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Associations of Chronic Kidney Disease in a Cohort of Stable First-degree Relatives of Chronic Kidney Disease Patients at a Tertiary Health Facility in South Eastern Nigeria

Bartholomew C. Ozuemba [a] and Chidiebele M. Ezeude [b*]

[a] Department of Internal Medicine, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.
[b] Department of Internal Medicine, Faculty of Medicine, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author BCO conception, design of the research and manuscript writing. Author CME literature review, manuscript writing, editing and review. Both authors read and approved the final manuscript.

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ABSTRACT

Background: First degree relatives (FDRs) of chronic kidney disease (CKD) patients have a greater prevalence of the risk factors for CKD than the general population and should be screened for kidney disease. There is paucity of data on the occurrence of CKD and its risk factors in the stable FDRs of CKD patients. This study was aimed at determining the associations between the various risk factors for CKD and hitherto undiagnosed CKD among the FDRs of the CKD patients.
Methodology: This was an observational prospective study involving 150 FDRs of CKD patients carried out in Nnewi, South-eastern Nigeria. Simple sampling technique was used to select the

**Corresponding author: E-mail: cm.ezeude@unizik.edu.ng;*

CKD probands while a stratified sampling technique was used to enroll the FDRs of the CKD subjects.
The subjects were screened for CKD using urine albumin creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR). These were repeated after three months for the FDRs with initial abnormal results (uACR ≥ 30mg/g and/or eGFR < 60ml/min/1.73m2) based on the definition of CKD. Also, the risk factors for CKD that included hypertension, diabetes mellitus (DM), obesity, age, gender, cigarette smoking, heavy alcohol consumption, hyperuricaemia, herbal medication use and dyslipidaemia were assessed.
Results: Age, gender, hypertension, cigarette smoking, heavy alcohol consumption, dyslipidaemia, hypercholestrolaemia and hyperuricaemia were found to have significant association with the occurrence of CKD in the FDRs of CKD patients (P < 0.001; P < 0.038; P < 0.001; P = 0.008; P < 0.001; P < 0.01 & P < 0.001 respectively).
There was no significant association between CKD and DM and herbal medication use (P = 0.782 & P = 0.081 respectively).
Logistic regression analysis showed that age (P = 0.009, OR 1.079, 95% C.I = 1.019 – 1.141), hypertension (P = 0.004, OR 10.602, 95% C.I = 2.085 – 53.920), and heavy alcohol consumption (P = 0.003, OR 12.657, 95% C.I = 2.316 – 69.159) were independent predictors for CKD among the FDRs.
Conclusion: Age, gender, hypertension, significant cigarette smoking, heavy alcohol consumption, dyslipidaemia, hypercholaestrolaemia and hyperuricaemia were significantly associated with the prevalence of CKD in FDRs of CKD patients while age, hypertension and heavy alcohol consumption were independent predictors of CKD in this group of subjects.

Keywords: Associations; chronic kidney disease; first degree relatives; stable.

1. INTRODUCTION

Chronic kidney disease (CKD) is be defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 or urinary albumin creatinine ratio (uACR) greater than or equal to 30 mg/g, persisting for 3 months or more, irrespective of the cause [1]. It is a progressive condition that affects more than 10% of the general population worldwide, amounting to more than 800 million individuals [2]. It is more prevalent in the older population, women, racial minorities, diabetic and hypertensive subjects and the burden is disproportionately large in low- and middle-income countries that are less well equipped to tackle its adverse outcomes [2]. It is a notable public health concern in both developing and developed countries and a risk factor for adverse outcomes in other diseases [3]. CKD is a preventable condition with risk factors that are non-modifiable or modifiable [4]. The non-modifiable risk factors are older age, male sex, African origin, and family history of CKD [4]. The modifiable risk factors are diabetes mellitus, hypertension, proteinuria, obesity, dyslipidaemia, hyperuricaemia and prolonged use of non-steroidal anti-inflammatory drugs [4]. First degree relatives of CKD patients have a greater prevalence of the risk factors for CKD than the general population and therefore should be screened for kidney disease [5].

A study identified age, female gender, hypertension, regular intake of herbal remedies and diabetes mellitus as significant risk factors for CKD [6]. Some other studies have reported various associations between the risk factors for CKD and undiagnosed CKD among the apparently healthy first-degree relatives (FDRs) of CKD patients. Schaeffner et al reported that elevated total cholesterol (TC), a high ratio of TC/HDL and low HDL were significantly associated with increased risk of developing renal dysfunction in apparently healthy subjects [7]. Still another study found a significant association between low levels of HDL and risk of incident CKD and CKD progression while the Framingham Offspring cohort study found that of 2,585 participants without preexisting kidney disease, higher body mass index (BMI) was associated with higher risk of developing CKD [8,9].

Bagchi et al in India found that older age, female sex, proteinuria and uncontrolled blood pressure were significantly associated with eGFR < 60ml/min/1.73m^2 while Wei et al in Southern China found that older age, female gender, hypertension, hyperglycaemia, hyperuricaemia, hypertriglyceridaemia, low HDL, increased body mass index and nephrotoxic medications were

independently associated with increased risk of CKD [10,11]. Similarly, hyperuricaemia and cigarette smoking were reported to be independent risk factors for CKD development and progression in two separate studies [12,13].

In developing countries like those of the sub-Saharan Africa, there is shortage of dialysis and renal transplant facilities which are the treatment options for end stage renal disease (ESRD). This, coupled with the trajectory rise the CKD cases due to increasing number of hypertensive and diabetic patients globally underscores the need for early detection, treatment and reversal of the modifiable risk factors for CKD in FDRs of CKD patients. This will not only reduce the occurrence of CKD and slow down its progression to ESRD, but will also reduce the economic burden of CKD globally.

The burden of CKD is increasing rapidly in Nigeria and it has been established that there is genetic clustering of CKD and its risk factors. Most studies done on CKD and its risk factors in Nigeria were among already-diagnosed CKD subjects and the general population. There is dearth of published studies on the prevalence and the risk factors of CKD among FDRs of CKD patients in Nigeria and a search of literature showed none in South-eastern Nigeria.

This study was aimed at determining the associations between the various risk factors for CKD and hitherto undiagnosed CKD among the FDRs of the CKD patients and thereby answering the research question: are the risk factors for CKD in the subjects with CKD prevalent in their stable first degree relatives?

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was an observational prospective study carried out among consenting adult first degree relatives of patients with CKD at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, South-Eastern Nigeria.

The study was conducted at the Nephrology Outpatient Clinic and Haemodialysis unit of NAUTH from September 2018 to August, 2019.

2.2 Study Population

The participants for the study comprise the first-degree relatives (parents, siblings and children) of CKD patients at NAUTH.

2.3 CKD Probands Selection

All the CKD patients (with eGFR < 60ml/min/1.73m^2) that attended Nephrology Outpatient Clinic and haemodialysis unit of NAUTH, were identified. The study purpose and benefits of early CKD detection and prevention among their family members were explained to them. Consecutive recruitment of 54 CKD patients that consented was done using a simple random sampling. Information on the diagnosis of their CKD and presumed aetiology was obtained from the hospital records.

2.4 Study Subject Selection

The study subjects were selected among the first-degree relatives (parents, siblings and children) of the CKD patients using stratified sampling technique. A pool of the names of the FDRs of CKD patients was made and a possible three selected by balloting, giving a total of 162 study subjects. This was done to ensure equal representation of the FDRs of each selected CKD proband so as to draw more precise conclusions. Selected FDRs were invited for the study by the CKD patients themselves. 162 FDRs commenced the study, while 12 were lost to follow-up and 150 completed the study.

The study subjects were seen on two occasions: at the baseline visit and at the follow-up visit. At the baseline assessment, the study questionnaire was filled, anthropometric and blood pressure measurements done and blood and urine samples were collected.

The follow-up visit was scheduled 3 months later for the subjects with estimated GFR < 60ml/min/1.73m^2 and/or urine ACR > 30mg/g at the baseline assessment. Follow up tests done were serum creatinine and urine ACR.

2.5 Inclusion and Exclusion Criteria for The Study Subjects

Consenting first degree relatives (FDR) of CKD patients aged 18 years and above were recruited into the study while those that were pregnant, had a febrile illness, urinary tract infection, clinical heart failure, previously diagnosed kidney disease or retroviral disease were excluded from participation in the study.

2.6 Instruments and Measurements

A researcher-structured questionnaire was used to extract relevant clinical and socio-

demographic data that included age, gender, marital status, occupational, educational and lifestyle history such as smoking and alcohol consumption. Weight was measured in kilograms to the nearest 0.1 kg using a weighing scale and height in meter with a stadiometer. Waist circumference was measured with a non-stretch metric tape to the nearest 0.1 centimeters at the midpoint between the iliac crest and lower coastal margin. Body mass index (BMI) was calculated as weight (in kg) divided by square of the height (in meters). Blood pressure was measured on the right arm using an Accoson mercury sphygmomanometer (Dekamet, England).

2.7 Sample Collection and Analysis

After an overnight fast based on pre-information, 6ml of blood was collected from each study subject. 1 ml of blood was dispensed into a fluoride oxalate container for fasting plasma glucose analysis. The remaining 5 ml of blood was dispensed into a sterile plain container and allowed to clot and retracted. The blood was centrifuged at 3000 rpm for 10 minutes and the serum separated into two aliquots and stored at -20 °C. The analysis of all the biochemical parameters was done within one month of collection. The biochemical parameters analyzed were serum creatinine, serum uric acid, fasting lipid profile (triglyceride, total cholesterol, high density lipoprotein and low density lipoprotein cholesterol) and retroviral screening. Samples were analyzed by a medical laboratory scientist at the laboratory of Nnamdi Azikiwe University Teaching Hospital.

The serum creatinine was determined using Jaffe method [14]. Serum uric acid was determined using colorimetric method [15]. Fasting plasma glucose was assayed colorimetrically using glucose oxidase method [16].

Urine samples were collected between 7am and 10am in the morning. Urinalysis was done using Combi 10 dipsticks to check for proteinuria and infection. Positive nitrite or leucocyte test indicated presence of urinary tract infection.

Retroviral screening was done using determine kit (Alere Determine™ HIV- 1/2, LOT 87029K100A, Japan).

Urinary albumin was estimated using turbidimetric immunoassay method (Lot No 30030164, AGAPEpeagent, Switzerland). Urinary creatinine was measured using Jaffe method [14]. Urinary albumin-creatinine ratio was calculated in milligram of albumin per gram of creatinine and results were interpreted as follows: less than 30mg/g was regarded as normal, between 30-300mg/g was regarded as moderately increased and greater than 300mg/g was regarded as severely increased [17].

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. This is available online at: www.kidney.org/kls/professionals/gfr/ calculator.cfm. The equation is stated below:

186 x (serum creatinine in mg/dl) $^{-1.154}$ x (age in years) x 0.742 (for female) x 1.210 (for blacks) [18].

2.8 Data Analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Software Group, 200W. Madison St., Chicago, IL; 60606 USA). Categorical data was presented as frequency and percentage. Test of associations was done using Chi square tests for categorical variables. Logistic regression analysis was used to determine the independent risk factors for CKD among FDRs. Results were presented in tables. P value < 0.05 was considered statistically significant.

2.9 Definition of Operational Terms

1. Chronic kidney disease was defined as estimated GFR < 60ml/min/1.73m^2 for > 3 months with or without evidence of kidney damage or if there was an indicator of kidney damage like albuminuria – in this study albuminuria was defined as urine albumin creatinine ratio (ACR) ≥ 30mg/g for > 3months [17].
2. Hypercholesterolaemia – total cholesterol ≥ 5.2 mmol/l [19].
3. Dyslipidaemia – total cholesterol/HDL ratio ≥ 5 [19].
4. Hyperuricaemia – serum uric acid ≥ 420µmol/l (7.0 mg/dl) [20].
5. Diabetes mellitus – defined as fasting plasma glucose of ≥ 7.0mmol/l (126mg/dl) or previous diagnosis of diabetes mellitus or individuals taking anti-diabetic agents [21].
6. Significant cigarette smoking – defined as smoking 20 cigarettes daily for more than one year [22].

7. Heavy alcohol consumption – defined as consumption of >210grams of alcohol per week [23].
8. Analgesic abuse – defined as cumulative lifetime use of more than 5000 pills of analgesics [24]. This will be calculated from multiplying the average number of pills consumed in a week by the duration of use in years [24].
9. Truncal obesity was defined as waist circumference ≥ 102cm in males and ≥ 88cm in females [25].
10. Underweight was defined as BM1 < 18.5, normal weight was defined as BMI of 18.5 to 24.9, overweight was defined as BMI of 25 to 29.9 and obesity was defined as a BM1 ≥ 30 [26].
11. Hypertension was defined as a systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg or use of antihypertensive medication for blood pressure control or history of hypertension [27].
12. Proband refers to a person in a family affected with a disease or condition that raises suspicion that other family members may have an increased propensity for the same disease or condition [28].

3. RESULTS

A total of 150 FDRs completed the study. The FDRs were made up of 69 (46.0%) males and 81 (54.0%) females and their mean age was 36.0 years, Also, majority, 72 (48.0%) of the FDRs were children of the CKD patients, 54 (36.0%) were siblings and 24 (16.0%) were parents of CKD patients. The prevalence of CKD among the FDRs was 26.7%.

3.1 Association between CKD in the FDRs and the Risk Factors

Risk factors that had significant association with development of CKD in FDRs included age, gender, hypertension, cigarette smoking, heavy alcohol consumption, dyslipidaemia, hypercholaestrolaemia and hyperuricaemia (Table 1).

There was no significant association between CKD and DM and herbal medications use (Table 1).

3.2 Predictors of CKD in the FDRs

After logistic regression analysis, age (OR 1.079), hypertension (OR 10.602), and heavy alcohol consumption (OR 12.657) were found to be independent predictors for CKD among the FDRs (Table 2).

4. DISCUSSION

4.1 Association between the Risk Factors for CKD and Occurrence of CKD in the FDRs

This study found that age, gender, hypertension, cigarette smoking, heavy alcohol consumption, dyslipidaemia, hypercholestrolaemia and hyperuricaemia had significant association with the risk of development of CKD in the FDRs of the CKD subjects.

Some other studies had similar findings. Shankar et al found significant association between heavy alcohol consumption and the development of CKD in the FDRs of CKD patients [29]. On the other hand, Koning et al reported an inverse association of alcohol consumption and the risk of development of CKD in the FDRs of CKD patients [23]. In their study of 620 CKD patients, Sertu et al found that urinary tract obstruction, hypertension, diabetes mellitus, cardiovascular disease and family history of CKD were positively associated with CKD [30]. Li et al found that older age. Male gender and obesity were independently associated with CKD in the FDRs of CKD patients [31]. Similarly, Egbi et al found that eGFR was negatively correlated with age, body mass index (BMI) and blood pressure (systolic and diastolic blood pressure) among adults in an agrarian Southern Nigerian community [32].

4.2 Independent Predictors of CKD in the FDRs of the CKD Probands

This study found that age, hypertension and heavy alcohol consumption were independent predictors of CKD in the FDRs, after logistic regression. This finding was similar to those of Wei et al and Tsai et al that reported that hypertension and older age were independent significant risk factors for CKD among the FDRs of CKD patients [11,33]. It is well known that eGFR decreases with ageing, therefore elderly people should be targeted for CKD screening and intervention. Okwuonu et al noted that old age, hypertension, family history of kidney disease, global obesity and central obesity were predictors of CKD among adults from the general population [34].

Table 1. Association between CKD in the FDRs and the risk factors at baseline

Variable		CKD		Test Stat	p-value
		Present	Absent		
Median age (and IQR) in years		50.0 (15.5)	30.0 (18.5)	U =715.0	< 0.001*
Gender	Male	24 (60.0)	45 (40.9)	χ^2= 4.304	0.038*
	Female	16 (40.0)	65 (59.1)		
Hypertension	Present	28 (70.0)	6 (5.5)	χ^2= 69.717	< 0.001*
	Absent	12 (30.0)	104 (94.5)		
Diabetes Mellitus	Present	6 (15.0)	13 (11.8)	χ^2= 0.268	0.782
	Absent	34 (85.0)	97 (88.2)		
Significant Cigarette Smoking	Present	7 (17.5)	4 (3.6)	χ^2= 8.296	0.008*
	Absent	33 (82.5)	106 (96.4)		
Heavy alcohol consumption	Present	17 (42.5)	9 (8.2)	χ^2= 24.110	< 0.001*
	Absent	23 (57.5)	101 (91.8)		
Herbal medication	Present	10 (25.0)	14 (12.7)	χ^2= 3.287	0.081
	Absent	30 (75.0)	96 (87.3)		
Dyslipidaemia	Present	26 (65.0)	13 (11.8)	χ^2= 43.120	< 0.001*
	Absent	14 (35.0)	97 (88.2)		
Hypercholestrolaemia	Present	25 (62.5)	15 (13.6)	χ^2= 35.815	< 0.001*
	Absent	15 (37.5)	95 (86.4)		
Hyperuricaemia	Present	17 (42.5)	14 (12.7)	χ^2= 15.859	< 0.001*
	Absent	23 (57.5)	96 (87.3)		

*U= Mann-Whitney U test applied. χ2= Chi square. * = statistically significant*

Table 2. Logistic regression of CKD and the independent risk factors

Variable		Slope	AOR	95% C.I.	p-value
Age in years		0.076	1.079	1.019 – 1.141	0.009*
Gender	Male	-0.330	0.719	0.164 – 3.144	0.661
	Female	Reference	-	-	
Hypertension	Present	2.361	10.602	2.085 – 53.920	0.004*
	Absent	Reference	-	-	
Significant Cigarette	Present	-0.433	0.648	0.056 – 7.472	0.728
Smoking	Absent	Reference	-	-	
Heavy alcohol	Present	2.538	12.657	2.316 – 69.159	0.003*
consumption	Absent	Reference	-	-	
Hypercholesterolaemia	Present	0.598	1.819	0.196 – 16.879	0.599
	Absent	Reference	-	-	
Dyslipidaemia	Present	0.369	1.447	0.141 – 14.864	0.756
	Absent	Reference	-	-	
Hyperuricaemia	Present	-0.600	0.549	0.125 – 2.416	0.428
	Absent	Reference	-	-	
Constant	-5.333	0.005	-	-	< 0.001

** = statistically significant, AOR = Adjusted Odd Ratio*

A study reported that cigarette smoking was an independent risk factor for the development and progression of CKD [35]. It was also a predictor of raised urine-albumin excretion rate in diabetics and hypertensives [8]. Similarly, hyperuricaemia was found to be an independent predictor of CKD development in non-CKD individuals [36].

Similar to our findings, Tsai et al equally found that age and hypertension were significant independent association of CKD in relatives of haemodialysis (HD) patients [33]. Finally, Bagchi et al also found that older age, female sex, proteinuria and uncontrolled blood pressure had significant association with eGFR < 60 ml/min/1.73m^2 [37].

5. CONCLUSION

Age, hypertension, significant cigarette smoking, heavy alcohol consumption, dyslipidaemia, hypercholesterolemia and hyperuricaemia were

all significantly associated with CKD in the FDRs of the CKD subjects while age, hypertension and heavy alcohol consumption were independent predictors of CKD in FDRs of CKD patients.

6. LIMITATIONS OF STUDY

The study was hospital-based and was carried out in Nnewi, a semi-urban city in South-Eastern Nigeria. Being a hospital-based study, the findings may not be generalized to what obtains in the wider society, similarly, having been conducted in a semi-urban city, the outcome may not represent what obtains in the rural communities.

7. RECOMMENDATIONS

More community-based studies on the associations of CKD and its risk factors in FDRs of CKD patients are needed locally. Individuals with family history of kidney disease should be routinely screened for kidney disease and for the risk factors for CKD, especially hypertension which was found in this study to be an independent risk factor for CKD at any contact with a medical practitioner. Health education of CKD patients on the high risk of their relatives having the risk factors for and or developing CKD and the merits of early screening for these in them should be done by doctors at any contact with CKD patients.

NOTE

This study has added to the current literature on the risk factors for CKD in FDRs of CKD patients in Nigeria and would stimulate further local studies on this important topic.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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