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Determining the Bulk of the Iceberg of Proteinuric Chronic Kidney Disease in School Children, in South West Nigeria

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Abstract

Introduction: Chronic kidney disease [CKD], as defined by the National Kidney Foundation/Kidney Disease and Outcome Quality Initiative (KDOQI) Group, refers to bilateral kidney injury and/or impaired kidney function of at least 3 months duration. Persistent proteinuria has been recognized as one of the early markers of chronic kidney disease and has been associated with persistent and progressive damage in both children and adult. This study was conducted with the aim of determining the prevalence and severity of persistent proteinuria over three months in primary school children in Ile-Ife. It was a cross-sectional study done over a period of six months. The subjects were 1335 primary school pupils, aged 6 to 14 years selected by multi stage random sampling method from twelve primary schools from a total of 96,301 pupils in the two Local Government Areas (LGA) of Ile-Ife, after meeting the recruitment criteria. The biodata, physical examination, blood pressure measurements and urine testing by dipstick were carried out on all the recruited pupils according to standard protocols while serial monitoring of proteinuria and estimated glomerular filtration rate was done for those with persistent proteinuria over 6 months. **Results:** Initially 34 (2.6%) of the subjects recruited had significant proteinuria with a M:F ratio of 1:1.6 following first screening and it was persistent in six (0.4%) of them subsequently over three months with a M:F ratio of 1:1.5. The severity of the persistent proteinuria was in the range of 30 mg/dL to 100 mg/dL. Three of them (50%) had worsened level of proteinuria from 30 mg/dL to 100 mg/dl on follow up. **Conclusion:** Children with undetected persistent proteinuria stand the risk of further glomerular damage over time.

Keywords

Persistent Proteinuria, Chronic Kidney Disease, Glomerular Damage

1. Introduction

Proteinuria implies a urinary excretion of at least 150 mg of protein in 24 hours [1]. In normal healthy children, urine protein is less than 4 mg/m^2/hour [1]. Excessive urinary protein is a potent nephrotoxin that has been associated with persistent and progressive kidney damage in both children and adults [2]. Significant proteinuria is ≥1+ (30 mg/dL) proteinuria by dipstick or proteinuria that is ≥4 mg/m^2/hr in a 24-hour urine sample [3]. It is also defined as a random urine protein/creatinine ratio [UPCR] ≥ 20 mg/mmol [3]. Proteinuria may be transient or persistent. Persistent proteinuria is defined as significant proteinuria that is present on two or more occasions [4]. It constitutes the single most important risk factor for future loss of kidney function, usually preceding glomerular filtration rate reduction [3] [5]. Urine testing is an essential component of medical examination, and the basic dipstick method is the most common screening procedure for the early detection of renal or urinary tract diseases in apparently healthy or asymptomatic subjects [5]. Such patients may benefit from subsequent medical interventions that will forestall or prevent additional kidney problems [6]. These dipsticks, which measure total protein or albumin are simple to use and have high specificity of 87% and sensitivity of 96% [7], thereby creating a practical advantage for the clinician. Chronic kidney disease [CKD], as defined by the National Kidney Foundation/ Kidney Disease and Outcome Quality Initiative (KDOQI) Group, refers to a bilateral kidney injury and/or impaired kidney function of at least 3 months duration [6]. Kidney injury manifests by the presence of micro-albuminuria or overt proteinuria, abnormal urine sediment such as red blood cell (RBC), RBC casts, white blood cell (WBC), WBC casts, cellular casts, granular casts, oval fat bodies, fatty casts, or free fats [6]. Mortality rate from CKD ranges between 20.3% and 58.3% in developing countries and is associated with poor outcomes, high cost and low access rate to dialysis [8]-[14]. The mortality rate in developed countries is about 20% [15].

According to KDOQI guidelines [6], when screening children for chronic kidney disease, urine protein should be measured in a spot urine sample, using either standard urine dipstick or total protein-to-creatinine ratio. Previous studies [16]-[21] done on the prevalence of persistent proteinuria in Nigeria were done over a shorter period of less than three months. These studies were not done with the objective of defining chronic kidney disease presenting with proteinuria using a timeframe minimum of 3 months, as recommended by the KDOQI Group [6].

2. Aim and Objectives

This was to use a cost effective screening tool "urinalysis dipstick" to detect persistent proteinuria of ≥3 month as an early marker of proteinuric CKD among the studied population and severity of the proteinuria relating it to their estimated glomerular filtration rate.

3. Methodology

The study was carried out among primary school pupils in Ile Ife, a town in Osun state, Nigeria. Ile Ife is a semi-urban population with two Local Government Areas (LGA), namely Ife Central LGA and Ife East LGA. According to the 2006 population censors figures [22], Ile-Ife has a total population of 355,341. Ife Central LGA has a population of 167,254 while Ife East LGA has 188,087. Both cover areas 111 km^2 and 172 km^2 respectively. The population of school age children in both local governments is 96,310. The study cut across both Local Governments Areas.

It was a cross-sectional study carried out over a six month period from 3rd June 2013 to 15th November 2013, following ethical clearance from the Local Inspectorate of Education (LIE), Ile Ife. Informed consent was obtained from the parents/guardians of selected subjects through the heads of schools selected for the study. The sample size was determined using the formula for estimating proportions [23],

$$N = P(1 - P)\, Z^2/\beta^2.$$

where:

N = the number of patients required for the study;

Z = the standard deviation from the true proportion of the disease and corresponds to 1.96 at 95% level of confidence;

β = the absolute sampling error that can be tolerated and was set at 1.5%;

P = the prevalence in previous study done;

P was set at 7.7% based on the previous work of Aladekomo [19].

The sum up was 1213 subjects; this was increased by 10% to 1335 so as to allow for those who may drop out of the study for various reasons.

The subjects were primary school pupils aged six to fourteen years.

Inclusion criteria include;

1) Consenting parents/guardian of children in the selected schools.

Exclusion criteria are;

1) Children on medications such as the Cephalosporins that could give false positive results for proteinuria.

2) Involvement in rigorous physical exercise (about 30 minutes) before urine sample collection.

3) Presence of fever (may give false positive proteinuria).

4) Menstruating adolescents at the time of study (and 3 days after menstruation).

5) False positive dipstick proteinuria results due to highly concentrated urine (specific gravity > 1.020), alkaline urine (pH > 8), and gross haematuria.

A multistage random sampling technique was employed. A list of all primary schools in Ile-Ife was obtained. Randomization was stratified for type of school (private or public), and also for LGA location. This was done to ensure that the study cut across the different social classes in both LGA in Ile Ife. Twelve schools were randomly selected by balloting from the list. These were made up of six

primary schools from each local government area consisting of three private and three government owned school. In each of the schools selected, the school register was consulted to know the enrolment figures by age and sex. A composite register was drawn for subjects aged six to fourteen years whose parents/guardians have consented. They were arranged according to their classes and a table of random numbers was then used to select 222 pupils from each of the six classes making a total of 1332. The remaining three were also randomly selected from the register to make up the sample size of 1335. Three hundred and eighty pupils were recruited from private schools, and the remaining 955 pupils were from public schools. A research proforma was administered on each pupil for their bio data, anthropometric and clinical data. History of previous hospital admission, use of any routine drugs and name of such was noted. General physical examination as well as systemic examination for meatal stenosis in the male subjects, renal mass and ascites was carried out on those with proteinuria.

Each child in light clothing and barefooted, had their weight and height measured. Urine samples were freshly voided and collected mid-stream in a universal bottle given prior to the pupils 11.00 am break. The pupils were not living in the school, therefore for convenience and to ensure freshly voided urine, 11 a.m, which is the usual mid-break in Nigerian primary schools, was chosen as the time of collection of the urine sample. The test strip used was Combi 10 and this was dipped into the fresh urine for approximately 1 second, and then drawn across the edge of the container to remove the excess urine. After 30 seconds, the test strip was compared with the colour scale and the result was recorded immediately. This is based on the principle of the protein error. The presence of protein in a buffer causes a change in pH that is proportional to the concentration of protein itself. Thus the dipstick impregnated with tetrabromophenol blue changes its colour from pale green to green and blue according to pH changes induced by the protein. Colour changes taking place after 2 minutes were regarded as of no significance. The amount of protein in the urine was assessed as negative, trace, 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (500 mg/dL).

Only pupils with initial positive results for proteinuria were screened the second time. Those who continued to have persistent proteinuria were followed up for the third and fourth time. The timing for the serial urinalysis was at 4 weeks interval over a 3 month period for those with persistent proteinuria that may be at risk of CKD.

The resting blood pressures of patients with persistent proteinuria were also measured. Resting blood pressure was determined by auscultation in the right arm after a 10-minute resting period using the mercury gravity sphygmomanometer with the appropriate bladder cuff sizes ensuring standard precaution [24]. Hypertension was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) > 95th percentile for age, gender and height on three different occasions. Stage 1 hypertension was taken as SBP and/or DBP ≥ 95th <

99th percentile + 5 mmHg for age, gender and height while stage 2 hypertension as SBP and/or DBP ≥ 99th percentile + 5 mmHg for age, gender and height. Pre-hypertension was defined as SBP and/or DBP ≥ 90th percentile but <95th percentile [24]. Normal blood pressure was taken as SBP and DBP < 90th percentile of the expected for age, gender and height. This was done by using the chart for blood pressure level for different gender by age and height percentiles according to The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. The mean arterial blood pressure was calculated using the formula; 2 (DBP) + SBP/3 (mmHg). Body mass index was calculated using the weight/height^2 (kg/m^2) formula and the percentile was assessed as defined by their BMI for age curves [25] [26]. They were also subjected to renal ultrasound on follow up and assessment of their estimated glomerular filtration rate eGFR using Schwatz formula [27], e GFR (mL/min/1.73m^2 = K × Ht(cm)/SCr(mg/dL), where K = 0.5 for adolescent female and 0.7 for an adolescent male, Ht- height in cm and SCr is serum creatinine.

Data analyses were performed using both descriptive and comparative statistics. Descriptive statistics comprising of mean, standard deviation, percentages and proportions were used for the age, anthropometry, and blood pressure profile as well as to determine prevalence of persistent proteinuria and hypertension among the subjects. The comparative statistics comprised of Chi-square test for categorical data, independent samples t-test and analysis of variance (ANOVA) for comparison of the mean. Survival analysis was done for subjects with transient and persistent proteinuria using Cox regression curve. Using the SPSS 16.0 for Windows evaluation version (2006 SPSS Inc.), p-value < 0.05 was regarded as statistically significant.

4. Results

A total of 1335 subjects were recruited for the study. The male to female ratio was 1:1.1 and the age and gender distributions are shown in **Table 1**, while **Table 2** shows the overall mean age, anthropometric and blood pressure profile of the subjects.

The level and severity of proteinuria

Thirty four subjects had proteinuria at first screening with the prevalence of 2.6%. The level of proteinuria in twenty nine (85.0%) of them was 1+ (30 mg/dL), four (11.8%) subjects had proteinuria in the range of 2+ (100 mg/dL) and one subject had proteinuria in the range of 3+ (500 mg/dL). Proteinuria was more common among children aged 11 to 12 years, while it was less common among children aged 6 - 8 years.

The week by week resolution of proteinuria in 28 of the subjects with proteinuria at first screening is shown in the survival curve for proteinuria, using Cox regression in **Figure 1**. Six subjects had persistent proteinuria during the course of the study; the chance of losing proteinuria overtime is 0.02 times, at confidence interval of 95%.

Table 1. Age and gender distribution of the subjects.

Age in years	Gender		Total (%)
	Male N (%)	Female N (%)	
6	74 (44.6)	92 (55.4)	166 (100.0)
7	62 (52.5)	56 (47.5)	118 (100.0)
8	56 (42.4)	76 (57.6)	132 (100.0)
9	100 (50.0)	100 (50.0)	200 (100.0)
10	101 (43.2)	133 (56.8)	234 (100.0)
11	82 (56.6)	63 (43.4)	145 (100.0)
12	86 (47.3)	96 (52.7)	182 (100.0)
13	63 (54.8)	52 (45.2)	115 (100.0)
14	24 (55.8)	19 (44.2)	43 (100.0)

Table 2. Age, anthropometric and blood pressure profile of the subjects.

Age, anthropometric and blood pressure characteristics	Overall mean ± SD N = 1335	Gender		p value
		Male N = 648	Female N = 687	
Age (years)	9.66 ± 2.27	9.76 ± 2.29	9.56 ± 2.24	0.110
Height (cm)	129.60 ± 11.43	129.27 ±10.79	130.01 ± 11.99	0.181
Weight (kg)	26.27 ± 6.18	26.12 ± 5.54	26.41 ± 6.72	0.379
Body mass index (kg/m^2)	15.44 ± 1.72	15.49 ± 1.60	15.38 ± 1.82	0.227
Systolic blood pressure (mmHg)	92.65 ± 11.94	91.71 ± 11.11	93.54 ± 12.61	0.005
Diastolic blood pressure (mmHg)	56.46 ± 9.67	55.60 ± 9.53	57.27 ± 9.73	0.002
Mean arterial blood pressure (mmHg)	68.52 ± 9.80	67.63 ± 9.43	69.36 ± 10.06	0.001

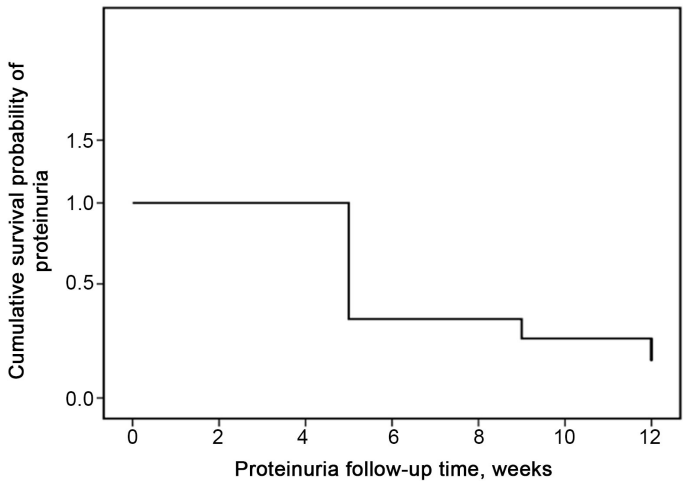

Figure 1. Survival curve for proteinuria over a duration of 12 weeks.

The occurrence of proteinuria in both genders shows a slight female preponderance. However, the difference in the prevalence of proteinuria between gender is not significant (Chi square = 8.375, df = 4, p = 0.07). The most severe level of proteinuria was found in an 11 year old female.

The prevalence of persistent proteinuria among the subjects was 0.4%. The pattern and progression of proteinuria in subjects with persistent proteinuria is as shown in Table 3.

All the six subjects with persistent proteinuria had their height below the 50th percentile of the expected for their age and gender. Four (70%) of them had height < 10th percentile. None of the pupils with proteinuria had palpable renal mass, ascites or meatal stenosis. In the absence of gross haematuria, four (66.7%) of those with persistent proteinuria had dipstick detected red blood cell in their urine.

Table 4 shows the summary of the anthropometry and clinical parameters of the subjects with Persistent proteinuria.

5. Discussion

Persistent significant proteinuria is a recognized early marker of kidney damage and a risk factor for developing chronic kidney disease and, eventually end-stage renal disease (ESRD) [28]. A dipstick proteinuria of 1+ or greater has been found to confer an increased risk for all-cause mortality, independent of age and estimated glomerular filtration rate [29]. In this study, an initial screening for proteinuria detected 34 subjects (2.6%) but on subsequent follow up, the number decreased to six subjects (0.4%) with persistent proteinuria over three months. This is similar to the finding in Korean school children where proteinuria was reportedly present at routine urine testing in up to 10% of school-aged children, however, this decreased to 0.1% at repeated testing [30]. With those factors that may give false positive proteinuria reasonably eliminated, subclinical glomerulonephritis could be a possible cause of the transient proteinuria which is seen often in children and resolves over time. In a study of 8954 school children in Finland [31], most children who tested positive for proteinuria on initial evaluation were also found to "lose" their proteinuria at follow-up. A study involving

Table 3. The pattern and progression of proteinuria in subjects with persistent proteinuria.

S/N	Age (years)	Gender	Level of Proteinuria at various encounters			
			1st (baseline)	2nd (at 4 weeks)	3rd (at 8 weeks)	4th (≥12 weeks)
1	10	female	1+ (30 mg/dL)	1+ (30 mg/dL)	2+ (100 mg/dL)	2+ (100 mg/dL)
2	11	male	1+ (30 mg/dL)	1+ (30 mg/dL)	1+ (30 mg/dL)	1+ (30 mg/dL)
3	11	male	1+ (50 mg/dL)	1+ (30 mg/dL)	2+ (100 mg/dL)	2+(100 mg/dL)
4	11	female	3+ (500 mg/dL)	2+ (100 mg/dL)	2+ (100 mg/dL)	2+(100 mg/dL)
5	11	female	1+ (30 mg/dL)	1+ (30 mg/dL)	1+ (30 mg/dL)	2+(100 mg/dl)
6	13	female	1+ (30 mg/dL)	1+ (30 mg/dL)	1+ (30 mg/dL)	1+ (30 mg/dL)

Table 4. Summary of anthropometric and laboratory data of subjects with persistent proteinuria.

Subject	Age (years)	Sex	Weight (kg)	Height (cm)	Height percentile for age and gender	BMI[a], Kg/m^2	BMI percentile for age and gender	SBP/DBP (mmHg)[b]	Serum creatinine (mg/dL)[c] (µmol/l)	eGFR[d]	Proteinuria at:		Renal ultrasound BPD/TD/CT[e], cm
											1st screening	4th screening	
1	11	M	24.5	125.0	<3rd percentile	15.7	<25th percentile	100/60	0.66 (58.0)	104.2	1+ (30 mg/dL)	1+ (30 mg/dL)	Right kidney: 8.3/3.4/4.2 Left kidney: 8.2/3.6/4.1 Both kidneys are shrunken with preserved corticomedullary differentiation.
2	10	F	26.1	127.4	5th percentile	16.1	<50th percentile	110/50	NA	NA	1+ (30 mg/dL)	2+ (100 mg/dL)	NA
3	11	M	28.9	141.0	<50th percentile	14.6	<10th percentile	90/70	0.50 (44.0)	155.1	1+ (30 mg/dL)	2+ (100 mg/dL)	Right kidney: 9.0/3.1/6.1 Left kidney: 9.1/3.8/5.3 Both kidneys are shrunken with preserved corticomedullary differentiation.
4	11	F	25.5	143.4	<50th percentile	13.0	<3rd percentile	120/70	1.24 (110.0)	63.4	1+ (30 mg/dL)	2+ (100 mg/dL)	NA
5	13	F	36.6	147.1	<3rd percentile	16.6	<25th percentile	80/50	1.26 (111.0)	64.2	1+ (30 mg/dL)	1+ (30 mg/dL)	NA
6	11	F	27.8	133.2	<10th percentile	16.4	<50th percentile	90/60	0.65 (57.0)	113.6	3+ (500 mg/dL)	2+ (100 mg/dL)	Right kidney: 8.4/3.3/4.9 Left kidney: 8.6/4.4/5.5 Both kidneys are shrunken with preserved corticomedullary differentiation.

NA –means result not available due to unwillingness on the part of the parent/guardian.

mass screening of school-aged children in Asia also revealed similar findings [32] [33] [34]. The overall prevalence of proteinuria and persistent proteinuria of 2.6% and 0.4% respectively in this study are lower than what was reported by Aladekomo *et al.* [19] where the overall prevalence was 7.7% and that of persistent proteinuria 3.8%. The lower prevalence in this study may be partly due to the wider exclusion criteria for the causes of false positive proteinuria in index study and the longer period of follow up (three months) as against 48 to 72 hours in the study by Aladekomo *et al.* [19]. The six pupils with persistent proteinuria out of 1335 pupils translate to 4495 per million children population. This is huge; early diagnosis and treatment of persistent proteinuria to prevent disease progression is necessary. It is a major way to reduce morbidity, mortality

as well as financial burden that parents and government would have to bear should progression to more advance stages, 3 - 5 CKD occur in these children. Proteinuria is a recognized key biomarker in nephrology and has been found to be central to making diagnosis and risk assessment in kidney diseases [35]. Proteinuria, in particular albuminuria, is a potentially significant modifiable risk factor for cardiovascular disease and the progression of kidney disease [36]. Unhindered and progressive proteinuria leads to activation of inflammatory and fibrotic pathways hereby causing both interstitial fibrosis and glomerulosclerosis [37] [38]. Targeting proteinuria reduction has been noted as a means of preservation of renal function in proteinuric CKD and this translates into improved cardiovascular outcomes [35]. Currently, early treatment with angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor-1 blocker is recommended for the treatment of persistent proteinuria [39]. ACE inhibitors also reduce the rate of progression of kidney disease, and the risk of dialysis or transplantation by up to 50% in patients with proteinuria [39] [40] [41]. In index study, none of the children who had persistent proteinuria for over three months was less than 10 years of age. Similarly, earlier studies showed that the mean age of Nigerian children with CKD between 9.1 and 11.6 years [8] [9] [10] [42]. Dodge *et al.* [43], showed that persistent proteinuria prevalence increased with age, peaked during adolescence, and was higher in girls. A male to female ratio of 1:2 was found among pupils with persistent proteinuria while a male to female ratio of 1.8:1 was reported by Aladekomo *et al.* [19]. More female subjects had persistent proteinuria in our study; however, not much inference can be made from the male to female ratio because of the small number of subjects with persistent proteinuria in this study. The impact of kidney disease on growth is demonstrated in this study as four of the subjects with persistent proteinuria had heights that were less than the 10th percentile expected for age and gender, while the height of the remaining two were less than the 50th percentile. CKD is associated with poor growth due to chronic loss of protein in the urine among other factors.

Four of the six subjects with persistent proteinuria had blood identified in their urine by dipstick. This suggests a glomerular disease as earlier studies [44] [45], demonstrated that coexisting proteinuria and haematuria, and the degree of haematuria correlated with the severity of the morphological alteration in the glomeruli in asymptomatic children [45].

None of the subjects with persistent proteinuria was hypertensive in index study. The relationship between hypertension and proteinuria could be that of a cause and effect or vice versa. It could be that the ongoing kidney damage was not yet severe enough to cause hypertension or that those that had hypertension were yet to develop end organ damage involving the kidneys is also a plausible explanation. A longer period of follow up may show otherwise. It is good to note that not all proteinuric kidney disease cause hypertension. The results of the present study were in agreement with observations from previous studies [46]

[47] revealing that in developing countries, a large number of subjects have proteinuria in the absence of hypertension. On the other hand, the hypertension could have been psychological, that is, "white coat hypertension".

Only two of the six subjects with persistent proteinuria for >3 months actually had renal ultrasound done as the others were not willing. This was because there was no overt symptom of renal disease in these subjects and the primary care givers did not see the need to allow an otherwise "well looking" child be subjected to further evaluation. This demonstrates the poor health seeking attitude of people in resource poor country where out of pocket payment for health care is the order and poverty/ignorance may influence their choices [48]. The ultrasound done showed bilaterally reduced kidneys though the cortico-medullary differentiation is preserved. Likewise the estimated glomerular filtration rate showed that majority still had normal eGFR *i.e.* CKD stage 1 while two of them had CKD stage 2. This is in support of earlier study [42] that showed that the later stages of CKD are seen in the hospital unlike the early asymptomatic stages.

In conclusion, the prevalence of proteinuric CKD in the studied population was 0.45% as determined by persistent proteinuria alone over >3 months duration. The target of intervention in early stages of proteinuric CKD is to halt the progressive damaging impact of the traffic of protein in the nephron. Early detection of proteinuric CKD using persistent proteinuria will aid in accomplishing this target. The presence of ultrasound revealed bilaterally shrunken kidneys in asymptomatic children with persistent proteinuria as seen in index study is an evidence of renal damage. It is therefore suggested that routine screening for proteinuria should be incorporated to the School Health Program, and children with persistent proteinuria should be referred to the nephrologist for appropriate evaluation, treatment and follow up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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