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Original Article (Pages: 10659-10668)

Resistive Index as a Marker of Renal Pathology in Children with Chronic Kidney Disease; Is It Useful?

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Abstract

Background

Chronic kidney disease is a global health concern, its detection and diagnosis in earlier stages is also a great challenge that can alleviate this burden. Kidney biopsy is important to establish histopathological patterns. But, it is invasive. We aimed to evaluate the correlation of renal resistive index (RI) measured by Doppler ultrasound with the progression of chronic kidney disease and to evaluate its significance as non-invasive marker of renal histological damage.

Materials and Methods

This is a prospective cross sectional study conducted at El Minia Pediatric University Hospital, El Minia, Egypt, and included a total of 57 children: 38 patients with different stages of chronic kidney disease (group I), and 19 healthy children served as controls (group II). Full history, examinations and some laboratory investigations as 24th protein in urine, serum urea and creatinine concentrations were done. All participants underwent renal Doppler ultrasonography and a kidney biopsy was taken from CKD patients.

Results: Resistive index was significantly higher in patients group (group I) compared to control group. In CKD patients there was a significant positive correlation between RI and stages of CKD ($r=0.47$, $p<0.05$). Also, there was a significant positive correlation between RI and histological indices. However, significant negative association was found between RI and both eGFR ($r=-0.49$, $p<0.05$), and renal length ($r=-0.40$, $p<0.05$).

Conclusion

Resistive index increases with the progression of CKD and it is correlated with the histological indices. So, RI as a non-invasive technique could be considered as a marker of renal function and histological damage in CKD patients and it could be a non-invasive indicator for monitoring the progression of renal disease.

Key Words: Children, Chronic Kidney Disease, Doppler Ultrasound, Resistive Index.

*Please cite this article as: Swelam SH, El-Khodary AR, Mahgoob MH, Elian MM, Gayyed MF, Mostafa Mohammed H. Resistive Index as a Marker of Renal Pathology in Children with Chronic Kidney Disease; Is It Useful? Int J Pediatr 2020; 8(1): 10659-668. DOI: **10.22038/ijp.2019.44376.3677**

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Received date: Aug.23, 2019; Accepted date: Dec.12, 2019

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1- INTRODUCTION

Chronic kidney disease (CKD) is a significant global health concern which is associated with an increased risk of multiple organ dysfunctions (1), it is a certain risk factor for end-stage renal disease (ESRD), especially in pediatric patients. Globally, chronic kidney disease takes the 18th position of the causes of death over the last 20 years (2), it is estimated that prevalence of CKD is 15% in developed countries (3). In Egypt, it has been reported that prevalence of CKD was 483 per million populations (4). The proper management of earlier stages of CKD is effective to slow the progression of renal failure. Clinically, data obtained from kidney biopsy is considered as a gold standard that establishes the histopathological patterns concerning renal injury. But, biopsy is invasive and may be correlated with various disorders such as gross hematuria and some massive complications which may result in renal failure (5).

On the other hand, Doppler ultrasonography is a noninvasive maneuver, intensively used for the evaluation of chronic kidney diseases and a number of studies indicated the potential of Doppler sonography as an effective tool for the assessment of renal dysfunction. Some morphological changes of the injured kidney can be detected by ultrasonography such as parenchymal echogenicity, corticomedullary differentiation and changes in its size, but these are not specific for the assessment of renal failure (6), also, these morphological changes "detected by ultrasonography" appear much later than the certain indicators of CKD such as increasing creatinine levels (7). Resistive index (RI) is a parameter that indicates the intrarenal arterial resistance. Resistive index is increased in various kidney diseases (8), and some studies reported that RI is associated with renal function and patient prognosis (9). It has been previously reported that increasing RI is correlated with Glomerulosclerosis (GS), tubulointerstitial (TI) damage and the incidence of vascular lesions (10), but other studies had controversial results (11); while few studies investigated renal histology in different CKD stages and this may be due to the small sample size. The objective of this study is to evaluate the role of resistive index as non-invasive marker for predicting renal pathology in children with chronic kidney disease.

2- MATERIALS AND METHODS

2-1. Subjects and methods

This study was a randomized sample study and was conducted in the Pediatric Nephrology unit at El Minia Pediatric University Hospital, El Minia, Egypt, during the period from May 2016 to June 2017. A total of 57 children (26 boys and 31 girls) aged 4-14 years were included in this study. These children were classified to two groups as follows:

Group (I): Chronic kidney disease (CKD): Included 38 children with different stages of chronic kidney disease (stage 1-5).

Group (II), Control: Included 19 healthy children with matching age and sex serving as controls.

We excluded children with hyper coagulopathy disease and/or receiving anticoagulant drugs, anemic and hypertensive ones from this study. For CKD group, we excluded all patients with hepatitis B, C (portal hypertension). Patients of chronic kidney disease were diagnosed according to guidelines of Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (12), the classifications were made as follows: stage 1: (eGFR mL/min/1.73 m^2) > 90; stage 2: eGFR = 60:89; stage 3: eGFR = 30:59; stage 4: eGFR = 15:29; and stage 5: eGFR < 15 or dialysis.

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From all participants, full history was taken including demographic data and for CKD group, the collected data were: symptoms at onset of the disease, hematuria or any kidney problem, history of hypertension, progression and duration of symptoms, history of medication as regards (type, dose and frequency) and duration of hemodialysis. Complete clinical examination was taken including anthropometric measures (weight using LAICA personal scale code. PS2008B1and height in cm), and blood pressure was determined.

Some laboratory investigations were determined such as 24th protein in urine, serum urea and creatinine concentrations and estimated glomerular filtration rate (eGFR) was calculated by Schwartz equation using body height and creatinine value as follow:

GFR (ml/min/1. 73 m^2) = (0. 41 × Height in cm) / Creatinine in mg/dl.) (13).

2-2. Doppler Ultrasonography

Bilateral Color Doppler Imaging was used to assess renal blood flow velocity at Radiology Department, El Minia University Hospital. It was performed by NemioXG devic (Toshiba Medical Systems, Tochigi, Japan). All participants were scanned laying down on the left lateral position, then on the right lateral position or a supine or decubitus position to achieve an accurate a scan as possible. Ultrasound scan was performed for CKD group before taking the renal biopsy during 24 h. Doppler signals were generally obtained from renal artery lying between the superior mesenteric artery and the corresponding renal vein, arcuate arteries at the corticomedullary junction and/or interlobar arteries along the border of medullary pyramids. The RI for each vessel was calculated as an average value obtained from three to five waveforms. After the measurements of homodynamic parameters such as peak systolic velocity (PSV) and end diastolic velocity (EDV), the resistive index (RI) was calculated by the following equation: RI = (PSV- EDV)/ PSV. Also, the renal length was recorded.

2-3. Histological part

Renal tru-cut biopsies were taken from all CKD patients under ultrasonic guide and scored for histological damage in terms of: arteriolosclerosis (AS), glomerulosclerosis (GS), and tubulointerstitial (TI) damage scores according to scoring systems of Asaba et al. (14). They were evaluated by haematoxylin and eosin stain (H&E), Masson Trichrome stain and periodic acid‑methenamine silver‑stain (PAS).

For GS score, it was done as follows: 0, no GS; 1, matrix expansion or GS <25%; 2, GS= 26‑50%; 3, GS= 51‑75%; and 4, GS >75%. Regarding AS score, it was evaluated as: 0, normal; 1, medial thickening; 2, segmental hyalinosis; 3, global hyalinosis; and 4, luminal occlusion with thrombus. As regards TI score, it was assessed as: 0, normal; 1, mild fibrosis around the vasculature; 2, mild fibrosis around the tubules; 3, moderate fibrosis with tubular casts; and 4, severe fibrosis (14).

2-4. Ethical considerations

Written consents were obtained from patients' caregivers for patients less than 16 years old. The study was conducted according to the declarations of Helsinki and approved by the Faculty of Medicine Scientific Committee in Minia University (No: 116-11-2014).

2-5. Statistical analysis

Data was statistically analyzed using SPSS software version 22.0 (Statistical Package for Social Sciences) for windows. Descriptive statistics were expressed in the form of mean ± standard deviation (SD); while for categorical data they were presented in the form of frequency and percentage. Comparisons between groups

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for continuous variables, normally distributed data were performed by T-test or Mann–Whitney test for the not normally distributed data. Correlations between variables were evaluated by Pearson's and Spearman's rank correlation test. P-value of (< 0.05) was considered as a significant difference and if P-value was (< 0.01), the difference is considered as highly significant.

3- RESULTS

A total of 57 children were included in this investigation, of these, CKD patients group (group I) had 38 subjects with different stages of CKD (9 cases, "23.7%" in each stage 1, 2 and 5, 6 cases "15.7%" diagnosed as stage 3 and 5 cases "13.4%" with stage 4). Regarding pathology of CKD patients, it included 7 cases (18.4%) with chronic interstitial nephritis, 3 cases (7.9%) with end stage renal disease (ESRD), 12 cases (31.6%) with f Focal segmental glomerulosclerosis , 7 cases (18.4%) with lupus nephritis (LN), 3 cases (7.9%) with Membranoproliferative glomerulonephritis (MPGN), 2 cases (5.3%) with Crescentic glomerulonephritis and 4 cases (10.4%) with Minimal change disease (**Table.1**).

Table-1: Clinical backgrounds of CKD patients (group I, n=38).

Variables		CKD Patients, (n=38) No. (%)
Stage of CKD	Stage 1	9 (23.7%)
	Stage 2	9 (23.7%)
	Stage 3	6 (15.7%)
	Stage 4	5 (13.2%)
	Stage 5	9 (23.7%)
Pathology	Chronic interstitial nephritis	7 (18.4%)
	ESRD	3 (7.9%)
	Focal segmental GN	12 (31.6%)
	lupus nephritis	7 (18.4%)
	Membrano-proliferative GN	3 (7.9%)
	Crescentic- GN	2 (5.3%)
	Minimal change disease	4 (10.5%)

GN: glomerulonephritis.

Table.2 summarizes the baseline characteristics of the CKD patients, the mean age of them was 9.3 years, 17 of them were boys and 21 were girls, the mean weight was 31.8 kg and the mean height was 118.4 cm. The mean Systolic blood pressure (SBP) was 133.9 and for Diastolic blood pressure (DBP) was 82.2. Regarding laboratory data, the mean urea concentration was 108.1 (mg/dl), Creatinine concentration was 3.51 (mg/dl), mean of estimated glomerular filtration rate (eGFR) was 53.7 mL/min/1.73 m^2 and the mean 24^{th} urinary protein was 1.41 (g/dl).

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Table-2: Baseline characteristics of the CKD patients (n=38).

Variables	CKD Patients (n=38)
Demographic	
Age (year)	9.3 ± 2.7
Gender, male	17 (44.7%)
Weight (kg)	31.8 ± 9.5
Height (cm)	118.4 ± 16.4
Blood pressure	
Systolic BP (mm/hg)	133.9 ± 23.3
Diastolic BP (mm/hg)	82.2 ± 12.8
Laboratory	
Urea (mg/dl)	108.1 ± 72.3
Creatinine (mg/dl)	3.51 ± 2.70
eGFR (mL/min/1.73 m^2)	53.7 ± 36.5
24^{th} protein in urine (g/dl)	1.41 ± 0.97

Quantitative data is presented in (Mean ± SD), while for categorical data it was presented in the form of frequency (%); BP: blood pressure; estimated glomerular filtration rate.

Results of Doppler ultrasound are presented in **Table.3** and **Figure.1**. CKD patients group had significantly higher resistive index (0.81±0.22) compared to control group (0.53±0.04) ($p<0.01$). However, in contrast, CKD group had significantly ($p<0.01$) smaller renal length than control. Also, the results indicated that resistive index increased with the progression of CKD (CKD stages), but the obvious significant difference was found between stage 5 and the other four stages, while there was no significant difference among these four stages (1, 2, 3 and 4). Conversely, the opposite trend of results was found in renal length, it was decreased with the progression of CKD stages, the higher mean was found in stage 1 (9.55±0.63 cm), however, the lower means were recorded in stage 4 (8.360.47 cm), and stage 5 (6.76 cm) with a significant differences between these stages (**Table.4**).

Table-3: Comparison between groups as regards resistive index and renal length.

Variables	Group (I) CKD (n=38), (M ± SD)	Group (II) Control (n=19), (M ± SD)	P- value
Resistive index	0.81 ± 0.22	0.53 ± 0.04	0.00**
Renal length (cm)	8.44 ± 1.38	9.51 ± 0.87	0.00**

**Significant ($p<0.01$).

Table-4: Comparison among CKD stages as regards resistive index and renal length.

Variables	CKD Stages				
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Resistive index	0.72^{b} ± 0.22	0.72^{b} ± 0.16	0.76^{b} ± 0.23	0.79^{b} ± 0.24	1.01^{a} ± 0.19
Renal length (cm)	9.55^{a} ± 0.63	8.74^{ab} ± 1.04	8.91^{ab} ± 0.67	8.36^{b} ± 0.47	6.76^{c} ± 1.44

a,b,c: Means with the different superscripts are significantly different.

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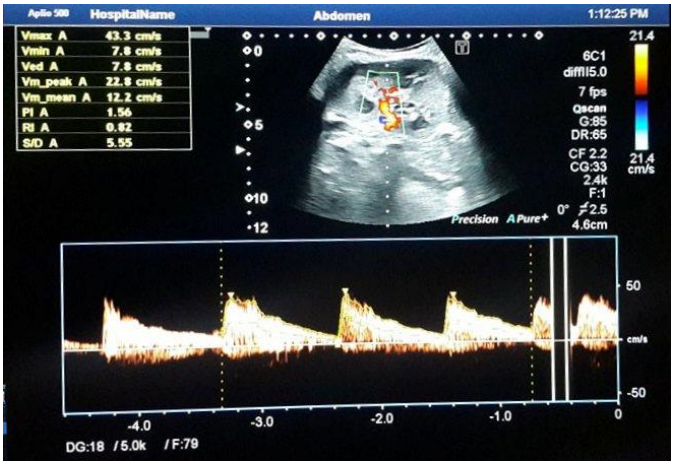

Fig.1: Doppler ultrasound image of a case in stage 4 CKD (RI=0.82).

Significant positive correlation was found between resistive index and systolic blood pressure, urea and creatinine concentrations, stage of CKD, and histological indices (GS, AR and TI scores) **(Figure 2, 3)**. However, significant ($p<0.01$) negative association was found between resistive index and both eGFR ($r=-0.49$), and renal length ($r=-0.40$); while no correlation was noticed between RI and age, height, weight, diastolic BP and 24th protein in urine (**Table.5**). Regarding the correlation between renal length and other variables (also, in **Table.5**), Urea and creatinine concentrations, stages of CKD and all histological indices (GS, AR and TI scores) were negatively associated ($p<0.01$) with renal length, however, body weight and height and eGFR were positively correlated ($p<0.01$) with renal length and no correlation was observed between both blood pressure and 24th protein in urine and renal length.

Table-5: Correlation of resistive index and renal length with other variables in CKD patients group.

Variables	Resistive index Correlation coefficient (*r*)	Renal length Correlation coefficient (*r*)
Age	0.17^{NS}	0.18^{NS}
Weight (kg)	-0.12 ^{NS}	0.55**
Height (cm)	-0.05 ^{NS}	0.38*
Systolic BP (mm/hg)	0.42**	0.01^{NS}
Diastolic BP (mm/hg)	0.21 ^{NS}	0.06 ^{NS}
Resistive index	-	-0.40**
Renal length (cm)	-0.40**	-
Urea (mg/dl)	0.63**	-0.72**
Creatinine (mg/dl)	0.54**	-0.68**
eGFR (mL/min/1.73 m^2)	-0.49**	0.65**
24th protein in urine (gm/dl)	-0.08 ^{NS}	0.23^{NS}
Stage of CKD	0.47**	-0.69**
GS Score	0.44**	-0.38**
AR Score	0.49**	-0.63**
TI Score	0.37*	-0.59**

** Significant ($p<0.01$), * significant ($p<0.05$), NS: Not significant.

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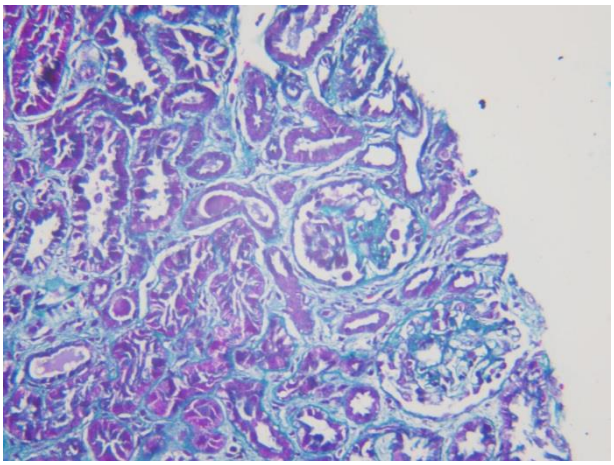

Fig.2: Section in the kidney shows focal segmental glomerulosclerosis (Masson Trichrome, x400).

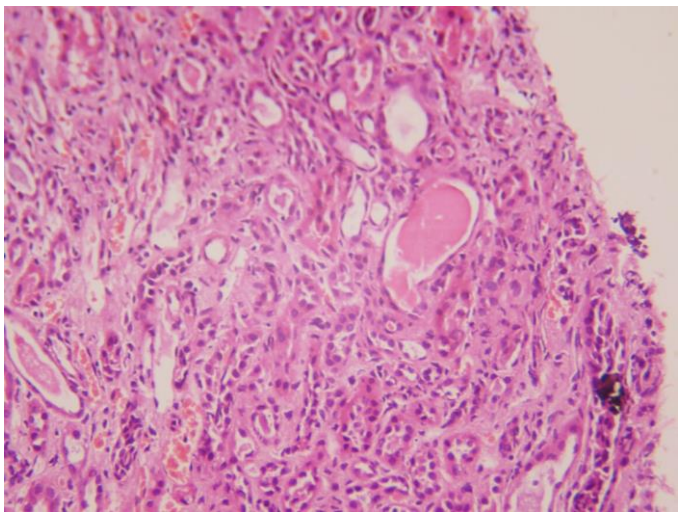

Fig.3: Section in the kidney shows tubular degeneration and tubular casts (H&E, x400).

4- DISCUSSION

The objective of this study was to evaluate the role of resistive index as non-invasive marker for predicting renal pathology in children with chronic kidney disease. From all Doppler ultrasound indices, renal resistive index "which is considered a reflection of renal parenchymal resistance" was the best marker of CKD stages. In our study, we found that RI was significantly higher in CKD patients compared to normal control ones. As matched with our findings, Ikee et al. (15) reported that the optimum range of resistive index is 0.5 to 0.7. Our findings were confirmed by previous studies (15- 20) which reported that RI was increased in CKD patients. Also, the obtained significant negative correlation between eGFR and RI in our study confirms and to some extent explains this result. On the other hand, others reported that increased RI may not always be a result of renal dysfunction, it may affected by many cardiovascular factors such as vascular compliance, pulsatility index and heart rate (21). Our results indicated that RI was increased with the progression of CKD stage, these findings are inconsistent with previous studies (14, 20, 22). These results may be explained by the fact that, progressive chronic renal disease is believed to reflect a nonspecific renal

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scarring process involving all renal components, this process results in a reduction in the number and area of post glomerular capillaries. Renal scarring ultimately leads to a reduction in the intrarenal vessel area, which in turn may be responsible for an increased intrarenal vascular resistance. The same findings were found in a study by Bige et al. (16).

These findings support the hypothesis of increase in RI with the progression of kidney disease stage in children. Also, our findings showed significant correlations between RI and histological damage scores (GS, AR and TI scores). These results are in agreement with Ikee et al. (15) who found that AS is significantly correlated with elevated RI. Also, Hanamura et al. (22) found that RI was strongly associated with TI lesions. Advanced kidney injury is really related with interstitial fibrosis with tubular atrophy and loss of capillaries, it has been reported that TI damage is a histological parameter that strongly correlates with renal function (22), even so, it is not known why TI damage can cause an increase in RI. But, it is thought that alterations in postglomerular vessels by interstitial fibrosis can cause increased resistance to renal cortical blood flow, with a subsequent reduction of glomerular perfusion, independent of the severity of glomerulosclerosis (23).

Additionally, Liu (24) reported that renal fibrosis "particularly tubulointerstitial fibrosis" is the common outcome of almost all cases of progressive CKD and renal fibrosis is also a reliable predictor of prognosis and a major determinant of renal insufficiency. In agreement with our findings, a study has shown that RI is correlated with histological changes and poor renal outcome in chronic kidney diseases patients (16). One of our study findings is that, renal length was significantly smaller in CKD patients than controls and it decreased with the progression of CKD stage. Similar results were obtained by Makusidi et al. (25) who found that there is a positive strong correlation between renal length and degree of kidney function. In patients with CKD, kidney size changes over time, with atrophy related directly to the decline in renal function (26). Also, it was documented that renal length is significantly correlated with glomerular filtration rate (27). Furthermore, Emamian et al. (28) reported a positive correlation was found between renal length and creatinine clearance. On the other hand, Chen et al. (29) found that the renal length showed weak correlation with renal function. They added that kidney length is often affected by the body size of a patient and multiple conditions, including diabetic nephropathy and amyloid nephropathy which may also cause kidney enlargement.

5- CONCLUSION

In summary, on the basis of our observations, RI increases with progression of CKD and this is supported by the significant inverse correlation between RI and glomerular filtration rate. Also, we can suggest that RI was considered as a marker of renal function and histological damage in CKD patients and it could be a non-invasive indicator for monitoring the progression of renal disease. But we could not completely confirm that RI is able to replace renal biopsy. One of our study limitations is the small sample size. So, further studies with larger sample size should be conducted to evaluate the accuracy of Doppler ultrasound parameters for the evaluation of kidney function and histological damage.

6- ACKNOWLEDGEMENTS

The authors thank all participants who were included in this project and their relatives, besides the clinical staff of Pediatric Nephrology unit at El Minia Pediatric University Hospital, El Minia,

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Egypt who were involved with the completion of the study.

7- CONFLICT OF INTEREST: None.

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