MOB, AOA, AA.
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