

Role of Diffusion Tensor Imaging in renal parenchymal changes

Shimona Saini, Vikas Kumar¹, Prakashini Koteshwara

Department of Radiodiagnosis and Imaging, KMC, Manipal, Karnataka, ¹Department of Radiodiagnosis, PGIMER Dr Ram Manohar Lohia Hospital, New Delhi, India

Correspondence: Dr. Shimona Saini, Department of Radiodiagnosis and Imaging, KMC, Manipal - 576 104, Karnataka, India.
E-mail: dr.shimona.saini@gmail.com

Abstract

Context: Diffusion Tensor Imaging (DTI) is a reliable noninvasive tool to assess renal function with medullary Fractional Anisotropy (FA) values showing the most consistent results. **Aims:** Evaluation of FA, Apparent Diffusion Coefficient (ADC) for detecting diabetic nephropathy (DN) using 1.5-Tesla magnetic resonance imaging (MRI). To determine FA and ADC values in chronic kidney disease (CKD) patients and controls, and comparing these with estimated glomerular filtration rate (eGFR) and categorizing the stage of CKD. **Patients and Methods:** Thirty nondiabetic volunteers underwent DTI. The study included 83 diabetics, 30 frank urine proteinuric, 30 micro-albuminuric, 23 normo-albuminuric with only raised blood sugar patients. Patients were stratified by eGFR into groups: eGFR <60 and eGFR >60 ml/min. ADC and FA values in cortex and medulla were compared between controls and study groups. **Statistical Analysis Used:** Analysis of variance and Pearson correlation using SPSS 16 were performed. **Results:** There was significant difference of FA medulla in controls versus albuminuric and micro-albuminuric versus frank proteinuric patients ($P < 0.001$). Also, there was significant difference between cortical ADC values between normal, microalbuminuric/proteinuric groups ($P = 0.010$, $P = 0.000$, respectively). Significant difference between medullary FA values of patients with eGFR >60 and eGFR <60 versus normal controls ($P < 0.001$) was noted. With declining renal function from normal to CKD category 5, a negative correlation between medullary FA ($r = -0.785$, $P = 0.001$) and ADC cortex values ($r = -0.436$, $P = 0.001$) was noted. A strong positive correlation between medullary FA and cortex ADC with eGFR ($r = 0.598$ and 0.344 , respectively) was noted. **Conclusion:** Medullary FA of diabetics with relatively intact kidney function were significantly lower than those of controls. Hence, drop in medullary FA values can be an indicator of early nephropathy/patients at risk where eGFR is in near normal range. Cortical ADC and medullary FA demonstrated a significant correlation with eGFR with the latter showing a stronger positive correlation.

Key words: Apparent Diffusion Coefficient; chronic kidney disease; diabetic nephropathy; estimated glomerular filtration rate; Fractional anisotropy

Introduction

Diabetic nephropathy (DN) is the most common (44%) cause of end-stage renal disease (ESRD). According to a population-based study, ESRD incidence data from India revealed it to be higher than the previously

estimated, with DN being the leading cause. Changes are required in health-care policies for the optimal care of chronic kidney disease (CKD) patients and efficient resource utilization for early diagnosis of those with ESRD.^[1]

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Discovery of biomarkers that identify patients in the early stages of DN will permit targeted, intensified treatment to high-risk patient groups and promote clinical trials for new therapies.

High doses of thiamine and its derivative benfotiamine have been shown to retard the development of micro-albuminuria in experimental DN.^[2] Sulodexide, a glycosaminoglycan, significantly reduced albuminuria in micro- or macro-albuminuric type-1 and type-2 diabetic patients.^[3]

Even though certain risk factors such as glomerular filtration rate (GFR) and micro-albuminuria have been identified for progression to DN, these do not accurately predict progression in individual diabetic patients. Lack of precision of GFR calculated by equations based on serum creatinine values makes it a suboptimal parameter to identify early-stage kidney disease; micro-albuminuria may indicate early damage but regresses in a significant proportion of diabetic patients. Hence, these indices, are not highly specific and sensitive as all of them show significant alteration only in advanced stages of renal dysfunction.

In Diffusion Tensor imaging (DTI), data is acquired not only about the magnitude of water's mobility [Apparent Diffusion Coefficient (ADC)], but also its directionality and is denoted by Fractional Anisotropy (FA). Noninvasive techniques such as renal DTI gives an opportunity to understand the pathophysiological processes of renal disease by providing the knowledge of the structure and function of renal tubules.^[4]

Hence, in this study we intend to compare the FA and ADC values between normal healthy control group and patients with diabetic nephropathy in early stages as evident clinically by normo-albuminuria, micro-albuminuria and eGFR greater than 60 ml/min. We also intend to determine the trend in change in values of FA and ADC with disease progression.

Materials and Methods

Selection and description of patients

Eighty-three patients (63 males, 20 females, age range 50–80 years, mean age-61 years) with known diabetes were selected on the basis of elevated blood glucose level and with or without urine proteinuria. Tests for urine microalbumin and protein were performed. Patients with normal microalbumin levels (0–30 mg/l) and urine protein levels were grouped as normo-albuminuria patients. Patients with raised microalbumin (>30 mg/l) with negative urine protein were classified as having early stage of renal disease and grouped as micro-albuminuria patients. Patients with positive urine protein were classified as having proteinuria/macro-albuminuria, indicating middle and late

stage renal disease. Serum creatinine was assessed and eGFR was calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Patients with DN were stratified by eGFR into two groups –eGFR <60 and >60 ml/min/1.73 m².

Inclusion criteria

Our study included diabetic patient with nephropathy, diabetic patients with normal urine micro-albumin and absent protein levels, as well as healthy controls. The normal control group included healthy volunteers who were nondiabetic and had creatinine values within normal limits, i.e. normal renal function.

Exclusion criteria

Patients with small kidneys with loss of corticomedullary junction, pyelonephritis/urinary tract infection, abnormal renal anatomy as revealed by magnetic resonance imaging (MRI), were excluded from our study. Other exclusion criteria were medically unstable patients, claustrophobic patients and patients with cardiac pacemaker.

Equipment

Each participant was scanned in a supine position with a PHILIPS 1.5-T MRI scanner using 8-channel abdominal SENSE XL TORSO coil to accommodate diabetic patients. Following initial localizer scans, coronal BTFE MR images (respiratory-triggered, TR/TE = 3.5/1.76 ms, slice thickness = 7 mm, FOV = 355 × 87 mm) were obtained to delineate the medullary and cortical kidney regions. A respiratory-triggered single-shot Diffusion Tensor-echo planar imaging sequence (coronal acquisition) was obtained using 6 directions and three different b values of 0, 400 and 600 mm²/sec. Balanced Turbo Field Echo (BTFE) images were directly applied to the corresponding ADC and FA maps to obtain the mean cortical and medullary ADC and FA values.

Image analysis

Freehand regions of interest (ROIs) were delineated in the cortex and medulla of the kidneys. Medullary ROIs were focused primarily on renal pyramid regions with aligned nephrons. A minimum of 10 pixels/ROI was also incorporated to limit the effects of noise. Three medullary and three cortical ROIs were selected to ensure adequate sampling. Comparison of ADC and mean FA of medulla and cortex between controls, normo-albuminuria, micro-albuminuria, and proteinuria group was tabulated.

Study design

This was a hospital-based, time-bound prospective study conducted over a period of 24 months in the Department of Radiodiagnosis and Imaging. Written informed consent was obtained from all patients after explaining the nature of the examination. All examinations were performed in accordance with the rules laid down by the ethical committee.

Statistical analysis

Statistical analysis was done with SPSS version 16. One-way analysis of variance (ANOVA) test was used to evaluate the difference between the study groups and the variables, and the level of significance was set at $P \leq 0.001$. Pearson correlation test was used to correlate the mean FA and the ADC values with eGFR in the medulla and cortex ($r > 0$).

Results

Comparison of mean Fractional Anisotropy values in different study groups

Using one-way ANOVA, we found significant difference between FA values in the medulla of healthy controls versus patients with micro-albuminuria and those with overt proteinuria/macro-albuminuria ($P < 0.001$). Medullary FA values between patients with micro-albuminuria and patients with overt proteinuria/macro-albuminuria (P value $< .001$) also revealed a significant difference [Table 1].

However, no significant difference was found between cortical FA values between micro and proteinuric/macro-albuminuric group of patients (P value = 0.375). Hence, in future with help of DTI based on medullary FA values nephropathy at an early stage can be diagnosed. This will also enable clinical intervention at time when disease may be efficiently treated and facilitate clinical trials of new therapeutic strategies.

Comparison of Apparent Diffusion Coefficient values in different study groups

Using one-way ANOVA test, we found significant difference between cortical ADC values in normal and micro or macro-albuminuric/proteinuric groups ($P = 0.010$, $P = 0.000$, respectively) [Table 2].

Decreasing trend of average ADC values in the cortex was found with disease progression, i.e., from patients with micro-albuminuria to frank proteinuria. However, medullary values showed an initial increase and no change in late stage disease when compared to the control group.

Comparison of mean Fractional Anisotropy values in relation to estimated glomerular filtration rate

One-way ANOVA test showed significant difference between average medullary FA values of patient with eGFR >60 ml/min/1.73 m² and eGFR <60 ml/min/1.73 m² and normal healthy controls ($P < 0.001$) [Table 3; Figure 1].

However, significant difference between patients with eGFR >60 ml/min/1.73 m² and eGFR <60 ml/min/1.73 m² was not found ($P = 0.455$).

Comparison of mean Apparent Diffusion Coefficient values in relation to estimated glomerular filtration rate

The average ADC values of cortex between normal healthy controls and patients with eGFR <60 showed a significant difference ($P < 0.001$). However, statistical difference was

Table 1: Decreasing trend of FA medullary values from normal control group to patients with overt proteinuria

FA values	Cortex	Medulla
Control	0.390±0.026	0.496±0.030
Micro-albuminuria	0.494±0.028	0.400±0.027
Proteinuria	0.507±0.051	0.361±0.0305

FA: Fractional anisotropy

Table 2: Decreasing trend of cortical ADC values from normal control group to patients with overt proteinuria

ADC values	Cortex	Medulla
Control	1.923±0.131	1.818±0.155
Micro-albuminuria	1.790±0.193	1.866±0.162
Proteinuria	1.715±0.188	1.816±0.165

ADC: Apparent Diffusion Coefficient

Table 3: Trend of FA medullary values with declining renal function with respect to eGFR

FA values	Mean eGFR (ml/min/1.73 m ²)	Cortex FA	Medulla FA
Control	90±17	0.390±0.026	0.496±0.030
eGFR >60 (n=22)	76±28	0.496±0.032	0.387±0.034
eGFR <60 (n=38)	34±17	0.503±0.046	0.377±0.034

FA: Fractional anisotropy, eGFR: Estimated glomerular filtration rate

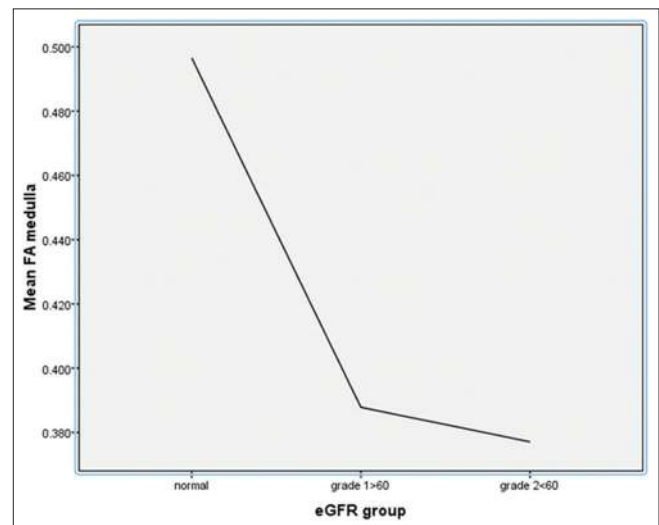


Figure 1: Downward trend in medullary FA values in controls and diabetics with estimated glomerular filtration rate >60 and <60 ml/min/1.73 m² groups

not found for mean ADC values of cortex between normal healthy controls and patients with eGFR >60 . Hence, ADC values are only helpful for detecting moderate-to-severe renal injury [Table 4; Figure 2].

Pearson product-moment correlation coefficient was calculated to analyze the relationship between the mean medullary FA values and eGFR. Between the two variables, that is, the medullary FA value and eGFR, a positive correlation was found, with $r = 0.598$ ($r > 0$) and

$P = 0.001$. Overall, the test revealed a strong positive correlation between eGFR and mean medullary FA values [Figure 3].

Pearson product-moment correlation coefficient was calculated to evaluate the relationship between the mean ADC values of cortex and eGFR. The test revealed a positive correlation between the two variables, i.e., ADC cortex and eGFR $r = 0.344$ ($r > 0$) and $P = 0.001$. Overall, we found a weak positive correlation between eGFR and average ADC values in cortex [Figure 4].

Comparison of Fractional Anisotropy value in patients with normo-albuminuria versus micro albuminuria

On comparing FA medullary values in normal healthy controls and diabetic patients with normal microalbumin levels but raised blood glucose, we found a slight increase in medullary FA values in the latter group;

Table 4: Decreasing trend of ADC cortical values with declining renal function with respect to eGFR

ADC values	MeaneGFR (ml/min/1.73 m ²)	Cortex ADC	MedullaADC
Control	90±17	1.923±0.131	1.818±0.155
eGFR >60 (n=22)	76±28	1.807±0.151	1.860±0.122
eGFR <60(n=38)	34±17	1.721±0.208	1.830±0.185

ADC: Apparent Diffusion Coefficient, eGFR: Estimated glomerular filtration rate

Table 5: Mild increase in FA medullary value in diabetic patients with no evidence of urine microalbuminuria compared to microalbuminuric patients

FA values	Cortex	Medulla
Normal control	0.390±0.033	0.4960.030
Normo-albuminuria	0.372±0.021	0.499±0.026
Micro-albuminuria	0.496±0.045	0.400±0.027

FA: Fractional anisotropy

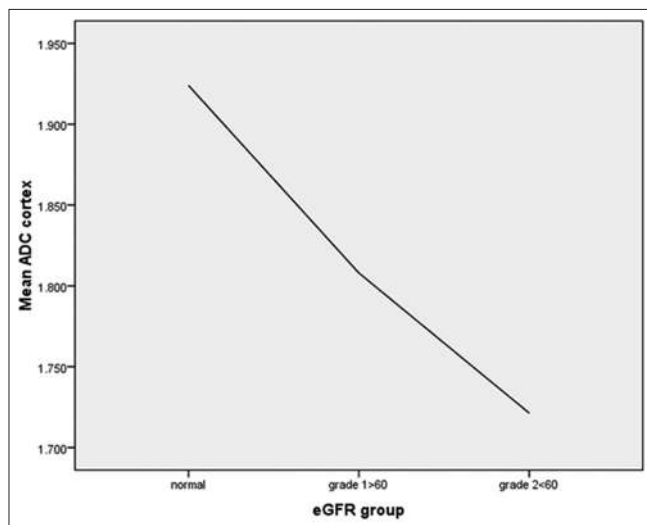


Figure 2: Downward trend in cortical ADC values in control and diabetics with estimated glomerular filtration rate >60 and eGFR <60 ml/min/1.73 m² groups

however, the increase was not significant (P value = 0.993) [Table 5].

Correlation with various stages of chronic kidney disease

Study group patients ($n = 60$, including patients with micro-albuminuria and overt proteinuria) were stratified into stages of CKD as per the NKF-KDOQI guidelines. CKD categories 4 and 5 were merged into one stage. With declining renal function from normal to CKD category 5, we found a negative correlation between medullary FA values ($r = -0.785$, $P = 0.001$) and ADC cortex values ($r = -0.436$, $P = 0.001$) [Figure 5].

Thus, medullary FA was more useful ($r = 0.785$) in detecting the early stages of nephropathy and was also a reliable indicator of disease progression. Whereas cortical ADC ($r = 0.436$) showed a downward trend from normal to CKD 5, which was useful in detecting only middle and late-stage disease with statistical significance.

Discussion

In early nephropathy stages, GFR rises (hyperfiltration stage) and diagnosis may be difficult. In the earlier stages of DN, GFR will be normal or increased, hence, detection of disease in this stage is very important to halt or reverse renal damage. A reduction in GFR reflects reduction in hyperfiltration, hence, a lower rate of water transfer across the interstitial space leads to reduced diffusion. When frank proteinuria occurs, histopathological abnormalities are advanced, i.e., progressive glomerulosclerosis and tubulointerstitial fibrosis occur restricting water diffusion.

FA reflects the directionality of molecular displacement by diffusion and varies between zero (isotropic diffusion, no preferred direction of diffusion) and 1 (purely anisotropic diffusion, only one particular direction of diffusion

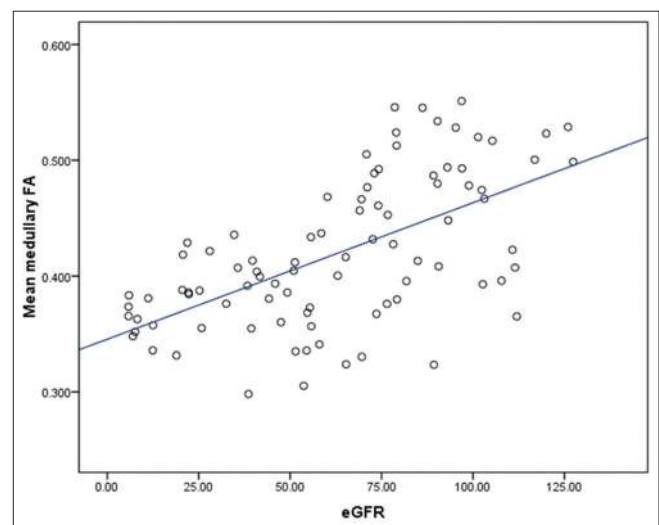


Figure 3: Scatter plot showing positive correlation values with eGFR of medullary FA

restriction). Changes in the water content of the renal tissue and intrarenal blood and tubular flow affect the renal ADC values, whereas the FA values represent molecular diffusion which depends on the transport of water molecules in a preferential direction in collecting ducts, tubules, and vessels that are radially aligned towards the pelvis.^[5]

Changes in Fractional Anisotropy values

Patients with eGFR >90ml/min/1.73 m² are expected to have intact renal function with reversible stage of nephropathy. Hence, by identifying the drop in FA medullary values at early stage where there is a rise in eGFR due to hyperfiltration, clinical/laboratory detection is difficult unless close follow-up is available. Thus, patients with relatively intact renal function but changes at the microstructural level can be identified by changes in FA

value. Thus, declining FA values can help us in predicting patients at risk of kidney damage. We got similar results as in study done by Lu *et al.*^[6]

We also found significant difference in medullary FA with *P* value of <0.001 when compared with the microalbuminuric, which is a much earlier stage or reversible stage of nephropathy and the proteinuric groups of patients. Hence, as the disease progresses there is more isotropy, i.e., the well aligned tubules in medulla become disorganized, leading to decrease in medullary FA.

Hence, we can conclude that FA value represents changes at the microstructure level in early stages where clinically eGFR may be normal and micro-albuminuria may be negative. This change in values may be attributed to increased basement membrane thickening and swelling of tubular cells occurring at the microstructure level, which alters the anisotropy of well-aligned tubules. We noted a decreasing trend in FA medulla values with increasing stage of CKD [Image 1]. These results are in accordance with the study by Wang *et al.*^[7]

Changes in Apparent Diffusion Coefficient values

We noted a significant decline in ADC values in the cortex between healthy controls and diabetic patients with eGFR <60, i.e., late stages; indicating that as the disease progresses there is decrease in renal blood flow causing decline in the mean ADC values (which depends on perfusion and flow effects).

However, we got a weak positive correlation between cortical ADC (*r* = 0.344) values compared to medullary FA values (0.598) for disease progression or worsening grades of CKD. Thus, we conclude that disease progression can be well-evaluated with FA values than ADC. This is

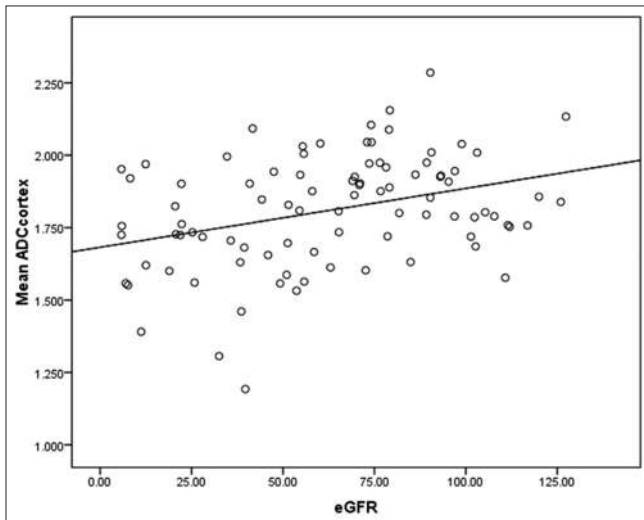


Figure 4: Scatter plot showing positive correlation of cortical ADC values with eGFR

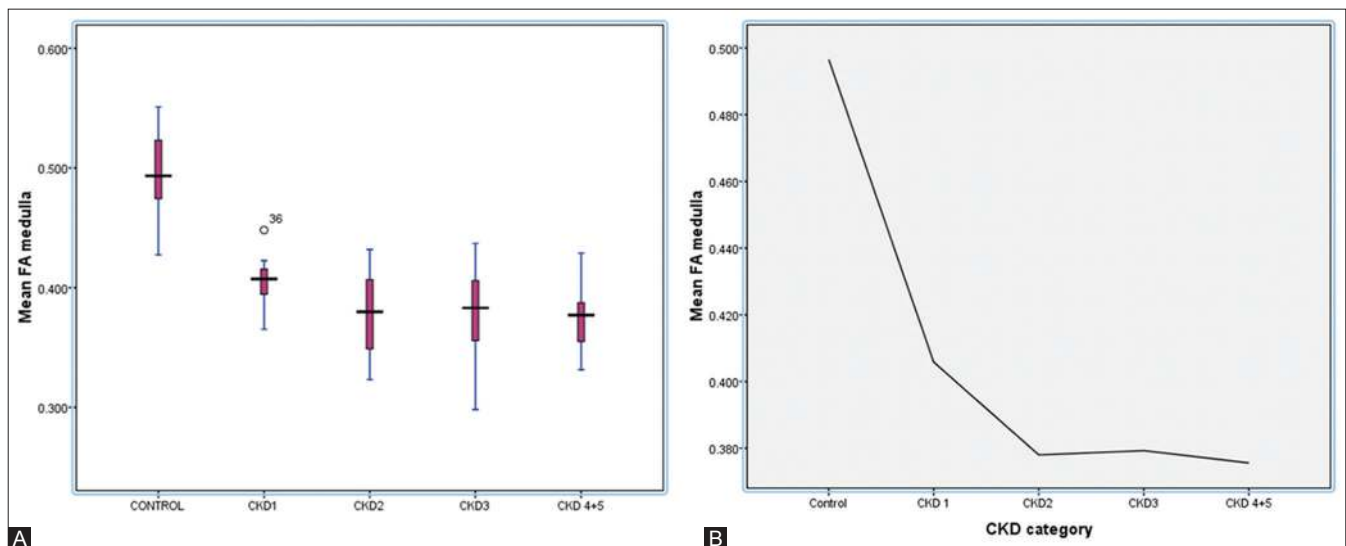


Figure 5 (A and B): (A) Box plot showing medullary FA value in five stages of CKD from control to patients, demonstrating the inter subject variability of renal medullary FA values. (B) Downward trend of mean medullary FA values with progressive increase in stage of chronic kidney disease

in contrast to the study done by Lu *et al.*^[6] where there was no correlation between eGFR and ADC cortex and ADC medulla and FA cortex values. We noted a statistical difference in cortical ADC values between normal healthy controls versus micro-albuminuric patients (P value = 0.01) and normal healthy controls versus proteinuric patients (P value = 0.000). We noted a decreasing trend in cortical ADC values in accordance with previously published literature.^[7,8]

In our study, we found a significant difference ($P < 0.05$) between cortical ADC values in CKD stage 3 and stage 4-5 and healthy controls, and no statistical difference was found between CKD stage 1-2 and controls ($P > 0.05$). These results are similar to the study by Wang *et al.*^[7]

This decreasing trend in ADC values in cortex as GFR decreases may be explained by restricted water diffusion movement in the extravascular and intercellular space by interstitial fibrosis, glomerulosclerosis and tubule atrophy as the disease progresses to ESRD. Thus, renal ADC values are only helpful in detecting moderate-to-severe renal injury [Image 1].

A recent study by Chen *et al.*^[9] stratified patients into a control group without diabetes (NC), diabetics with

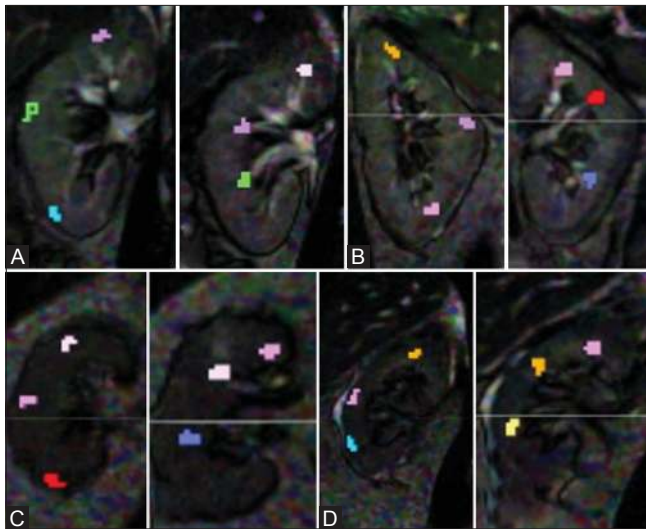


Image1: FA and ADC value in various stages of chronic kidney disease (CKD stage I >90 , CKD stage II $60-90$, CKD stage III $30-59$, end-stage renal disease CKD stage V $15-29$ ml/min/ $1.73m^2$). (A) Mean FA medulla and ADC cortex values in stage I diabetic patients with eGFR-113 are 0.433 ± 0.126 and 2.168 ± 0.187 , respectively. (B) Mean FA medulla and ADC cortex values in stage II diabetic patients with eGFR-81 are 0.394 ± 0.146 and 1.750 ± 0.196 , respectively. (C) Mean FA medulla and ADC cortex values in stage III diabetic patients with eGFR-51.3 are 0.384 ± 0.086 and 1.610 ± 0.225 , respectively. (D) Mean FA medulla and ADC cortex values in diabetic patient in end-stage CKD V with eGFR-11.2 ml/min/ $1.73m^2$ are 0.373 ± 0.101 and $1.540 \pm 0.310 \times 10^3$ mm²/s, respectively. Hence, a continuous declining trend in FA values of medulla and cortical ADC values from CKD stage I to end-stage renal disease (CKD 5) was observed. However, FA values of cortex and ADC values of medulla did not show any specific trend

normo-albuminuria and the micro-albuminuria group (8 h overnight albuminuria = 20 μ g/min to 200 μ g/min).

In our study, we noted an increase in FA medullary values between normal healthy controls and diabetic patients with normal urine microalbumin level; however, this was not statistically significant (P value = 0.993). These results are in accordance with the study by Chen *et al.*^[9] who also found increase in medullary FA value in normo-albuminuric patients compared to the control group. This can be explained by the phenomenon of compensatory hyperfiltration which occurs in the initial stages of DN. They postulated that, in the very early stages of DN, interstitial fibrosis occurs as a result of alteration at microstructural level. The structure of majority of renal tubules at this stage remains intact. These aforementioned microstructural changes in the tubular wall may strengthen their anisotropy. Hence, explaining the increasing trend in FA medullary values.

Most CKDs affecting the renal parenchyma possibly alter directed diffusion (FA) before free diffusion (ADC). So, DTI is the more appropriate modality for functional evaluation of kidneys compared to diffusion-weighted imaging.

There are some limitations of our study. First, there is a lack of histopathological correlation in identifying medullary FA and cortical ADC values as reliable indicators for detecting DN at reversible stage. Second, indistinct corticomedullary differentiation in patients with ESRD can lead to false placement of ROI.

Conclusion

Thus, according to our study data, we can conclude that medullary FA is a more reliable indicator than cortical ADC in detecting early nephropathy changes, especially in diabetics. However, both FA and ADC values were well correlated with eGFR and worsening stages of kidney disease. Significant decrease in medullary FA values with statistical correlation was seen from the stage of reversible nephropathy to ESRD.

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Conflicts of interest

There are no conflicts of interest.

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