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Cardiovascular determinants of renal dysfunction among children and adolescents in South West Nigeria

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Abstract*: Background:* New evidences reveal significant association of cardiovascular risk factors to development of chronic kidney disease among children and adolescents but there is paucity of data from Africa.

Objectives: We examined the association of cardiovascular risk factors to renal dysfunction among Nigerian pediatric subjects.

Materials and method: This was a prospective, cross-sectional study of pediatrics aged 2 to 17 years. Blood pressure, body mass index, serum lipids and creatinine were determined. Their glomerular filtration rate was calculated using the revised *Schwartz* equation. Data was analyzed with SPSS 20. Test of association was by Chi square at P <0.05.

Results: We studied 114 children and adolescents. There were 55 (48.2%) males and 59 (51.8%) females with mean age of 8.99±4.26 years. There were 68 (53.5%) children and 53 adolescents (46.5%). Four (3.5%) subjects had proteinuria ≥1+.

Renal dysfunction (eGFR <60ml/min/1.73m^2) was found among 9 (7.9%) participants. Renal dysfunction was higher among children than adolescents (13.1% v 1.9%) (p = 0.027).

The presence and clustering of risk factors were higher among subjects with renal dysfunction (p value 0.466, 95% CI 0.19-28.3). Low HDL-c (44.4%), pre-hypertension (22.2%) and overweight (22.2%) were the most prevalent risk factors among those with renal dysfunction.

Only age demonstrated relationship to renal dysfunction in terms of mean difference (p value 0.007, 95% CI, 1.125-6.818).

Conclusions: The prevalence and clustering of cardiovascular risk factors is higher among children with renal dysfunction. Age showed association to renal dysfunction. Dyslipidemia and high body mass have propensity to influence the development of pediatric CKD.

Keywords: Cardiovascular risk factors, renal dysfunction, association, pediatrics, Nigeria, Africa.

Introduction

Emerging trends indicate that the 21st century children and adolescents are at a higher risk of developing chronic kidney disease (CKD) from Cardiovascular Disease risk factors as a result of the rising prevalence of hypertension, obesity, diabetes, dyslipidemia and inactivity among pediatrics. Such increases have been linked to shared familial factors such as genes and home environment.[1,2]

A landmark study in Canada demonstrated higher body mass index z-score among pediatric nephrology patients than their non-obese counterparts.[3] Obesity-related glomerulopathy (with larger kidney sizes) is now common among obese children while essential hypertension has been shown to begin much earlier in pre-adult life than was initially thought with potential for impact on early development of CVD and CKD.[3-7] In fact, low birth weight was demonstrated to be associated with reduced nephron mass,[8] an important emerging risk factor for CKD thereby indicating a possible tripartite relationship between hypertension, low birth weight and CKD.

Studies, including the landmark *Bogalusa* study in Louisiana, United States of America (USA) showed that high serum lipids levels track from early childhood into adulthood.[9-10] More poignantly, hypertriglyceridemia and low HDL-c have been identified as definite risk factors for CKD.[11,12]

These new evidence suggest strongly that new efforts must be geared towards re-evaluating children and

adolescents at-risk of CKD. However, while there have been many studies on cardiovascular risks among children in Nigeria, to our knowledge, only one sought their association to CKD using proteinuria by dipstick as surrogate marker of renal disease.[13] We therefore set out to determine the prevalence of renal dysfunction (using Creatinine-based assay) and its relationship (if any) to known CVD risk factors among children and adolescents in Nigeria.

Materials and method

This was a cross-sectional study conducted between December 2015 and June 2016 in Ondo West Local government area of Ondo State, Southwestern Nigeria among children and adolescents attending the primary and secondary schools in *Litaye* rural community where residents are predominantly farmers. Consecutive children and adolescents whose parents/guardians gave consent were included in the study. Those outside the age bracket of 2 and 17 years, with established chronic illnesses by physical examination or documented medical report, who were acutely ill and whose parents/ guardians did not give consent were excluded from the study.

Consent was obtained from the community head, school authorities and parents/guardians before proceeding with the study. Community awareness and acceptance of the study was facilitated by a step-wise approach; two initial visits were paid to the community head (*Baale*) and elders, following which we visited the Heads of the schools involved. Finally, the school authorities transmitted our intention to the parents/guardians who then gave consent.

Their bio data, blood pressure and anthropometric measurements were recorded in a proforma. Their weights and heights were obtained by means of a standard stadiometer (*RGZ-160 Lincon* Mark Medical England) to the nearest 0.1kg and 0.1m respectively using standard protocol[14] Their body mass index (BMI) was calculated using the formula, weight (in kilogrammes)/height^2 (in meters). Their BMI was adjusted for age and gender using the World Health Organization/Centre for Disease Control Growth Chart for children and adolescents aged 2-20 years. Those with BMI of ≥85 to <95th percentile and ≥95th percentile were classified as overweight and obese respectively.[15]

Their blood pressure (BP) was measured using *Accossons Mercury* Sphygmomanometer with the appropriate cuff sizes for age on the right upper arm in the sitting position after 5 minutes rest and taken to the nearest 2mmHg. The systolic (SBP) and diastolic blood pressure (DBP) were converted to their percentiles for age, gender and height using the appropriate chart.[16] Prehypertension was defined as SBP ≥90th to <95th percentile; Stage 1 hypertension as SBP≥99th percentile to ≤ Stage 2 hypertension. Stage 3 hypertension was defined as SBP>99th percentile plus 5mmHg according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[17]

Blood samples were collected for serum creatinine and lipids in Lithium heparin specimen tubes. Samples that were not analyzed immediately were separated and stored at -20^{o}C. Serum creatinine was assayed using the *Jaffe* (alkaline picrate) method. We determined their renal function using the estimated Glomerular Filtration Rate (eGFR). This was calculated using the bedside creatinine based *Schwartz* equation for GFR, *K x (height in centimeter/serum creatinine in mg/dl)* where K = 0.55 for children aged 2-12 years and females aged >12 years and 0.70 for males >12 years.[18] Renal dysfunction was defined as estimated glomerular filtration rate <60ml/ min/1.73m^2.[19]

In accordance to the National Cholesterol Education Programme, hypercholesterolemia was defined as total cholesterol (TC) above 5.2mmol/L and Low Density Lipoprotein-cholesterol (LDL-c) above 3.3mmol/L. Borderline TC and LDL-c were set at 4.4-5.1mmol/L and 2.8-3.3mmol/L respectively.[20] Low High Density Lipoprotein-cholesterol (HDL-c) and hypertriglyceridemia (TG) were set at <1.2mmol/L and >3.3mmol/L respectively.

Urine samples for analysis were obtained after adequate counselling of adolescents and parents/guardians of children who needed supervision. Urinalysis was carried out with *Combi 10 Unistrip*®. Proteinuria by dipstix of ≥1+ (corresponding to ≥30mg albuminuria) in the absence of leucocytes and nitrites was taken as significant. Subjects with abnormal clinical and laboratory parameters were re-visited during the period of study and re-evaluated. An individualized feedback slip was presented to each child.

Analysis of data: Data was analyzed with SPSS version 20. Continuous variables were expressed as frequency and percentage. Mean ± standard deviation was used as measure central tendency for a uniformly distributed population. The subjects were subdivided into two groups; those with reduced eGFR (<60ml/min/1.73m^2) and those with normal GFR (≥60ml/min/1.73m^2). Chi square test and Fisher's exact test were used to determine association between categorical and nominal variables. Independent sample T-test was used to compare means between two groups. Significant association was defined as $p < 0.05$ at 95% Confidence Interval.

Ethical clearance: Ethical clearance was obtained from the Health Research Committee for the Ondo State Specialist Hospital, Akure.

Results

One hundred and fourteen children and adolescents were studied. There were 55 (48.2%) males and 59 (51.8%) females with overall mean age of 8.99±4.26 years. There were 68 (53.5%) children and 53 adolescents (46.5%). Four (3.5%) subjects had proteinuria ≥1+ predominantly

among the females. Three subjects (2.6%) had 1+ proteinuria while 1 subject (0.9%) had 2+ proteinuria. No subject had more than 2+ proteinuria (table 1).

Table 1: General characteristics of the study population

Parameters	N=114	Percentage	Male n=55, (%)	Female n=59, (%)
Age grade				
2-9 years	61	53.3%%	30 (54.6)	31 (52.6)
10-17 years	53	46.5%	25 (45.4)	28 (47.4)
Class				
Pre-primary	29	25.4%	16 (29.1)	13 (22.0)
Primary	43	37.7%	21 (38.2)	22 (37.3)
Secondary	42	36.8%	18 (32.7)	24 (40.7)
Dipstick proteinuria				
Negative	107	93.9%	54 (98.2)	53 (89.8)
Trace	3	2.6%	1 (1.8)	2 (3.4)
1+	3	2.6%	0	3 (5.1)
≥2+	1	0.9%	0	1 (1.7)

In table 2, renal dysfunction (eGFR <60ml/min/1.73m^2) was found among 9 (7.9%) participants. There were 5 (55.6%) males and 4 females (44.4%). There were 8 (88.9%) children and 1 (11.1%) adolescents. The proportional distribution of renal dysfunction was significantly higher among children(p value = 0.027). There was no significant difference in gender distribution of renal dysfunction (p value = 0.455).

Table 2: Age and gender distribution and prevalence of risk factors among study subjects

Parameters	eGR†<60ml/ min/1.73m^2	eGFR†≥60ml/ min/1.73m^2	P value
Gender			
Male	5 (55.6%)	50 (47.6%)	0.455
Female	4 (44.4%)	55 (52.4%)	
Age group			
Children	8 (88.9%)	53 (50.5%)	0.027
Adolescents	1 (11.1%)	52 (49.5%)	
Number of risk factors			
One risk factor	4 (66.7%)	43 (81.1%)	0.353
>One risk factor	2 (33.3%)	10 (18.9%)	

†Estimated glomerular filtration rate

The presence and clustering of risk factors were higher among subjects with renal dysfunction who had eGFR <60ml/min/1.73m^2 (p value 0.466, 95% CI 0.19-28.3). Low HDL-c (44.4%), pre-hypertension (22.2%) and overweight (22.2%) were the most prevalent risk factors among those with renal dysfunction (table 3).

There was no significant difference in the means of SBP, DBP, BMI TC and lipid fractions between subjects with normal and low eGFR (<60ml/min/1.73m^2). Only age demonstrated relationship to renal dysfunction in terms of mean difference (p value 0.007, 95% CI, 1.125-6.818) (table 4).

Table 3: Proportion of risk factors among subjects with reduced and normal estimated Glomerular Filtration Rates

Risk factors	eGFR†<6ml min/1.73m^2 (N=9)	eGFR† ≥60ml/ min/1.73m^2 (N=105)	P value
Overweight	2 (22.2%)	9 (8.5%)	0.191
Obesity	1 (11.1%)	6 (5.7%)	0.447
Prehypertension	2 (22.2%)	16 (15.2%)	0.452
Hypertension	0	4 (3.8%)	0.716
Total cholesterol >5.3mmol/L	0	6 (5.7%)	0.665
HDL-c‡	4 (44.4%)	30 (28.6%)	0.238
Proteinuria	0	4 (3.8%)	0.714
Presence of one risk factor	4 (44.4%)	31 (29.5%)	0.302
>1 risk factor	2 (22.2%)	4 (3.8%)	0.466

†Estimated glomerular filtration rate, ‡High density lipoprotein-cholesterol

Table 4: Comparison between the means of subjects with reduced and normal estimated Glomerular Filtration Rates

Parameters	eGFR†<60ml/ min/1.73 m^2	eGFR†≥60ml/ min/1.73m2	P value	95% CI
Age (years)	5.3 (±4.3)	9.3 (±4.1)	0.007	1.125-6.818
Body Mass Index (kg/m^2)	16.8 (±3.09)	16.8 (3.2)	0.589	-1.547-2.710
Systolic Blood Pressure (mmHg)	97.9 (±16.3)	98.4 (16.6)	0.210	-4.075-18.293
Diastolic Blood Pressure (mmHg)	57.9 (±11.7)	58.1 (12.0)	0.180	-1.793-8.693
Serum Total cholesterol (mmol/L)	4.2 (±0.7)	4.2 (0.8)	0.943	-0.585-0.628
Serum Triglyceride (mmol/L)	1.9 (0.3)	1.9 (0.3)	0.505	-0.141-0.285
Serum LDL-c$^{\phi}$ (mmol/L)	2.2 (0.5)	2.1 (0.7)	0.871	-0.508-0.431
Serum HDL-c‡ (mmol/L)	1.2 (0.2)	1.2 (0.2)	0.791	-0.134-0.176

†Estimated glomerular filtration rateϕ Low density lipoprotein -cholesterol,‡High density lipoprotein-cholesterol

Discussion

Reduced GFR, a measure of renal function was observed in 7.9% of the subjects. Unlike the adult CKD prevalence, it has been difficult to arrive at a global prevalence for pediatric CKD due to various challenges which include lack of national registry data across the globe and differences in disease etiology between adults and pediatrics.[21] Creatinine-based prevalence as high as 11-12% based on different criteria have been reported for CKD in some parts of Asia and Europe even though they were hospital-based surveys.[22-23]

Earlier studies of renal disorders among children employed proteinuria as surrogate marker because of the greater likelihood of glomerulonephritis as etiology rather than hypertension, obesity or diabetes which are

considered rarities among children. In a systematic review of thirty five eligible papers on kidney disease among children in Sub-Sahara Africa (SSA), only two measured serum creatinine, and only so as a secondary endpoint. Incidentally, only the Kenyan authors went ahead to report their findings (in which case all the subjects had normal creatinine).[24-26]

The incidence and prevalence of all stages of CKD in children has been on the upward trend globally. In the United States of America for instance, a diagnosis of CKD was made among 2.7 per 1,000 children in 2018 compared to 15 per million population in 2008.[27-28] In the last decade, new evidences show that there is a significant increase in the association between CKD and some CVD risk factors such as diabetes mellitus (diabetic nephropathy) obesity (obesity-related glomerulopathy) and dyslipidemia among children and adolescents.[11,29,30]

One-third of our subjects had BMI in the overweight and obesity range. Obesity has long been described as a cause of nephropathy in pediatrics.[3] In one case, overweight and prehypertension co-occurred. The complex interrelationship between obesity and hypertension in the pathogenesis of atherosclerotic damage may be a double-headed assault on renal vasculature and invariably result in structural damage.[3-5]

The high proportion (44.4%) of reduced HDL-c among subjects with a low eGFR is a key finding in this study. This is because low HDL-c has been identified as a definite risk factor for development of CKD in the pediatrics.[11] Low HDL-c in the presence of hypertriglyceridemia causes renal artery atherosclerosis thus leading to reduced renal perfusion and eventually reduced GFR among other pathologies.[31]

The higher prevalence of renal dysfunction among children over adolescents in our study suggests that CKD may indeed begin earlier than usually thought. This finding coincides with a predominance of CVD risk factors in that age group though we do not have sufficient data to prove association. However, it is possible that early manifestation of CVD risk factors can give sufficient time for these factors to result into CKD, at least in theory. A recent study showed that elderly individuals who were first overweight at relatively younger ages of 26 or 36 years had approximately twice the odds of developing CKD if they remained overweight up until 60-64 years when compared with their age-matched controls who first became overweight at age 60–64 years.[32] Whether this can be extrapolated to children remains to be seen. While it is known that many risk factors in early childhood may peter out as a child grows in age, other studies have tracked significant risk factors into adulthood.[33-34] The specific role ageing plays in childhood development of CKD is yet to be fully understood but atherosclerotic changes from the effect of CVD risk factors have been demonstrated in early childhood.[35]

The absence of hypertension among our subjects with a low GFR appears to fit in with traditional perception that essential hypertension is not a likely cause of CKD among children rather than asequelae. In the study by Ezeonwu et al, a prevalence of 0.3% was obtained.[13] However, the small number of our subject population may be responsible for the seeming lack of hypertension as recent findings show strong evidences in support of a rising prevalence of essential hypertension in early childhood and its association to CKD development.[7,36,37]

In a recent World Kidney Day report of 2016, hypertension was listed as the third most common cause of End Stage Renal Disease and early CKD (10-19%).[38]

More so, the existence of a direct but complexly interwoven relationship between hypertension and obesity in the initiation of CKD and its progression has been shown.[5] The mechanisms include activation of the Renin Angiotensin Aldosterone System (RAAS) in persons who are obese, effect of the metabolic syndrome in the obese, atherosclerosis, insulin resistance, production of pro-inflammatory cytokines and reduced nitric oxide production in obesity-associated sleep apnea.[5]

This study was limited by its small sample size and exclusion of hyperglycemia from the studied risk factors. Nonetheless, we were able to demonstrate a high prevalence of CVD risk factors among subjects with reduced renal function below cut off.

Conclusion

The prevalence of renal dysfunction was high in our study suggesting that CKD arising from CVD risk factors may not be as rare as previously thought among children and adolescents. There is a tendency for age to influence the development of CKD. Cardiovascular clustering among younger pediatric subjects with low GFR is evident from this study with the likelihood of dyslipidemia, high BMI and prehypertension playing a leading role.

Conflict of Interest: None
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