# Diffusion tensor imaging of renal parenchyma in pediatric patients with chronic kidney disease: Correlation with serum biomarkers

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***Short title:*** DTI of pediatric CRPD

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# Diffusion tensor imaging of renal parenchyma in pediatric patients with chronic kidney disease: Correlation with serum biomarkers

## ABSTRACT

**Purpose:** to demonstrate role of diffusion tensor imaging (DTI) in diagnosis of pediatric chronic kidney disease (CKD) using fraction anisotropy (FA) and apparent diffusion coefficient (ADC).

**Material and methods:** Prospective study done on 35 CKD patients (19 boys, 16 girls; mean age 12.2±2.7 years) and 19 age and sex-matched volunteers. Patients with sclerotic (*n* = 25) and non-sclerotic (n= 10) CKD that underwent DTI of kidney.

**Results:** Mean FA of renal cortex/ medulla in CKD (0.20±0.07, and 0.18±0.08) was significantly lower (p = 0.001) from volunteers (0.27±0.08, 0.31±0.09). Cutoff renal FA of cortex/ medulla used for diagnosis of CKD was 0.23, and 0.22 with AUC of 0.828, 0.828 and accuracy of 82.9%, 80.7%. Mean ADC of renal cortex/ medulla in CKD (1.98±0.23 and 2.03±0.23 X10-3mm2/s) was significantly higher (p = 0.001) that of volunteers (1.65±0.134 and 1.68±0.16 X10-3mm2/s. Cutoff renal ADC of cortex/medulla used to diagnosis of CKD were 1.75 and 1.85X$10^{-3}$$mm^2$/s with AUC of 0.828, 0.910, 0.828 and 0.81 and accuracy of 82.9%, 84.1%, 80.7% and 79.5%. FA of renal cortex/medulla in sclerotic CKD was significantly different (p = 0.001) than non-sclerotic CKD (0.26±0.07 and 0.25±0.08). The FA of renal cortex/medulla in CKD patients correlated with serum creatinine (r = -0.468; p = 0.000, r =-0.381; p = 0.001), e GFR (r = 0.364; p = 0.002, r = 0.318; p = 0.007).

**Conclusion:** FA and ADC of renal cortex/ medulla can help in diagnosis of CKD, FA cortex/ medulla predicts sclerotic CKD and correlated with some of serum biomarkers.



**Keywords:** Diffusion, tensor, MR imaging, pediatric, kidney


**Abbreviations:** DTI: diffusion tensor imaging

ADC: Apparent diffusion coefficient

FA: Factional anisotropy.

CKD: chronic kidney disease

**What's known?**

Early detection of chronic kidney disease in pediatric is important for prognosis and treatment planning. Renal biopsy is the only diagnostic method for detection of chronic kidney disease. Few recent studies discuss the role of diffusion tensor imaging in diagnosis of chronic kidney disease in adults

**What new**

Diffusion tensor parameters including fractional anisotropy and apparent diffusion coefficient of the renal cortex/ medulla can help in the diagnosis of chronic kidney disease, and fractional anisotropy of the renal cortex/ medulla can predicts sclerotic chronic kidney disease and correlated with some of serum biomarkers of the disease.

# INTRODUCTION

Chronic kidney disease (CKD) is a clinical syndrome characterized by a gradual loss of kidney function over time. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines have defined CKD as abnormalities of kidney structure or function, lasting for more than 3 months, with implications to health. Children with CKD usually present with disease impact on growth as well as a cardiovascular complication that not only influences the health of the patient during childhood but also having an impact on the life of the adult that this child will become **(1-2)**. Kidney fibrosis refers to the deposition of the pathological matrix in the interstitial space, in the walls of glomerular capillaries, and around arterioles secondary to immunological, mechanical, metabolic, and toxic insults. Renal scarring results in a progressive loss of renal function and end-stage renal failure that requires life-long dialysis or kidney transplantation. Histologically end-stage kidney disease manifests itself as fibrotic lesions affecting each compartment; glomerulosclerosis, vascular sclerosis, and tubulointerstitial fibrosis that can predict and contributes to functional the demise of the kidney **(3-4).**

Serum markers such as creatinine and blood urea nitrogen levels and estimated glomerular filteration rate (e GFR) are useful parameters for estimating renal function and severity grading but cannot reflect morphological changes of the kidney. Ultrasonography, CT, and MR can provide anatomic images without functional information. Contrast agents in CT and gadolinium-based MRI may cause nephrotoxicity and systemic nephrogenic fibrosis respectively, thereby limiting their use in CKD patients. Radioisotope scintigraphy is the only established imaging modality to assess renal function by measuring (GFR), but it leads to radiation exposure and has a low spatial resolution. Assessment of renal microstructure is an important step for the diagnosis and monitoring of renal diseases and it is currently performed by renal biopsy which is an invasive procedure carrying the risk of side effects and sampling bias **(5-6)**.

Diffusion-weighted imaging (DWI) is an imaging modality that uses diffusion of water molecules to characterize the structural changes of the tissue. DWI provides information about the magnitude of free water diffusion in tissues. DWI is used to assess disorders of the brain, liver, thyroid, and bone marrow **(7-11).** Diffusion tensor imaging (DTI) represented by vectors with magnitude and direction can evaluate diffusion in multiple various directions to investigate the three-dimensional structure of the tissue. DTI with more measurements can also analyze the principal directions of diffusion and its anisotropic nature. Many more directions (typically more than 30 directions) were probed in DTI to describe the full diffusion tensor. DTI was used in the assessment of normal renal parenchyma **(12),** renal allograft **(13-14)**, renal fibrosis **(15-16)**, glomerulonephritis **(17)**, chronic diffuse renal parenchymal disease **(18-20),** and diabetic nephropathy in humans **(21-22)** and rats **(23)**.

**Aim**

The aim of this work is to demonstrate the role of DTI of pediatric CKD and correlate renal fractional anisotropy (FA) and apparent diffusion coefficient (ADC) with a clinical and pathological staging of CKD disease.

## MATERIAL AND METHODS

### Patients

Institutional board approval for the study and informed consent from parents of children and controls was obtained. This study was done on 38 children with a history of chronic kidney disease with high serum creatinine and low e GFR that underwent renal biopsy. The inclusion criteria were untreated pediatric patients diagnosis of chronic kidney disease based upon Kidney Disease Improving Global Outcomes (KDIGO) guidelines **(1)**. Exclusion criteria were patients with other chronic liver, blood disease, or neoplastic disease. The final study group composed of 35 patients (19 boys, 16 girls with a mean age of 12.23±2.79 years). They underwent routine MR imaging and diffusion tensor imaging of the kidneys. Nine age and sex-matched healthy volunteers (10 boy and 9 girls; mean age, 11.0±2.50 year) who had no previous medical history or renal disease with normal kidney function tests were included as a control group.

### Renal biopsy

Under sterilized conditions and local anesthesia, an ultrasound-guided biopsy was performed. Patients lied in prone or lateral decubitus position and a 16-gauge core needle was used. Cores were sent for light and electron microscopy evaluation. Glomerulosclerosis and tubulointerstitial fibrosis are consequences of CKD progression secondary to an imbalance between excessive synthesis and reduced breakdown of the extracellular matrix replacing the renal cells. Thus, sclerotic renal parenchyma aimed be defined radiologically from others non-sclerotic renal disease **(24)**.

### Serum and urinary biomarkers

Serum creatinine was measured automatically on a COBAS INTEGRA 400 plus Instrument (Germany), using chemicals of Roche Diagnostic, Indianapolis, IN (Germany). The Bedside Schwartz equation is used for estimating glomerular filtration rate (e GFR) from serum creatinine **(25)**.

**Diffusion tensor imaging**

Fasting from food and water for 6 hours before the MR imaging was done by all patients. The MR imaging was done using a 1.5 Tesla scanner (Ingenia, Philips, Best, Netherlands) using a bipolar diffusion encoding gradient. Anterior 16-channel phased-array torso surface coil with another posterior body coil embedded in the table was applied. To reduce the respiratory motion artifacts respiratory-triggered acquisition controlled by a 5-mm coronal navigator slice was placed on the dome of the liver. There was homogeneity of the magnetic field secondary to isotropy of B1. To reduce the artifacts on diffusion tensor images, automatic multiangle-projection shim, and chemical shift selective fat-suppression techniques were applied. Axial T2-weighted Fast Recovery Fast Spin Echo sequence (TR/TE = 3200 /110ms) and T1-weighted images (TR/ TE = 600/25 ms) with following parameters: matrix= 92x 88, field of view (FOV) = 222x 224 $mm^2$ and slice thickness =5 mm and gap interval= 0.5mm were obtained. Diffusion tensor imaging was obtained using a single-shot echo-planar imaging sequence (TR/TE 3200/ 90 ms) with parallel imaging. Diffusion gradients were applied with the following parameters: *b*-value = 0 and 1000 s/ $mm^2$, FOV = 222 × 224 $mm^2$, data matrix = 92 × 88, voxel dimensions = 2.43× 2.54 × 2.5 $mm^3$, slice thickness = 2.5 mm, with no gap and the scan duration =7 to 8 minutes. The diffusion tensor protocol was applied along 32 diffusion gradients encoding directions with tetrahedron geometrical directions.

**Image analysis**

Image analysis was performed by only one radiologist with a 20-year experience in the MR imaging and he was blinded to the clinical and laboratory findings of the patients. The FA color maps were created, where color brightness indicates the FA value. Three single-pixel seed regions of interest (ROI) **(fig1)** were placed in the anterior, middle, and posterior parts of the renal cortex/medulla away from the blood vessels. The FA and ADC of different regions of the renal cortex/medulla were calculated. The mean values of both kidneys represent the renal FA and ADC per subject and were used for the

statistical analysis. The FA and ADC values were calculated according to previous studies **(26-27)**.

**Statistical analysis**

The statistical analysis of data was done by using statistical package for social science (SPSS, Inc., Chicago, IL, USA) software, Version 22.0. Armonk, NY: IBM Corp. The mean and standard deviation of the FA, ADC, serum creatinine and e GFR was calculated. The analysis of data was done to test the statistically significant difference. To compare between two groups, one sample student t-test was used. To compare between more two groups, the Chi-Square test was used. A receiver operating characteristic (ROC) curve was done to evaluate the diagnostic capability of the FA and ADC of the renal cortex/medulla used to diagnose CKD and differentiatie sclerotic versus non-sclerotic kidney disease. The area under the curve (AUC), sensitivity, specificity, and accuracy were calculated. Pearson's correlation test was done to correlate the FA and ADC of the renal cortex/medulla with laboratory parameters. The p-value was considered significant if ≤0.05 at a confidence interval of 95%. The Spearman's rank-order correlation is used to determine the strength and the direction of a linear relationship between FA and ADC of renal parenchyma and laboratory biomarkers (serum creatinine and e GFR).

## RESULT

**Table (1)** shows the demographic, clinical, serum, urinary biomarkers and DTI parameters of CKD patients versus volunteers and sclerotic versus non-sclerotic CKD. **Table (2)** shows the correlation between FA, ADC with serum creatinine and e GFR.

Mean FA value of the renal cortex/medulla of CKD patients (0.20±0.07, 0.18±0.08) was significantly lower ($p$=0.001) than that of the volunteers (0.27±0.08, 0.32±0.09). The cut-off value of FA of the cortex/medulla used to diagnose CKD were 0.23, 0.22, AUC was 0.828, 0.848 and accuracy was 82.9%, 80.7% **(Fig 2)**. Mean ADC value of the renal cortex/medulla of CKD patients (1.98±0.23, 2.03±0.23) was significantly higher (p=0.001) than that of the volunteers (1.65±0.134, 1.68±0.16). The cutoff value of ADC of the cortex/medulla used to diagnose CKD were 1.75, 1.85, AUC was 0.910, 0.81and accuracy was 84.1%, 79.5% **(Fig 3).**

The renal FA of renal cortex/medulla in pathologically proven sclerotic CKD (0.17±0.05, 0.16±0.06) was statistically lower ($p$ =0.001 respectively) than that of non-sclerotic CKD (0.26±0.06, 0.24±0.08). The renal ADC of the renal medulla in pathologically proven sclerotic CKD (2.04±0.22X$10^{-3}$$mm^2$/s) was higher ($p$ =0.362) than that of non-sclerotic CKD (1.99±0.25 X$10^{-3}$$mm^2$/s)**.**

The FA of the renal cortex/medulla in patients with CKD correlated with serum creatinine ($r$= -0.468, $P$=0.001, $r$=-0.381, $p$=0.001 respectively) and e GFR ($r$=0.364, P=0.002, r=0.318, p=0.007 respectively). The ADC of the renal cortex/medulla in patients with CKD correlated with serum creatinine ($r$=0.157, $p$ =0.193, $r$ =-0.115, $p$=0.342 respectively) and e GFR ($r$=-0.157, $p$=0.193 $r$=0.097, $p$=0.425 respectively).

## DISCUSSION

The main findings in this study that there is a significant difference in the FA and ADC of the renal cortex/ medulla in CKD compared to volunteers, and patients with sclerotic CKD compared to non-sclerotic CKD. Also, a correlation between DTI parameters and laboratory parameters, including the serum creatinine and e GFR was found.

The FA value represents the capability of DTI to detect anisotropic diffusion. It is mostly related to a preferential direction of medullary molecular diffusion due to the radial orientation of the renal vessels and tubules, in addition to the contribution to microcirculation **(28).** In this study, the mean FA value of the renal cortex/medulla in patients with chronic kidney disease is statistically reduced from that of volunteers. This may be attributed to the reduction of diffusion anisotropy, possibly caused by structural parenchymal changes seen in CKD, such as cellular infiltration, interstitial fibrosis, and tubular atrophy in various CKD. Medullary FA was a sensitive and accurate marker for the detection of CKD, this, in turn, is coping with many authors who considered that medullary FA as a marker for renal structural integrity alteration and potential useful index for kidney disease diagnosis **(28).**

Mean diffusivity quantifies cellular and membrane density where an increase in mean diffusivity indicates disease processes such as edema or necrosis. Whereas the FA is related to the water molecule transport in the collecting tubules, the ADC is mainly influenced by perfusion **(28)**. In this study, the ADC value of the renal cortex/medulla in patients with CKD is statistically higher than that of volunteers. Disrupted microcirculation and molecular diffusion by structural parenchymal changes influence the cortical and medullary perfusion and subsequently affect the mean diffusivity **(28).** Cortical ADC was also a sensitive biomarker for structural changes in renal parenchyma which can be added to medullary FA for CKD diagnosis in this study. Some studies reported that the ADC value was lower in the disease group than that of control subjects

**(29-30)**, and another study (**28)** didn't find this relation. Another study added that the ADC value is significantly lower in the medulla than the cortex for both patients and controls (P=0.01) **(31)**. This difference from our study may be attributed to different hydration status of the patients, duration of the disease, parameters of DTI in addition to variable grades of arteriolosclerosis and glomerulosclerosis.

Correlation of the DTI parameter with CKD pathologic subtypes were not studied before, it is needed to understand the types of structural changes and its effect on FA and ADC. In this study, there is a significant difference in the FA of renal cortex/medulla in patients with sclerotic CKD compared to non-sclerotic kidney disease. Deposition of the hyaline matrix in the renal cortex/medulla in sclerotic renal disease results in nodular and diffuse glomerulosclerosis, tubular damage, and interstitial fibrosis will hinder the preferential diffusion of water molecules across the renal tubules in addition to blood stasis. This will result in reduced FA value in both the renal cortex/medulla. ADC value also reduced in both the renal cortex/medulla despite being statistically insignificant likely due to a small number of the study population **(25, 30).**

FA of renal cortex/medulla appears to be potentially sensitive biomarkers for the detection of sclerotic CKD, this could be explained that FA depends more on molecular diffusion than perfusion. In sclerotic CKD tubulointerstitial fibrosis or interstitial fibrosis may precede or predominate the glomerulosclerosis and capillary atrophy. Furthermore, as some described that interstitial fibrosis is better correlated with renal function loss than is glomerulosclerosis we could also say that interstitial fibrosis could related with DTI than glomerulosclerosis **(35).**

In this study, the FA and ADC of the renal cortex/ medulla in patients with CKD were correlated with serum creatinine and e GFR. Spearman's correlation was tested and resulted in a negative and positive correlation between the FA of the cortex/medulla and serum creatinine and e GFR respectively. One study

reported that there is decreasing trend in FA medulla values with an increasing stage of CKD is noted **(36)**. However, others couldn't find this correlation in their study and attributed it to the marked heterogeneity of the study population **(28)**. One study added that ADC showed a positive correlation with e GFR (r=0.72) and a negative correlation with renal interstitial infiltrations (r=-0.44) **(32)**. Another study added that the cortical ADC showed a positive correlation with e GFR of the transplanted kidneys **(33)**. Another study added that Cortical FA positively correlated to serum creatinine ($P$ = .006) and negatively correlated to eGFR ($P$ = .03) **(15).**

This study has limitations. First, this study included a small number of patients that limits the statistical analysis. However, further multi-center studies upon a larger number of pediatric CKD are recommended. Second, the FA and ADC were calculated from a single seed region of interest of the renal cortex/medulla. Application of advanced post-processing methods such as histogram analysis and diffusion kurtosis, IVIM-DWI and artificial intelligence may improve the results because they measured more parameters that give an idea about the microstructural change of the renal parenchyma **(37-41)**. The differentiation between the cortex and the medulla is of special interest because those tissues differ in the context of functionality, structure as well as diffusion parameters, such as ADC and FA values **(42)**.

**Conclusion:**

We concluded that FA and ADC of renal cortex/ medulla can help in diagnosis of CKD, FA cortex/ medulla predicts sclerotic CKD and correlated with some of serum biomarkers.

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## Compliance with Ethical Standards

**Funding**

None

**Informed consent**

Obtained from guardian of the children

**Institutional Review Board [IRB]**

IRB approval was obtained

**Ethical approval**

The study adhered to the Declaration of Helsinki, and approved by the ethics committee at our university.

**Authors contributions**

Conceptualisation and Methodology: Marwa Ramadan Abd Almoaty

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## TABLES

**Table (1): Demographic, serum and diffusion parameters of CKD patients and controls and between sclerotic CKD and non-sclerotic CKD.**

| | **CKD** N=35 | **Control** N=19 | **p-value** |
|---|---|---|---|
| **Demographic** | | | |
| Age (years) | 12.2±2.7 (7-18) | 11.0±2.5(6-15) | 0.23 |
| Sex (M-F) | 19/16 | 10/9 | 0.16 |
| **Serum parameter**s | | | |
| -Serum creatinine (mg/dl) | 1.41±0.267 | 0.89±0.22 | 0.001 |
| -e GFR | 47.6±7.12 | 73.2±16.5 | 0.001 |
| **Diffusion parameters** | | | |
| Cortex :FA | 0.20±0.07 | 0.27±0.08 | 0.001 |
| ADC ($X10^{-3}mm^2/s$) | 1.98±0.23 | 1.65±0.13 | 0.001 |
| Medulla : FA | 0.18±0.08 | 0.31±0.09 | 0.001 |
| ADC ($X10^{-3}mm^2/s$) | 2.03±0.23 | 1.68±0.16 | 0.001 |
| **Pathologic subtypes** | **Sclerotic CKD** (N=25) | **Non-sclerotic CKD** )N=10( | **p-value** |
| **Diffusion parameters** | | | |
| Cortex :FA | 0.17±0.05 | 0.26±0.06 | 0.001 |
| ADC ($X10^{-3}mm^2/s$) | 1.98±0.17 | 2.0±0.349 | 0.813 |
| Medulla : FA | 0.16±0.06 | 0.24±0.08 | 0.001 |
| ADC ($X10^{-3}mm^2/s$) | 2.046±0.2 | 1.99±0.25 | 0.362 |

**Table (2) correlation between the FA, ADC and serum creatinine and e GFR**

| | | FA cortex | FA medualla | ADC cortex | ADC medulla |
|---|---|---|---|---|---|
| **creatinine** | r | -.468** | -.381** | .157 | -.115 |
| | p | .001 | .001 | .193 | .342 |
| **e-GFR** | r | .364** | .318** | -.157 | .097 |
| | p | .002 | .007 | .193 | .425 |

## FIGURE LEGENDS

**Figure (1) Region of interest localization:** DTI color map of kidne shows the localization of ROI within the cortex/medulla of both kidneys in child with CRPD.

**Figure (2) ROC of FA:** The cut-off value of FA of the cortex/medulla used to diagnose CKD ware 0.23, 0.22, AUC were 0.828, 0.848 and accuracy was 82.9%,80.7%

**Figure (3) ROC of ADC:** The cutoff value of ADC of the cortex/medulla used to diagnose CKD were 1.75, 1.85, AUC were 0.910, 0.81and accuracy was 84.1%, 79.5%