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Carotid Intima Media Thickness Measurements in Nigerian Pre-dialysis CKD Patients

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Abstract
Background: *Cardiovascular disease complications are the commonest causes of mortality in patients with Chronic Kidney Disease (CKD). Carotid intima-media thickness (CIMT) measurements provide information on arterial wall thickness. This study explores CIMT in CKD patients.*
Methods: *one hundred and seven pre-dialysis CKD patients were consecutively recruited. Eighty one healthy subjects served as control. A pre-tested questionnaire was administered and physical examination done. Fasting blood samples were collected. CIMT was measured using high resolution B mode ultrasonography at 3 sites - the distal common carotid artery, the internal carotid artery and the carotid bulb. The mean value was calculated.*
Results: *CIMT was significantly increased in CKD patients. Mean CIMT among CKD patients was 0.120 ± 0.015mm and 0.092 ± 0.034mm in controls, p<0.001. CIMT correlated significantly with age, eGFR, creatinine level, triglyceride level, and history of diabetes. Serum creatinine however best predicted CIMT. There was no correlation between CIMT and total cholesterol, HDL, LDL, calcium phosphate product and blood pressure in the CKD patients.*
Conclusion: *CIMT is increased in CKD patients suggesting that carotid atherosclerosis is more prevalent in them. It is recommended that CIMT measurements be done in our CKD patients to identify patients at high risk of cardiovascular episodes for possible intervention.*
Keywords: *Carotid artery, intima-media thickness, chronic kidney disease, Nigeria.*

Introduction

Chronic kidney disease (CKD) is a global public health problem. It is defined by the Kidney Disease Outcome Quality Initiative of National Kidney Foundation (K/DOQI-NKF) as either Kidney damage (defined as pathologic abnormalities or markers of damage, including abnormalities of blood, or urine test, or imaging studies) with or without decrease in GFR; or a decrease in GFR < 60ml/min/1.73m^2; for 3 or more months[1].

There is an increasing trend in the prevalence of end stage renal disease (ESRD). Studies in some developing countries show prevalence rates of

CKD comparable to those from developed countries. In Nigeria and other parts of Africa, CKD is a common disease accounting for a significant proportion of patients dying in a typical hospital medical ward. Ulasi, et al in Enugu, South East Nigeria found that ESRD accounted for 7.96% of all medical admissions and 41.69% of renal admissions over a 14 years period[2]. Nigerian Association of Nephrology guidelines for the detection and management of CKD reported that hospital prevalence studies of advanced CKD represent 6% -12% of medical admissions while small community studies found that prevalence of CKD ranges between 19% - 30%[3].

Various complications occur in CKD which include: anaemia, cardiovascular disease (CVD), CKD-mineral and bone disorders, skin disease, gastrointestinal complications, metabolic abnormalities, endocrine abnormalities, muscle dysfunction and uremic neuropathies. Cardiovascular disease is the main cause of death in CKD before patients get to ESRD[4]. Atherosclerotic changes which predict cardiovascular events are considerably high in CKD patients[5]. Factors that are implicated include lipid disorders, increased oxidative stress, chronic inflammation, anaemia, hypertension, and hyperhomocysteinemia, disorders of calcium and phosphorus metabolism and metabolic deficiencies of glucose. An early sign of atherosclerosis is thickening of the arterial wall, and carotid intima-media thickness measurements provide information on arterial wall thickness.

CIMT is a non-invasive marker of arterial wall alteration which can be easily assessed in the carotid arteries by high resolution B mode ultrasound. It is relatively inexpensive, yields pathophysiological information at early stages of the disease and can be performed repeatedly with no adverse effects[6].

There is paucity of information on vascular changes and arteriosclerosis in CKD patients in black Sub-Saharan Africans. This study therefore aims to determine the association between carotid intima- media thickness of CKD patients and the following selected factors: age, estimated GFR (eGFR), calcium phosphate product, lipid profile, blood pressure, and blood sugar.

Methods

This study was cross sectional, case controlled and hospital based conducted over a period of 6 months, at a tertiary institution in South-east Nigeria.

One hundred and seven consenting CKD patients were consecutively recruited. Eighty one (81) subjects who were screened and had no kidney disease served as controls. The control groups were sex and ages matched with the CKD patients and were neither hypertensive nor diabetic.

Screening exercises to exclude CKD in control subjects included blood pressure measurement, urinalysis, measurement of serum creatinine and calculation of eGFR using the MDRD equation. Hypertension and diabetes mellitus were also excluded in the control group. Inclusion criteria were: adult patients of both sexes between 18 and 70 years with CKD. The following were excluded from the study: Patients who declined consent, patients with acute kidney injury, renal cell carcinoma, multiple myeloma, and lymphoma.

Ethical clearance was obtained from the Research and Ethics committee of the hospital.

Screening questionnaire to identify symptoms of CKD was pretested on 10 consecutive subjects to assess performance. This was reviewed and applied to consenting patients and controls. Anthropometric data comprising height and weight were collected and a detailed physical examination done at the point of recruitment of patients and control subjects into the study. Systolic and diastolic blood pressures (SBP and DBP) respectively were measured with Accusson mercury sphygmomanometer using standard procedure. Mean arterial blood pressure (MAP) was calculated from the Pulse pressure and DBP using standard formulae. Values $\geq$ 140/90mmHg or MAP > 110mmHg was taken as hypertension [7].

Fasting blood samples for calcium, phosphorus, lipid profile, glucose and 2 hour post prandial glucose were collected from participants. Creatinine clearance was calculated using the MDRD formula and the degree of renal impairment classified [1].

After a brief explanation of the procedure, each participant was placed in supine position. Manual measurements of the Intima Media Thickness (IMT) of the distal common carotid artery, the bulb [6] and the internal carotid artery was done in the longitudinal/transverse angles with the head rotated to the opposite side of examination using a high resolution B mode ultrasonography and 6-13 MZ transducer. The maximum IMT at the segments were measured[8]. The mean intima-media thickness value of the three different segments was calculated.

Statistical analysis was done using the Statistical Package for Social Science (SSPS Inc. Chicago, IL) version 17 statistical software. The frequencies, mean, and standard deviation were generated. Numerical variables were analysed with z test and categorical variables with chi square. A p value of less than 0.05 was taken as statistically significant. Logistic regression analysis was used for independent associations with CIMT.

Results

Table 1 showed the sex distribution of the study participants. There was no significant gender difference between the CKD patients and the controls. Majority of the CKD patients were in stages 3 and 4 (26.2% and 40.2% respectively), table 2.

Table 3 depicted the characteristics and basic data of CKD patients compared to controls. There was no significant difference between the CKD patients and controls in terms of mean age, weight, height, body mass index (BMI), serum calcium and high density lipoprotein (HDL) levels. However, the CKD patients had higher mean arterial pressure (MAP), serum creatinine, phosphate, calcium-phosphate product (CPP), total cholesterol, low density lipoprotein (LDL), and triglyceride than controls. The mean carotid intima media thickness (CIMT) was significantly higher in CKD patients than controls. This was observed in the distal carotid artery (DCA), internal carotid artery (ICA), and carotid artery bulb. The p values were all < 0.001. Fifty two percent (52%) of the CKD patients were on lipid lowering agents, while 66% were on antihypertensive medication.

Table 4 showed the association between mean carotid intima media thickness and CKD stage. There was significant association between CKD stage and mean CIMT. Those with stage 5 CKD had higher mean CIMT compared to other stages. The association between mean CIMT and age group of the CKD patients were depicted in table 5. There was a significant association between the various age groups and mean CIMT. The older age groups had significantly higher CIMT than the younger age groups, $p < 0.001$.

Table 6 showed the correlation between CIMT with various variables affecting it. Age of the patient, history of diabetes mellitus, serum fasting triglyceride level, and serum creatinine level correlated positively with CIMT. The higher the age, triglyceride level, blood sugar and serum creatinine levels, the higher the CIMT. The eGFR showed a negative correlation. The lower the eGFR, the higher the CIMT. Serum calcium, phosphorus, calcium-phosphate product, blood pressures, total cholesterol, HDL, and LDL did not correlate with CIMT.

Table 7 showed the logistic regression analysis of the variables that showed significant correlation in table 6. Age, eGFR and serum creatinine predicted CIMT with serum creatinine being the best predictor. The higher the serum creatinine level, the more likely a CKD patient is to having higher intimal thickening.

Table 1: Sex Distribution of the Study Population

Sex	CKD	Control	Total	P-Value
Male	63 (58.9%)	44 (54.3%)	107 (56.9%)	
Female	44 (41.1%)	37 (45.7%)	81 (43.1%)	
Total	107 (100%).	81 (100%)	188 (100%)	0.532

Table 2: CKD Stages of Patients

CKD Stages	No Of Patients	(%)
Stage 2	11	10.6
Stage 3	28	26.2
Stage 4	44	41.1
Stage 5	24	22.4
TOTAL	107	100

Table 3: Basic Demographic, Laboratory and Doppler Echocardiographic Characteristics of the Study Participants

Parameter	CKD(N=107) Mean±SD	Controls(N=81) Mean±SD	P-value
Age(years)	41.81 ± 13.95	40.56 ± 13.05	0.530
Weight(kg)	64.74 ± 24.38	68.8 ± 14.95	0.054
Height(m)	1.67 ± 0.10	1.68 ± 0.09	0.479
BMI(kg/m^2)	23.92 ± 3.30	24.75 ± 4.22	0.132
MAP (mm/Hg)	106.93 ± 11.60	91.12 ± 6.30	< 0.001
Creatinine	324 ± 182.5	87.6 ± 17.2	< 0.001
eGFR (mls/min)	27.93 ± 16.17	96 ± 15.3	< 0.001
Ca^{2+} (mmol/l)	2.34 ± 1.75	2.46 ± 01	0.074
PO_4 (mmol/l)	1.75 ± 0.42	1.25 ± 0.21	< 0.001
CPP($mmol^2/l^2$)	4.07 ± 0.98	2.91 ± 0.62	< 0.001
Total cholesterol (mmol/l)	5.61 ± 0.64	4.67 ± 0.45	0.04
HDL (mmol/l)	0.96 ± 0.52	0.88 ± 0.61	0.42
LDL (mmol/l)	3.26 ± 1.72	3.12 ± 1.20	< 0.001
Triglyceride (mmol/l)	1.99 ± 0.74	1.58 ± 0.43	< 0.001
Lipid lowering agents	56 (52%)	0	< 0.001
Antihypertensive agents	71 (66%)	0	< 0.001
CIMT Mean (cm)	0.120±0.015	0.092±0.034	< 0.001
CIMT DCA (cm)	0.123±0.017	0.090±0.022	< 0.001
CIMT ICA (cm)	0.111±0.016	0.080±0.026	< 0.001
CIMT Bulb (cm)	0.127±0.018	0.110±0.081	< 0.001

Table 4: Association between mean CIMT and CKD Stages

CKD Stage	Mean IMT			
	DCA (cm)	ICA (cm)	BULB (cm)	Mean (DCC+ICA+BULB)
2	0.114±0.010	0.101±0.008	0.124±0.010	0.113±0.007
3	0.122±0.015	0.110±0.014	0.129±0.017	0.0120±0.014
4	0.121±0.019	0.110±0.017	0.126±0.020	0.119±0.017
5	0.130±0.017	0.117±0.018	0.139±0.016	0.127±0.015
P-value	<0.001	<0.001	0.047	<0.001

Table 5: Association between CIMT and Age Group of CKD patients

Age Group	Mean IMT			
	DCC (cm)	ICA (cm)	BULB (cm)	Mean (DCC+ICA+BULB)
<20years	0.120±0.003	0.105±0.007	0.135±0.021	0.120±0.009
20-29years	0.109±0.009	0.093±0.010	0.109±0.015	0.101±0.010
30-39years	0.120±0.010	0.109±0.007	0.125±0.15	0.118±0.008
40-49years	0.127±0.010	0.112±0.012	0.130±0.09	0.123±0.009
50-59years	0.131±0.012	0.119±0.016	0.138±0.010	0.123±0.011
60-69years	0.122±0.017	0.129±0.013	0.140±0.014	0.139±0.012
P-value	<0.001	<0.001	<0.001	<0.001

Table 6: Correlation of CIMT with Selected Variables

Variables	Coefficient (r)	P-value
Age (years)	0.731	0.000*
Egfr	-0.251	0.010*
Ca^{2+}	0.033	0.749
PO_4	0.015	0.884
CPP	0.010	0.924
SBP	0.100	0.307
DBP	0.036	0.718
MAP	0.066	0.506
DM	0.338	0.003*
TOTAL CHOL	0.019	0.411
TRIGLYCERIDE	0.332	0.004*
HDL	0.096	0.219
LDL	0.074	0.402
Cr	0.142	<0.001*

Table 7: Logistic Regression of CIMT and Important Variables Associated with It

Parameters	**B**	**S.E.**	**Wald**	**df**	**P-value**	**Exp(B)**
Age	0.499	0.243	4.226	1	0.040*	1.648
eGFR	3.966	1.759	5.083	1	0.024*	52.755
DM	0.441	1.475	0.089	1	0.765	0.644
Cr	5.101	1.544	4.122	1	0.007*	2.914
Triglyceride	1.218	1.634	3.132	1	0.382	3.211
Constant	-62.272	29.118	4.574	1	0.032	0.000

Discussion

The subjects studied were all black Ibo Nigerians (black race is an adverse risk factor in kidney diseases)[9]. CIMT varies with ethnicity and is found to be higher among blacks[10].

The patients were mostly young and middle aged as against the older age group in CKD patients found in developed countries[11]. Studies in most parts of sub-Saharan Africa show that chronic kidney diseases occur in relatively younger age group [2,12].

CIMT values (mean DCA, ICA, Bulb and mean values for the three segments) were significantly higher in CKD patients. Studies done earlier by Balsam et al,[13] Kumar et al[14] and Prasdal et al [15] show similar findings, though these were in non-black patients. Atheromatous plaques were significantly higher in CKD patients in these studies. Abolhassan et al demonstrated similar findings in a haemodialysis group[16]. This demonstrates increased carotid atherosclerosis/ arteriosclerosis in CKD patients.

CIMT increased significantly with age among CKD patients. Earlier studies also demonstrated an increase of CIMT with age. Age has been considered the most important and independent risk factor for increased CIMT and arteriosclerosis [17].

CIMT values showed significant negative correlation with eGFR. Values increased significantly as eGFR reduced. This finding is similar to earlier studies[16]. Accelerated atherosclerosis as eGFR falls explained this. In our study, serum creatinine a determinant of eGFR was the best predictor of CIMT.

Arterial hypertension is very common among patients with CKD. Previous studies did not confirm any role of blood pressure as a determinant of CIMT in CKD patients[18]. This study also did not find any association between systolic, diastolic and mean arterial blood pressures with CIMT. This can be explained by the fact that most hypertensive CKD patients receive long term anti-hypertensive medications.

Diabetes mellitus is a risk factor for CKD and atherosclerosis/arteriosclerosis. This study showed a significant correlation between CIMT and diabetes. Patients with diabetic nephropathy have

increased CIMT in comparison to subjects without complications[19].

This study found no correlation between CIMT and serum levels of calcium, phosphorus, calcium phosphorus product which is compatible with recent studies. However, earlier studies done showed a significant correlation between CIMT and serum phosphorus in patients on haemodialysis.

Our study showed a significant correlation between CIMT and triglyceride level however there was no correlation between CIMT and total cholesterol, LDL and HDL levels. Lipid abnormalities are associated with subclinical atherosclerosis however there are conflicting data on the role of lipid profile in the progression of CIMT in CKD patients. Associations between CIMT and lipid disorders have inconsistently been reported in CKD patients. Several studies showed no relationship between lipid profile and CIMT in haemodialysis (HD) patients[20]. However, other studies demonstrated independent association between total cholesterol, LDL-C, triglycerides and CIMT in HD patients[19].

In conclusion, CIMT was significantly higher among CKD patients hence carotid atherosclerosis/arteriosclerosis is commoner in black Nigerian Ibo CKD patients than the control population. There was also positive correlation between CIMT in CKD patients and stages of CKD. The more advanced the CKD stage, the higher the prevalence of CIMT. The noted increased intimal media thickness at various segments (common carotid, internal carotid and the bulb) of the carotid artery shows the systemic nature of atherosclerosis.

Carotid intimal media thickness is an alternative end point for cardiovascular morbidity and mortality. We recommend that it should be assessed in our high risk patients like CKD patients since the procedure for its detection is non-invasive and can be done repeatedly.

Our study has some limitations. Many of the CKD patients were already on medications which included antihypertensive and lipid lowering agents. This may have influenced the strength of the associations of CIMT with blood pressure and lipid profile. Also the study being cross-sectional could not assess the effect of blood pressure control on CIMT in CKD patients. Other factors that may have impact on the progression of sub-clinical atherosclerosis e.g. C Reactive Protein, homocysteine level and genetic markers were not assessed.

Conflict of interest statement: None declared

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