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Renal Doppler Indices in Children with Nephrotic Syndrome: Findings from a Tertiary Hospital in Nigeria

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Summary: The resistive and pulsatility indices are known tools for assessing renal function in kidney diseases, especially in proteinuric conditions like Paediatric Nephrotic syndrome (NS) which is a glomerular disease. However, there is a limited knowledge in the use of Doppler Resistive and pulsatility indices in the management of this disease condition. This was a case control study involving 53 cases and 57 controls. The Doppler parameters, resistive index (RI) and pulsatility index (PI) of the renal interlobar arteries were determined for the upper, middle, and lower poles bilaterally for both controls and cases. The mean RI on the right and left were 0.59 ± 0.06 and 0.58 ± 0.06 respectively for the NS cases whereas for the controls it was 0.61 ± 0.05 and 0.60 ± 0.04 on the right and left respectively. The mean PI on the right and left measured 0.96 ± 0.16 and 0.94 ± 0.15 respectively for the NS cases while that for the control cases measured 0.98 ± 0.13.and 0.95 ± 0.12 on the right and left respectively. Although, the interlobar arteries mean RIs were generally less than that for the controls, but only the left middle pole showed statistically significant mean difference (p= 0.004). There was also statistically significant mean difference (p= 0.048) between the cases and controls in the left middle pole PI. However, no correlation was found when the renal RI and PI are compared with the serum albumin and creatinine. Although there was no statistical significance between the mean RI and PI of the NS cases and controls, except in the left middle pole RI, it is recommended that Doppler ultrasound should still be part of management of Nephrotic syndrome patients especially those who have developed end stage renal disease in order to monitor their renal function.

Keywords*:* Paediatric, Nephrotic Syndrome, Renal, Resistive Index, Pulsatility Index

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INTRODUCTION

Nephrotic syndrome is a major cause of chronic renal disease among the paediatric age group (Gbadegesin & Smoyer, 2008) It is basically a manifestation of many glomerular diseases and a leading cause of significant renal morbidity and mortality in Nigeria (Abdurrahman et al, 1990; Anochie & Eke, 2003; O. M. Ibadin & Ofovwe, 2003; Ocheke et al., 2010) Nephrotic syndrome is a form of chronic kidney disease in which there is massive proteinuria, hypoalbuminaemia, and anasarca. (Gbadegesin & Smoyer, 2008; Lane & Langman, 2011). Nephrotic syndrome, also known as nephrosis is technically defined as the presence of nephrotic- range proteinuria (>40mg/m /hr), or urine protein to creatinine ratio of >2-3mg/mg, hypoalbuminaemia (<2.5g/dl) and oedema. Other clinical conditions like hyperlipidaemia may also be present (Gbadegesin & Smoyer, 2008; Hendrickse & Adeniyi, 1979; Lane & Langman, 2011).

According to Lane and Langman, Nephrotic syndrome can be classified based on the aetiology and response to steroid therapy. (Lane & Langman, 2011). The aetiological classes include idiopathic or primary, congenital and secondary nephrotic syndromes.

The idiopathic nephrotic syndrome is basically of an unknown cause and these include minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, IgM nephropathy, mesangioproliferative glomerulonephritis and idiopathic crescentic glomerulonephritis. They have all been implicated as causes of idiopathic nephrotic syndrome, the diagnosis of which are made at biopsy (Gbadegesin & Smoyer, 2008; Lane & Langman, 2011; Mohammed, Al-badri, Al-latteef, Mohammed, & Abdulhussain, 2009).

The congenital nephrotic syndrome is the type that appears within the first 3months of life, while the secondary is due to known causes (Ademola et al., 2012; Dathan, Heyworth, & MacIver, 1974; Hellier, Webster, & Eisinger, 1972; Hull & Goldsmith, 2008; Novis et al. 1988; Ojo & Akinkugbe, 1967; Orth & Ritz, 1998).

Based on the response to steroid therapy, Nephrotic syndrome can also be classified into: Steroid-sensitive nephrotic syndrome (SSNS), Steroid-resistant

nephrotic syndrome (SRNS), Steroid-dependent nephrotic syndrome (SDNS), and Frequent relapsing nephrotic syndrome (FRNS) (Gbadegesin & Smoyer, 2008).

Renal Resistive index (RI) has been shown as a prognostic instrument in assessing the progression of renal disease, especially in hypertension, as well as proteinuria (Parolini et al., 2009). Studies have demonstrated that high RI, proteinuria and hypertension are known risk factors for the progression to chronic kidney disease (Parolini et al., 2009; Radermacher, Ellis, & Haller, 2002; Sugiura & Wada, 2009). An initially high RI denotes poor prognosis. (Parolini et al., 2009). This eventually leads to more rapid disease progression. Studies have demonstrated that high RI, proteinuria and hypertension are known risk factors for the progression of chronic kidney disease, though an association between RI and specific histological subtype has not been shown to be of statistical significance (Parolini et al., 2009; Radermacher et al., 2002; Sugiura & Wada, 2009).

The generally acceptable normal value of the renal RI is taken as ≤ 0.7 (Mostbek et al., 1991). However, a slightly higher RI value (0.72± 0.03) has been shown in healthy young children of age four and a half years and below. Thus, the RI value of 0.70 is only applicable for older children (Sigirci et al., 2006). It is notable that a significant correlation has been shown between the RI, glomerular sclerosis and focal interstitial fibrosis (Mostbek et al., 1991). Similar to the resistive index, though with less emphasis, the clinical significance of the pulsatility index (PI) has been documented in previous studies. It has been shown to increase in chronic kidney disease and correlates with the severity of renal disease (Petersen et al., 1997; Petersen, et al, 2006). An inverse correlation has been reported between age and PI, which ranges between 0.96 and 1.27 in healthy children (Sigirci et al., 2006). However, there is apparently very limited studies on renal RI and PI in nephrotic syndrome. The aim of this study therefore was to find out if RI and PI can be used to predict the outcome and/ or monitor progression and regression of nephrotic syndrome among peadiatric age group especially in resource poor settings.

MATERIALS AND METHODS

Study settings

The University College Hospital (UCH) Ibadan is the first and foremost premier teaching hospital situated in Western Nigeria with 850 bed spaces. On the average, 30 new Nephrotic syndrome cases are seen annually by the paediatric department.

Ethical approval This was given by the institutional UI/UCH ethical review committee (UI/EC/13/0257).

The subjects

This was a case-control study in which 53 children with Nephrotic syndrome (diagnosed based on clinical findings, and the presence of albuminuria and hypoalbuminaemia) were recruited from the children emergency ward and children outpatient clinic of the University College Hospital over a period of 12 months from July 2013. The content of a consent form was duly explained to the parent/ guardian of the proposed cases and healthy controls in the local languages for those who were not literate. The consent form was filled and signed by those parents/ guardian who were literate and thumb printed by those who were not literate, while a verbal assent was also obtained from each child who was old enough to agree to the study. Age- matched healthy children of members of staff and friends were recruited as controls, after screening by urinalysis as well as B mode ultrasound. Every consenting subject (case and control) was recruited until the minimum sample size was attained.

Ultrasound Technique

The renal Doppler assessment was done in the lateral or lateral oblique position using Mindray M7, 2010 by Shenzhen Mindray bio- medical electronics company limited ultrasound machine with low frequency (2-5 KHz) transducer. The kidneys were scanned with the B mode to check for any gross or incidental abnormalities. The colour Doppler was then turned on to identify the interlobar arteries and the sample volume applied such that almost the entire arterial diameter is covered. The Pulse Repetition Frequency (PRF) and the wall filter were adjusted and optimized so as to avoid aliasing and allow for slow diastolic flow. Doppler angle was also kept below 60^0. (Boote, 2003). Three consecutive Doppler spectral patterns of velocity- time graph, that was representative of the arterial blood flow from early systolic to end of diastolic flow, were obtained before the RI and PI parameters were measured. The upper, middle and lower poles renal interlobar arteries RI and PI were assessed for each kidney and the average of the measurements taken (Figure 1). The mean of the values of these measurements (upper, middle and lower poles) were also taken for each of the two kidneys. Doppler parameters were measured at breath-holds, especially in children that could cooperate with instructions. However, in younger children, measurements were derived during slow respiration. (Sigirci et al., 2006; Zubarev, 2010).

The arterial Resistive Index (RI) was defined as (Peak Systolic velocity - End diastolic velocity) divided by (Peak Systolic Velocity) and Pulsatility Index (PI) was defined as (Peak systolic velocity - End diastolic velocity) / Mean systolic velocity, while their respective values were derived via the computer algorithm in the ultrasound machine.

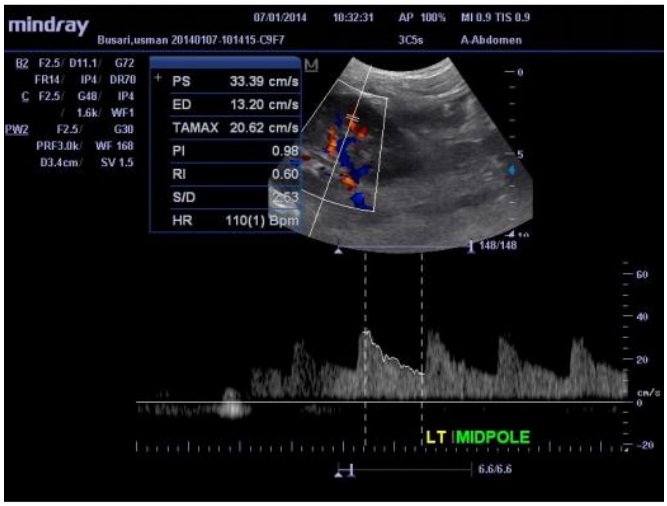

Figure 1: The Renal Doppler ultrasound of the left kidney midpole showing a typical doppler indices measurement.

Laboratory parameters

The results of the serum albumin and serum creatinine with urinary protein (dipstix) were also derived. The serum albumin and creatinine were derived by analyzing the subjects' serum, as they were compared to the locally standardized laboratory values. The urinalysis is however derived by using the qualitative method of dipstix, using the standardized colour code.

Statistical Analysis

The renal RI and PI for the cases and the control group, as well as the comparison between these groups were presented in tables. The association between the renal RI of NS cases and controls as well as renal PI of cases and controls were all determined by independent student t test. Likewise, the degrees of significance of the mean difference of RI and PI among the different levels of proteinuria were determined by analysis of variance (ANOVA). The level of significance was set at $p < .05$.

RESULTS

Sociodemographic Characteristic of the subjects

A total of One hundred and twelve children were recruited into the study, made up of fifty- five patients with nephrotic syndrome and fifty- seven healthy controls. However, two of the recruited NS cases did not complete the study. Hence, these were not included in the final analysis due to incomplete data collection. Thirty- two (60.4%) of the analysed cases were males, while thirty- four (59.6%) of the control group were males (Figure 2). The average age of the NS cases was 126.24 ± 40.11months, with a majority (56.6%) in the 10 - 15years age brackets. The mean age of the control subjects is slightly lower (117.63± 38.11months).

The age of diagnosis of nephrotic syndrome among the cases ranged between 24 and 158months (mean= 105.58 ± 40.09months). The NS cases were also predominantly either overweight or obese, when compared to the healthy control subjects. More than half (50.9%) of the NS cases showed BMI of ≥ 85 percentile, as shown in Table 1.

Table 1: Sociodemographic characteristics of the cases and the control.

	NS CASES		CONTROLS	
Parameters	N	%	N	%
Age (months)				
<60	6	11.3	2	3.5
60-119	15	28.3	25	43.9
120-179	30	56.6	28	49.1
180+	2	3.8	2	3.5
Weight (Kg)				
<25	15	28.3	29	50.9
25- 34.5	11	20.8	15	26.3
35- 44.5	15	28.3	11	19.3
45+	12	22.6	2	3.5
Height (cm)				
<110	6	11.3	2	3.5
110-129.5	14	26.4	23	40.4
130-149.5	16	30.2	20	35.1
150+	17	32.1	12	21.1
Body Mass Index (Kg/m^2)				
<5 Percentile	-	-	2	3.5
5- 84.9 Percentile	26	49.1	46	80.7
85- 94.9 Percentile	12	22.6	7	12.3
>95 Percentile	15	28.3	2	3.5

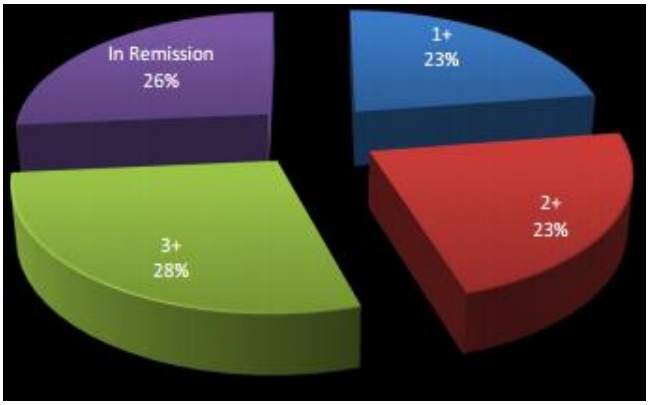

Figure 2. A pie chart of Urine dipstix analysis of Nephrotic syndrome (NS) cases showing the percentage and level of proteinuria of the patients

The serum albumin and creatinine measured 2.2 ± 1.0g/dl and 0.6 ± 0.5mg/dl respectively. The average duration of disease was about 20months. The dipstix urinalysis is depicted in Figure 2.

RI and PI findings

The mean RI value was 0.59, 0.59 and 0.58 as well as 0.59, 0.58 and 0.57 on the right and left respectively for each of upper, middle, and lower pole interlobar renal arteries in NS cases. These interlobar renal artery values were seen to be higher (yet <0.70) in controls, measuring 0.61, 0.61, and 0.60 on the right upper, middle and lower poles respectively, while on the left

Table 2. Resistive Indices (RI) of the Kidneys of Nephrotic Syndrome Cases and Control

	Cases	Controls	
Parameters	Mean ± SD	Mean ± SD	p- Value
Right Kidney			
Upper Pole RI	0.59 ± O.08	0.61 ± 0.05	0.065
Mid Pole RI	0.59 ± 0.08	0.61 ± 0.06	0.108
Lower Pole RI	0.58 ± 0.07	0.60 ±0.06	0.185
Average RI	0.59 ± 0.06	0.61 ± 0.05	0.059
Left Kidney			
Upper Pole RI	0.59 ± 0.07	0.60 ± 0.05	0.585
Mid Pole RI	0.58 ± 0.07	0.62 ± 0.05	0.004*
Lower Pole RI	0.57 ± 0.07	0.58 ± 0.05	0.638
Average RI	0.58 ± 0.06	0.60 ± 0.04	0.121

*p<0.05

Table 3. Pulsatility Indices (PI) of the Kidneys for the Nephrotic Syndrome (NS) Cases and Controls

	Cases	Controls	
Parameters	Mean ±SD	Mean ± SD	p- Value
Right Kidney			
Upper Pole PI	0.96 ±0.20	0.98 ± 0.15	0.582
Mid Pole PI	0.98 ± 0.18	1.00 ± 0.17	0.566
Lower Pole PI	0.94 ± 0.18	0.96 ± 0.15	0.404
Average PI	0.96 ± 0.16	0.98 ± 0.13	0.444
Left Kidney			
Upper Pole PI	0.96 ± 0.17	0.94 ± 0.15	0.638
Mid Pole PI	0.93 ± 0.19	1.00 ± 0.15	0.048*
Lower Pole PI	0.93 ± 0.17	0.92 ± 0.14	0.703
Average PI	0.94 ± 0.15	0.95 ± 0.12	0.623

*p<0.05

Table 4. Comparison of the Mean Resistive Index of the Different Degree of Proteinuria among the Nephrotic Syndrome children

	Right Kidney			Left Kidney		
Degree of Proteinuria	RI	f	P-value	RI	f	P-value
Upper Pole						
1+	0.564	0.301	0.742	0.631	4.819	0.014
2+	0.578			0.550		
3+	0.586			0.599		
Middle Pole						
1+	0.628	3.168	0.054	0.602	4.060	0.026
2+	0.554			0.558		
3+	0.586			0.599		
Lower Pole						
1+	0.603	2.606	0.088	0.608	2.211	0.124
2+	0.554			0.558		
3+	0.606			0.565		
Average of Poles						
1+	0.599	1.542	0.228	0.614	4.275	0.022
2+	0.560			0.550		
3+	0.596			0.592		

f is the ANOVA value; p value < 0.05 is significant. RI means Resistive index

Table 5. Comparison of the Mean Pulsatility Index of the Different Degree of Proteinuria among the Nephrotic Syndrome children

	Right Kidney			Left Kidney		
Degree of Proteinuria	PI	f	P-value	RI	f	P-value
Upper Pole						
1+	0.904	0.462	0.634	1.027	2.633	0.086
2+	0.929			0.877		
3+	0.977			0.991		
Middle Pole						
1+	1.073	3.511	0.040	0.971	3.050	0.060
2+	0.879			0.840		
3+	0.996			1.001		
Lower Pole						
1+	0.978	2.833	0.073	0.988	0.839	0.440
2+	0.852			0.900		
3+	1.005			0.919		
Average of Poles						
1+	0.985	1.764	1.186	0.995	2.420	0.103
2+	0.887			0.872		
3+	0.993			0.970		

f is the ANOVA value; p value < 0.05 is significant. PI means Pulsatility Index

upper, middle and lower poles measured 0.60, 0.62 and 0.58 respectively. The only statistically significant difference in mean was seen in the left middle pole which showed a mean RI of 0.58 in the NS cases and 0.62 in the control group (p= 0.004), as contained in Table 2.

The mean PI value was 0.96, 0.98 and 0.94 as well as 0.96, 0.93 and 0.93 on the right and left respectively for each of upper, middle, and lower pole interlobar renal arteries in NS cases. These interlobar renal artery values were seen to be higher in controls, measuring 0.98, 1.00, and 0.96 on the right upper, middle and lower poles respectively, while on the left the upper, middle and lower poles measured 0.94, 1.00, and 0.92 respectively. The only statistically significant difference in mean, even though marginal, was also seen in the left middle pole which showed a mean PI of 0.93 in the NS cases and 1.00 in the control group (p= 0.048), as depicted in Table 3.

Tables 4 and 5 showed the relationship between the mean RIs and PIs of the different degrees of proteinuria in the NS cases. There was no statistical difference in the mean values of RI except in the upper and middle poles of the left kidney (p= 0.014 and 0.026 respectively). Also the only statistically significant mean difference in PI was found on the right kidney middle pole (p= 0.040).

The duration of the disease, the serum albumin and creatinine did not affect the mean values of RI and PI of NS patients. Likewise, comparison of the RI and PI of the nephrotic cases with proteinuria and those in remission showed no statistical significance. There is also no statistical significance the serum parameters when correlated with the RI and PI of both kidneys in the cases.

DISCUSSION

Nephrotic syndrome has been reported as a major cause of childhood morbidity and mortality (Abdurrahman et al., 1990; Anochie & Eke, 2003; M. Ibadin & Abiodun, 1998; Ocheke et al., 2010), proteinuria has also been shown as a co- factor for progression into chronic renal failure. Nephrotic syndrome as a cause of renal parenchymal disease gives various sonographic patterns which include changes in parenchymal echogenicity, corticomedullary differentiation and renal size. In addition, renal resistive index has been shown to be of high prognostic value in chronic kidney disease, especially in proteinuric states to which Nephrotic syndrome belongs.

This study was able to document the normal parameters for the kidney dimensions, as well as renal interlobar arteries RI and PI as a reference for comparison with the parameters in the children with nephrotic syndrome.

The mean age of 126.24 months in children with NS in this study is higher than that from other regions where mean ages of 60.3 months and 36 months in Kuwait and Saudi Arabia were reported respectively (Kari, 2002; Zaki, Helin, Manandhar, Hunt, & Khalil, 1989). This may be due to demographic characteristic of the cases. The children are predominantly male in this study as seen in other studies (Asinobi et al., 1999; Chijioke & Adeniyi, 2003; M. Ibadin & Abiodun, 1998; Okoro, Okafor, & Nnoli, 2000; Zaki et al., 1989).

Majority of the children 92.7% showed normal serum creatinine, which is in agreement with a previous study done in Finland, where about 82.5% demonstrated normal serum creatinine (Koskimies et al, 1982).

The mean RI value is similar to the findings among the Americans who reported a 0.58 ± 0.05 as the mean RI among the patients with purely glomerular disease (Platt, Ellis, Rubin, DiPietro, & Sedman, 1990). In contrast, a recent study by Calabia et al in Spain reported a higher value, 0.69 ± 0.08 for renal RI among adults with diabetic nephropathy (Calabia et al., 2014). A previous study on vesicoureteric reflux in Austrian children also demonstrated a higher RI value of 0.77 ± 0.07 (Radmayr, Klauser, Maneschg, Bartsch, & Frauscher, 1999). This further buttresses the minimal or no affectation of the renal RI by glomerular disease (Platt et al., 1990).

A similar study from Taiwan among adolescents and young adults is in contrast to this study. Tsai et al reported no statistical significance between renal interlobar artery and albuminuria in non-diabetic patients. This is likely due to a different mode of classification of the 3 groups in the aforementioned study. The index study however classified the NS cases based on qualitative degrees of proteinuria.

This study is in concordance with findings among Turkish children, as demonstrated by Sigirci et al (Sigirci et al., 2006). There is similarity in the value of the renal interlobar artery value. This may be due to similarity in the age distribution of the subjects in both studies.

Not many studies have been carried out on the Doppler indices in childhood nephrotic syndrome hence no further comparison could be made.

In conclusion, this study has shown that there is significant difference in the left midpole RI and PI of the NS cases and controls.

Comparison of the mean renal RI among the 3 levels of proteinuria showed significant differences, however weak in the left kidney upper pole, midpole and average.

In contrast, there was no correlation between the serum parameters (serum albumin and creatinine) and the renal RI and PI.

Although there is weak correlation between renal Doppler indices in children with nephrotic syndrome,

it is recommended that renal ultrasound including Doppler scan should be included in the routine management especially those that have developed chronic renal disease.

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