Correlation between Albuminuria and Ankle Brachial Index among Nigerians with Chronic Kidney Disease

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Summary

BACKGROUND

Peripheral arterial disease (PAD), the most common manifestation of atherosclerosis and chronic kidney disease (CKD), has been described as an independent risk factor for its development. The combination of CKD and PAD multiplies the risk of cardiovascular disease. Ankle-brachial pressure index (ABPI) is a good marker of atherosclerosis and is useful for the diagnosis of PAD. The study aimed to determine the prevalence, pattern and predictors of PAD in patients with CKD.

MATERIALS AND METHODS

This was a cross-sectional study of patients with CKD with age and gender-matched controls. Medical history relating to CKD and PAD was obtained using a pre-tested questionnaire. The ABPI was measured using handheld Doppler ultrasound equipment. Blood samples were drawn for serum creatinine and spot urine for Urinary Albumin Creatinine Ratio (UACR).

RESULTS

One hundred and thirty-two subjects participated in the study, 66 cases and 66 controls. The mean ages were 47.5±15.9 years in cases and 41.6±11.6 years in controls. The mean ABPI (0.9±0.2 vs 1.0±0.1, p-0.01), eGFR (62.8±28.2 vs 98±23.1ml/min/1.73m^2, p-0.01) were lower in the cases compared to the controls while UACR was higher in the cases (3.1±1.1 vs 1.2±0.1, p-0.01. The prevalence of PAD was 36 (54.5%) and 15 (22.7%) among cases and controls, respectively (p < 0.01) while low eGFR OR, 3.9 (1.86-10.41), elevated Systolic blood pressure (SBP) OR, 1.83 (1.40-5.78) and UACR (t-3.663, p-0.023) were associated with PAD in CKD.

CONCLUSION

This study demonstrated that high prevalence of PAD among individuals with CKD while low eGFR, elevated SBP and microalbuminuria were clinical correlates of PAD in CKD.

Keywords: *Ankle Brachial Pressure Index, Cardiovascular Disease, Chronic Kidney Disease, Peripheral Arterial Disease*

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Introduction

Chronic kidney disease (CKD) patients are at increased risk for cardiovascular disease (CVD) and these CVD include accelerated atherosclerosis, stroke, heart failure, coronary artery disease (CAD) and peripheral arterial disease (PAD). The annual mortality from CVD in end-stage renal disease (ESRD) is substantially higher than in the general population, with mortality between 10-100 times higher in age-matched controls with normal kidney function.[1]

PAD is the most common manifestation of atherosclerosis and is characterized by atherosclerotic occlusive disease of the lower extremities.[2] It typically presents with intermittent claudication while critical limb ischaemia which is the most severe manifestation of the disease can lead to limb loss or even loss of life if not treated promptly. The worldwide prevalence of PAD is approximately 10% and the prevalence increases with age.[3] O'Hare *et al*[4], based on the results of the National Health and Nutrition Examination Survey (NHANES) 1999-2000, reported that 24% of the population aged 40 years or older with renal insufficiency have PAD compared with 3.7% in those with normal kidney function. In the dialysis population, according to the United States Renal Data System (USRD) report, the incidence of clinical PAD is 15%.[5]

Previous studies have shown that CKD is an independent risk factor for the development of PAD irrespective of the presence of other known traditional risk factors for PAD such as age, gender, hypertension, diabetes mellitus (DM), dyslipidemia, cigarette smoking and obesity.[5] These traditional risk factors which are either aetiological factors of CKD or comorbidities of the disease, multiply the risk of developing PAD in patients with CKD.

Various methods have been used to assess and predict CVD outcomes among patients with CKD and these include measurement of pulse wave velocity (PWV), carotid intima-media thickness (CIMT), left ventricular hypertrophy (LVH), left ventricular mass index (LVMI) and Ankle Brachial Pressure Index (ABPI).[6-9] ABPI is a measure of atherosclerosis and it measures the pressure in the ankle relative to the central blood pressure. It is a readily accessible tool and is an independent predictor of CVD and its outcomes in both pre-dialysis and dialysis patients with CKD.[10,11] ABPI values have been shown to independently predicts deaths, the five-year survival rate in patients with ABPI less than 0.4 was found to be 44% compared with 90% in patients with ABPI greater than 0.8 in a study by Cleven *et al*.[12] Low ABPI, asides from its usefulness in the diagnosis of PAD is also associated with an increased risk of vascular access failure.[13] Other consequences of untreated PAD include amputation, impaired functional capacity, poor quality of life, depression and specifically in CKD, rapid progression to ESRD, peritoneal dialysis technique failure and worsened kidney transplant survival. Furthermore, the combined effects of CKD and PAD in increasing all-cause mortality has been shown by many studies.[14,15] Early identification of PAD and its prompt treatments are a cost-effective way to reduce the burden of CVD among patients with CKD. The study objective was to assess the prevalence, pattern and predictors of PAD among patients with CKD using ABPI.

Material and Methods

This was a cross-sectional study of patients with CKD attending the Renal Clinics of the Medical Outpatient Department or admitted into the Renal wards of the University College Hospital, Ibadan, Nigeria. Participants

were recruited over a period of 18 months that spanned between April 2016 and September 2017. CKD was defined as estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m^2 and /or albuminuria for three months or more. To be included as cases, participants must be 18years or above with the diagnosis of CKD and must have given informed consent for participation in the study. While those excluded from the cases were patients with lower limb amputation and surgery involving the lower limbs. The controls were age and gender-matched individuals without kidney disease and excluded from the controls were participants with systemic hypertension, diabetes mellitus, lower limb amputation and surgery involving the lower limbs.

Sample size determination

The sample size was derived using the formula that compared the means of normally distributed samples of equal size and using ABPI parameters from Kumeo Ono *et al* [16] and Fu-An Chen [17].

$$N = \frac{(\sigma_1^2 + \sigma_2^2)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

Where N = the minimum sample size per group, μ_1 = mean of ABPI in control group (1.14), μ_2 = mean of ABPI in CKD patients (1.06), $\Delta = \mu 2 - \mu 1$ (anticipated difference the study wants to detect), σ_1 = standard deviation of ABPI in control group (0.08), σ_2 = standard deviation of ABPI in CKD patients (0.17), α = (level of significance) =5%, $Z_{1-\alpha/2}$ = (from two sided statistical table) = 1.96, $Z_{1-\beta}$ = (from two sided statistical table) = 1.28, 1 –β (power) = 90%, β is 10%. Where Z_α=standard normal deviate corresponding to 5% level of significance = 1.96, $Z_{1-\beta}$= standard normal deviate corresponding to a power of 90% = 1.28. This gave the minimum of 60 in each group. However, to allow for a non-response rate of 10%, the sample size is increased to 66 in each group.

Clinical Evaluation

Written informed consent was obtained from all participants. A pre-tested questionnaire was administered on all participants and information obtained were demographic details, level of education, aetiology and duration of CKD, history of hypertension, diabetes mellitus, dyslipidemia, lifestyle (history of cigarette smoking, alcohol consumption or other substance abuse) prior history of intermittent claudication or rest pain or leg amputation, prior history of stroke, heart failure or CAD. The Edinburgh claudication questionnaire was used to obtain questions on symptoms and severity of intermittent claudication on all participants. The participants were examined, and the anthropometric measurements were taken [weight (kg), height (m), waist and hip circumferences (cm)], from where Body Mass Index (BMI) and Waist Hip Ratio (WHR) were calculated. Blood pressure was measured using Mercury Sphygmomanometer with an appropriate cuff size. The participants were seated quietly for 10 minutes in a chair with feet on the floor and arm supported at the heart level and three measurements were taken and the average recorded. The participants' limbs were examined for features of PAD and these include discolouration, thinning of the skin, thickening of the nails, hair loss, dryness, coldness, tenderness, pulses and presence of ulcers.

Measurement of Ankle Brachial Pressure Index (ABPI)

All participants had measurements for ABPI after adequate participants' preparations which include refraining from cigarette smoking for at least two hours before the test, shoes and socks removed and belts and long sleeves loosened. Participants were asked to lie supine

on a couch with the limbs at the same level as the heart. A portable ABPI - 5mHz bidirectional Doppler with digital sphygmomanometer and chart recorder was used for the measurement of the blood pressure at the brachial and ankle using appropriate size cuff for the limbs. The brachial pulse was located with the fingers and the ultraphonic/coupling gel was applied over the cubital fossa until a good Doppler signal sound was obtained. The inflation-deflation-inflation method was used to determine the brachial and ankle systolic blood pressure. The cuff was inflated till the sound and waveform disappeared and then the cuff was inflated 20-30mmHg above the observed value. The cuff was then slowly deflated 2mmHg at a time until the sound reappeared. The pressure reading when the first sound appeared was taken as the systolic pressure and the cuff was completely deflated thereafter. The ankle pressures were taken by applying an appropriate cuff at the ankle and a doppler probe is applied over the posterior tibial artery or dorsalis pedis for doppler signal and waveform and pressure measurement taken in a similar version to the brachial pressure measurements. These measurements were repeated for both sides of the body.

Electrocardiography

A 12 lead electrocardiogram (ECG) was carried out on the participants using standard protocol for ECG procedure. The ECG tracings were read by a cardiologist.

Laboratory assays

Ten millilitres (10ml) of early morning spot urine were obtained from all participants for 10 points urinalysis and urinary albumin and creatinine assays. The urine albumin was determined using the turbidimetric immunoassay while the urine creatinine was obtained using the enzymatic colorimetric method. Urinary Albumin-Creatinine Ratio (UACR) was calculated from the obtained values. Ten millilitres (10ml) of venous blood were obtained from all participants after overnight fasting (8-10 hours). The blood specimens were used for the analyses of fasting plasma glucose (FPG), fasting plasma lipids, serum electrolytes, urea and creatinine, calcium, phosphate and albumin. eGFR was calculated from the serum creatinine using the CKD-EPI equation.

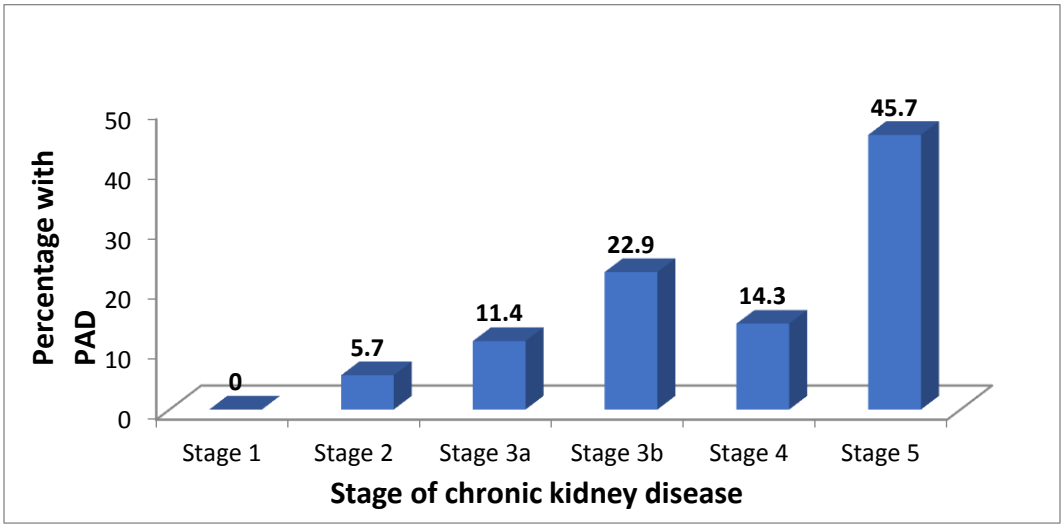

Figure 1: Severity of peripheral arterial disease among participants with chronic kidney disease

Definition of terms

PAD was defined by an ABPI≤. 0.9 while its severity was classified as follows: 0.91-≤ 1.30 normal, 0.71 - 0.90 mild PAD, 0.41 - 0.70 moderate PAD, less than 0.40 severe PAD and >1.30 was defined as incompressible arteries.[18]Hypertension was defined as blood pressure ≥ 140/ 90 mmHg or previous physician's diagnosis of hypertension or if patients were taking antihypertensive,[19] while Diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) level of ≥ 7.0mmol/1(126mg/dl), a random or 2hour post prandial blood glucose level of ≥ 11.1mmol/l (200mg /dl), or HBA1c > 6.5% or physician's diagnosis of DM or the use of hypoglycaemic agents in the previous 2 weeks.[20] Dyslipidaemia was defined by any one of the following: total cholesterol ≥ 200mg/dl or LDL cholesterol ≥ 100mg/dl or HDL cholesterol ≤ 40mg/dl or triglycerides ≥ 150mg/dl.[21] Current smoker was defined as those who had smoked at least 100 cigarettes in their lifetime and are still smoking or would have quit smoking within the preceding year while former smokers were those who had smoked at least 100 cigarettes in their lifetime but would have quit smoking more than one year earlier. Non-smokers were those who had smoked less than 100 cigarettes in their lifetime or who had never smoked.[22] BMI was classified following the World Health Organization (WHO) criteria and was as follows: underweight (<18.5kg/m2), normal weight (18.5 – 24.9 kg/m2), overweight (25.0 – 29.9 kg/m2), class I obesity (30.0 – 34.9 kg/m2), class II obesity (35.0 – 39.9 kg/m2) and class III obesity (≥ 40 kg/m2).[23] Central obesity was defined as WHR > 0.85 and 0.90 for females and males, respectively or waist circumference > 102cm and 88cm for males and females, respectively.[24] Occupational class was defined by the American International Group (AIG) classification.[25]

Data Management and Analysis

Data was entered using Statistical Package for Social Sciences (SPSS version 22). Frequencies and proportions were used to summarize qualitative variables while means and standard deviation were used for quantitative variables. The Chi-square test was used to compare socio-demographic characteristics of CKD cases and controls and to compare the proportion with PAD using an ABPI <0.9 as cut off. Multiple logistic regression was used to test the difference in proportion with the PAD between CKD cases and controls adjusting for any socio-demographic variables, lifestyle or other risk factors. Correlation between ABPI and other quantitative variables were assessed using Pearson's correlation and independent variable T-test as appropriate while the level of significance was set $p < 0.05$.

Ethical Clearance

Ethical approval was obtained from the joint University of Ibadan/University College Hospital Institutional review board (IRB) with the approval number UI/EC/15/0310.

Results

One hundred and thirty-two subjects participated in the study, 66 cases with CKD and 66 healthy controls. The mean age was 47.5±15.9 years in cases and 41.6±11.6years in the controls. Male participants were 36 (54.5%) and 32 (48.5%) among cases and controls, respectively while the majority of the cases 59 (89.4%) and controls 55 (83.3%) were of Yoruba ethnic group. The majority of the cases 35 (53.0%) were in the occupational class III compared to the controls 16 (24.3%), p – 0.02]. (Table 1).

Table 1: Baseline Characteristics of Participants

Variables	CKD group Mean (SD)/Frequency (%) n = 66	Healthy controls Mean (SD)/Frequency (%) n = 66	p - value
Gender			
Male	36 (54.5%)	32 (48.5%)	0.49
Female	30 (45.5%)	34 (51.5%)	
Mean Age (years)	47.5 ± 15.9	41.6 ± 11.6	0.10
Age (years)			
≤30	8 (12.1%)	11 (16.7%)	0.02
31-40	20 (30.3%)	24 (36.4%)	
41-50	12 (18.2%)	15 (22.7%)	
51-60	7 (10.6%)	12 (18.2%)	
>60	19 (28.8%)	4 (6.1%)	
Religion			
Christianity	42 (63.6%)	46 (69.7%)	0.46
Islam	24 (36.4%)	20 (30.3%)	
Ethnic group			
Yoruba	59 (89.4%)	55 (83.3%)	0.37
Igbo	6 (9.1%)	7 (10.6%)	
Others	1 (1.5%)	4 (6.1%)	
Occupational class			
I	21 (31.8%)	38 (57.6%)	0.02
II	10 (15.2%)	12 (18.2%)	
III	35 (53.0%)	16 (24.2%)	
Cigarette smoking			
Yes	7 (10.6%)	10 (15.2%)	0.44
No	59 (89.4%)	56 (84.8%)	
Stage of CKD			
1	4 (6.1%)		
2	3 (4.5%)		
3a	6 (9.1%)		
3b	11 (16.7%)		
4	13 (19.7%)		
5	29 (43.9%)		
Aetiology of CKD			
Hypertension	20 (30.3%)		
CGN	14 (21.2%)		
DM	10 (15.2%)		
Others	22 (33.3%)		
Duration of CKD (months)			
<3	12 (18.2%)		
3-6	17 (25.8%)		
>6-12	19 (28.8%)		
>12-60	14 (21.2%)		
>60	4 (6.1%)		

CKD- Chronic Kidney Disease, CGN- Chronic Glomerulonephritis, DM – Diabetes mellitus

The mean BMI was 24.9 ± 5.3 kg/m^2 in cases and 26.5 ± 4.7kg/m^2 among the controls, p - 0.08 while the mean HC was 95.2 ± 12.3cm in cases and 100 ± 10.7cm and the difference was statistically significant, p - 0.02. The mean ABPI among cases and controls were 0.9 ± 0.2 and 1.0 ± 0.1, respectively, and the difference was statistically significant (p - 0.01) while the mean eGFR was 62.8 ± 28.21ml/min/1.73m^2 in cases and 98 ± 23.1ml/min/1.73m^2 in controls, p - 0.01 (Table 2).

The mean HDL among cases and controls were 43.2 ± 9.4 and 47.7 ± 7.6mg/dl, respectively, p - 0.03.The mean SBP were 141.1 ± 31.8 and 117.9 ± 12.2mmHg in cases and controls respectively, p - 0.01, while DBP were 90.0 ± 16.9 and 75.1 ± 9.1mmHg, respectively, p - 0.01. The mean UACR was significantly higher in cases (3.1 ± 1.1mg/mMol) compared to the controls (1.2 ± 0.5mg/mMol), p - 0.01) (Table 2).

The prevalence of PAD was higher among cases 36 (54.5%) compared to the controls 15 (22.7%), respectively, p < 0.01 and was highest among patients in stage 5 CKD (45.7%). The distribution of PAD severity among individuals with CKD was mild 32 (48.5%), moderate 4 (6.0%) while no participant had severe PAD. (Figure 1).

Table 2: Clinical and Laboratory Characteristics of Participants

Variables	**CKD group Mean ± SD n = 66**	**Healthy controls Mean ± SD n = 66**	**p - value**
Body mass index (kg/m^2)	24.9 ± 5.3	26.5 ± 4.7	0.08
Waist circumference(cm)	86.2 ± 16.2	83.3 ± 12.4	0.25
Hip circumference(cm)	95.2 ± 12.3	100 ± 10.7	0.02
Waist- hip ratio	0.9 ± 0.1	0.8 ± 0.1	0.01
SBP mmHg)	141.1 ± 31.8	117.9 ± 12.2	0.01
DBP (mmHg)	90.0 ± 16.9	75.1 ± 9.1	0.01
ABPI	0.9 ± 0.2	1.0 ± 0.1	0.01
Serum creatinine(mg/dl)	4.4 ± 2.6	1.0 ± 0.2	0.01
Fasting plasma glucose(mg/dl)	91.8 ± 23.8	74.9 ± 12.7	0.01
Serum phosphorus(mg/dl)	4.6 ± 2.3	3.7 ± 3.4	0.06
Serum calcium(mg/dl)	8.6 ± 0.7	8.8 ± 0.8	0.16
Serum albumin(mg/dl)	3.4 ± 0.8	4.3 ± 0.4	0.01
Serum Total cholesterol(mg/dl)	191.8 ± 56.0	185.6 ± 38.8	0.51
Serum triglycerides(mg/dl)	106.4 ± 42.3	84.8 ± 35.0	0.02
Serum HDL-Cholesterol(mg/dl)	43.2 ± 9.4	47.7 ± 7.6	0.03
Serum LDL- Cholesterol(mg/dl)	125.8 ± 49.3	120.8 ± 36.1	0.51
eGFR (ml/min/1.73m^2)	62.8 ± 28.2	98 ± 23.1	0.01
UACR (mg/mMol)	3.1 ± 1.1	1.2 ± 0.5	0.01

Key: ABPI – Ankle Brachial Pressure Index, BMI – Body Mass Index, CKD – Chronic Kidney Disease, DBP – Diastolic Blood Pressure, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, SBP – Systolic Blood Pressure, UACR – Urinary Albumin Creatinine Ratio

On univariate analysis, the mean SBP, female gender, low eGFR and duration of CKD were significantly associated with PAD in the cases while BMI and WC tend towards significant association with PAD among the cases (Table 3).

On multivariate analysis, low eGFR [OR, 3.90 (1.8557-10.4123)] and SBP [OR, 1.83 (1.3998-5.7830)] were factors that predisposed patients with CKD to PAD (Table 4). As illustrated in table 5, the prevalence of PAD was highest among patients in stage 5 CKD (45.7%).

Table 3: Factors Associated with Peripheral Arterial Disease among Patients with Chronic Kidney Disease

Variables	**CKD with PAD Mean ± SD/ Frequency (%) n = 35**	**CKD without PAD Mean ± SD/ Frequency (%) n = 31**	**t-test/Chi square**	**p - value**
Age	49.4 ± 14.5	45.4 ± 17.6	0.996	0.32
BMI (kg/m^2)	26.1 ± 6.2	23.5 ±3.8	1.929	0.06
WC (cm)	89.5 ±13.9	82.2 ± 18.2	1.795	0.08
HC (cm)	95.5 ±14.5	94.4 ± 9.4	0.357	0.72
WHR	0.9 ± 0.1	0.9 ± 0.1	1.313	0.18
SBP (mmHg)	150.4 ± 31.3	132.2 ± 29.5	2.357	0.02
DBP (mmHg)	91.5 ± 18.5	89.3 ± 14.4	0.534	0.60
Serum creatinine (mg/dl)	4.5 ± 2.7	4.2 ± 2.7	0.336	0.74
FPG (mg/dl)	91.7 ± 25.4	91.9 ± 22.7	-0.034	0.97
Serum phosphorus (mg/dl)	4.7 ± 2.6	4.5 ± 1.7	0.339	0.74
Serum calcium (mg/dl)	8.7 ± 0.7	8.5 ± 0.8	0.759	0.45
Serum albumin (mg/dl)	3.3 ± 0.8	3.5 ± 0.9	-1.181	0.24
Serum total cholesterol (mg/dl)	182.1 ± 56.4	202.6 ± 55.2	-1.473	0.15
Serum triglycerides (mg/dl)	104.9 ± 39.6	106.3 ± 45.4)	-0.131	0.90
Serum HDL (mg/dl)	42.6 ± 10.0	44.0 ± 8.9	-0.591	0.56
Serum LDL (mg/dl)	117.6 ± 48.9	135.1 ± 49.7	-1.428	0.16
eGFR (ml/min/1.73m^2)	42.6 ± 16.9	58.3 ± 20.6	3.027	0.01
UACR (mg/mMol)	3.2 ± 1.0	2.8 ± 1.1	1.469	0.15
Female gender	20 (57.2%)	10 (32.2%)	4.816	0.03
Age > 40years	20 (57.1%)	17 (54.8%)	2.047	0.56
Yoruba ethnic group	32 91.4%)	27 (87.1%)	0.039	0.84
Overweight or obese	18 (51.4%)	9 (29.0%)	4.589	0.10
Abnormal WHR	18 (51.4%)	20 64.5%)	1.545	0.21
Abnormal WC	12 (34.3%)	6 (19.4%)	1.646	0.20
Dyslipidaemia	13 (37.1%)	7 (22.6%)	3.587	0.06
Dialysis status (Dialysing)	15 (42.9%)	12 (38.7%)	0.054	0.82
Aetiology of CKD (Hypertension)	18 (51.4%)	15 (48.4%)	0.060	0.81
Duration of CKD > 12 months	14 (40.0%)	4 (12.9%)	6.091	0.01
Cigarette smoking	2 (3.0%)	3 (4.6%)	0.208	0.65
LVH	12 (18.2%)	12 (18.2%)		

Key: BMI – Body Mass Index, CKD – Chronic Kidney Disease, DBP – Diastolic Blood Pressure, FPG – Fasting Plasma Glucose, HC – Hip Circumference, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, LVH – Left Ventricular Hypertrophy, SBP – Systolic Blood Pressure, SD – Standard Deviation, UACR – Urinary Albumin Creatinine Ratio. WC – Waist Circumference, WHR – Waist Hip Ratio.

Table 4: Logistic Regression of Factors Associated with Chronic Kidney Disease

Variables	Odd ratio (95% Confidence Interval)	p - value
Female Gender	0.449 (0.115-1.747)	0.25
BMI (kg/m^2)	0.994 (0.981-1.008)	0.41
Duration of dialysis (> 12 months)	1.020 (0.882-1.179)	0.79
Low eGFR (ml/min/1.73m^2)	3.901 (1.8557-10.4123)	0.04
Elevated (mmHg)	1.834 (1.3998-5.7830)	0.02
Microalbuminuria	1.631 (0.860-3.094)	0.13

BMI – Body Mass Index, eGFR – estimated Glomerular Filtration Rate, SBP – Systolic Blood Pressure

Table 5: Correlation between Ankle Brachial Pressure Index and Clinical Variables

Variable	Correlation coefficient	P value
BMI (kg/m^2)	-0.095	0.46
WC (cm)	-0.061	0.63
HC (cm)	0.070	0.58
WHR (cm)	-0.106	0.41
SBP (mmHg)	-0.363	0.03
DBP (mmHg)	-0.318	0.01
Duration of CKD (months)	-0.037	0.77
Duration of dialysis (months)	-0.258	0.04
eGFR (ml/min/1.73m^2)	-0.289	0.01
Serum phosphorus (mg/dl)	0.005	0.95
Serum calcium (mg/dl)	-0.054	0.53
Serum albumin (g/dL)	0.275	0.01
Serum total cholesterol (mg/dl)	0.024	0.78
Serum triglycerides (mg/dl)	-0.074	0.40
Serum HDL (mg/dl)	0.084	0.34
Serum LDL (mg/dl)	0.032	0.79
UACR (mg/mMol)	-0.324	0.01

Key: ABPI – Ankle Brachial Pressure Index, BMI – Body Mass Index, CKD – Chronic Kidney Disease, DBP – Diastolic Blood Pressure, HC – Hip Circumference, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, SBP – Systolic Blood Pressure, UACR – Urinary Albumin Creatinine Ratio, WC – Waist Circumference, WHR – Waist Hip Ratio.

Table 6: Linear Regression of Factors Associated with Abnormal Ankle Brachial Pressure Index in Chronic Kidney Disease

Variable	B	Standard Error	Beta	t	P value
DBP (mmHg)	-0.002	0.002	0.621	-0.849	0.399
SBP (mmHg)	1.483	0.158	-0.282	5.047	0.011
Duration of dialysis (months)	0.033	0.030	0.145	1.099	0.276
eGFR (ml/min/1.73m^2)	0.001	0.010	0.018	0.128	0.899
UACR (mg/mMol)	0.816	0.113	0.427	3.663	0.023

Key: DBP – Diastolic Blood Pressure, SBP – Systolic Blood Pressure, UACR – Urinary Albumin Creatinine Ratio

ABPI showed positive correlation with serum albumin (r = 0.275) and negative correlations with SBP (r = -0.363), DBP (r = -0.318), duration of dialysis (r= -0.258) and eGFR (r = -0.289) and UACR (r = -0.324) (Table 5).

The SBP (t - 5.047, p - 0.011) and UACR (t - 3.663, p - 0.023) were observed to be associated with ABPI on linear regression analysis (Table 6).

Discussion

This study found a significantly high prevalence of PAD among patients with CKD and the severity of PAD is directly related to the severity of kidney disease. Low eGFR and elevated SBP were factors independently associated with PAD among individuals with CKD. Furthermore, the study revealed a positive correlation between PAD and serum albumin and an inverse correlation with DBP, SBP, duration of dialysis, eGFR and UACR.

The prevalence of PAD among individuals with CKD in this study was found to be 54.5%. The observed prevalence of PAD is higher than the prevalence reported in other studies.

Ungprasert *et al* [26] found the prevalence of PAD in patients with CKD to be 22.4% while the National Health and Nutrition Evaluation Survey III (NHANES III) study reported a prevalence of 24% among participants with low eGFR.[4] A similar study among the Spanish population reported a prevalence of PAD in CKD to be 32%.[27] The higher prevalence of PAD in the index study could be explained by the late presentation that is usually encountered in patients with CKD in sub-Saharan African countries.[28]

In addition, close to 90% of the participants with CKD were in stage 3 or above and it is expected that a longer duration of disease would correlate with the high prevalence and increased severity of PAD. Meanwhile, the prevalence of PAD in our study was similar to the report by Agaba *et al* [29] who studied a similar population in Northern Nigeria, he reported a PAD prevalence of 51.7% amongst diabetics with ESRD. Likewise, Yingyi Luo *et al* [30] found a PAD prevalence of 41.9% among diabetic ESRD.

The index study observed that the prevalence of PAD increases with the increasing severity of CKD, as the prevalence of PAD increased progressively from 5.7% in stage 2 to 45.7% in stage 5. This finding is in tandem with a previous report by Wang *et al* [31] demonstrated that the markers of PAD Pulse Wave Velocity (PWV) increased from 8.5ml/s in stage 3 CKD to 11ml/s in patients with stage 5. Wattanakit *et al* [32] in the Atherosclerosis Risk in Communities (ARIC) Study reported the incidence rate per 1000 person-year for PAD were 4.7, 4.9 and 8.6 among individuals with eGFR ≥90ml/min/1.73m2, 59 - 89ml/min/1.73m2 and 15-59ml/min/1.73m2, respectively.

In this study, PAD was independently associated with elevated SBP, low eGFR and microalbuminuria. The find is in keeping with the report by Murabito *et al* [33] who observed hypertension [OR, 2.2 (1.4 - 3.5)] as one of the factors associated with the development of PAD. Other factors they observed to be associated with PAD in patients with CKD were age, smoking, elevated fibrinogen and coronary artery disease. Elevated SBP has been identified as a predictor of cardiovascular morbidity and mortality, moreover, hypertension is both a cause and consequence of CKD and which contributes to the pathogenesis of atherosclerosis which is the basic pathological process underlying PAD. In addition, hypertension was the most common aetiology of CKD from this study. The high prevalence of hypertension in

this cohort might have contributed to the high prevalence of PAD in CKD observed in this study.

The low eGFR was also observed to be associated with PAD in this cohort. A low eGFR is an independent predictor of PAD and CVD morbidity and mortality. This finding is similar to the report by Baber *et al* [34] who reported that the prevalence of PAD is 14.8% and 25.4% among adults with reduced eGFR alone OR, 1.58 (1.09 – 2.29), and both reduced eGFR and microalbuminuria OR, 2.26 (1.30 – 3.94), respectively.

Surprisingly, the common traditional factors such as increasing age and smoking were not found to be associated with PAD in this study. This could be explained by the fact that most of the participants in this study were less than 50years and less than 5% of the cohort was either a past or current smoker. This study showed a direct correlation between ABPI and serum albumin while there were inverse correlations with each serum creatinine, microalbuminuria, duration of dialysis and ABPI. The direct correlation between ABPI and serum albumin observed in this study is similar to the report by Fu *et al* [35]. Serum albumin is a marker of nutritional status and higher values support favourable patients' outcomes. Malnutrition whose components may include hypoalbuminemia is associated with Malnutrition Inflammation Syndrome (MIS), this inflammation may be associated with endothelial dysfunction and PAD.[36]

It is not surprising that ABPI as a measure of PAD and surrogate markers of CVD has an inverse correlation with serum creatinine, microalbuminuria and duration of dialysis. This finding was similar to the report by Garimella *et al* [37] and Foster *et al* [38] who observed that lower ABPI values correlated with increased UACR, increasing serum creatinine and low serum albumin values. The three parameters are directly or indirectly related to widespread endothelial dysfunction and invariably PAD and CVD. Furthermore, the longer a patient stays on dialysis, the higher the degree of PAD and risk of cardiovascular events.

The high prevalence of PAD in the CKD population estimates the enormity of the burden of CVD among patients with CKD. In most high-income countries (HICs), CVD contributes significantly to the huge morbidity and mortality associated with ESRD, in some series CVD was reported to be responsible for up to 37% of deaths among individuals with CKD, making it a leading cause of mortality among patients with CKD.[39-41] The incidence of CVD is rising in the sub-Saharan African region and CKD is one of the major contributors to this increase. [42-43] This suggests that the traditional CVD risk factors and factors specific to CKD play important role in the rising burden of CVD in the population.[44] The utility of the ABPI index is in its accessibility and affordability, especially in low and middle-income countries (LMICs) where the opportunity for extensive cardiovascular evaluation may pose a challenge.[45]

The study is not without its limitations which include a lack of follow up to determine the effects of PAD on CKD progression. However, these limitations were countered by the main strength of this study which includes, the enrolment of CKD cases across all stages of CKD, coupled with the inclusion of both dialyzed and non-dialyzed individuals.

Conclusion

The study has demonstrated a high prevalence of PAD among individuals with CKD and it tends to increase with the severity of CKD. Low eGFR, elevated SBP, microalbuminuria and reduced serum albumin

were the identified clinical correlates of PAD in patients with CKD. The incorporation of routine screening for PAD using ABPI should be adopted in the clinical evaluation of patients with CKD as a means of early detection and prompt treatment of CVD risk factors.

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