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# Using magnetic resonance diffusion tensor imaging to evaluate renal function changes in diabetic patients with early-stage chronic kidney disease

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AIM: To investigate the clinical value of diffusion tensor imaging (DTI) in assessing renal function changes in diabetic patients with early-stage chronic kidney disease (CKD), and the relationship of DTI parameters with estimated glomerular filtration rate (eGFR) and urinary biomarkers.

MATERIALS AND METHODS: Thirty-six patients with diabetes mellitus (DM; 30 CKD stage 1 and 6 CKD stage 2) and 26 healthy control subjects were enrolled. DTI was performed using a clinical 3 T MRI system. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values were calculated from the renal cortex and medulla. The correlation of the DTI parameters with eGFR and urinary biomarkers was evaluated.

RESULTS: FA values were significantly reduced in the renal cortex and medulla of DM group compared with the control group (cortical FA, $Z=-2.834$, $p=0.005$; medullary FA, $t=2.768$, $p=0.007$). In the DM group, FA values in the renal cortex and medulla were positively correlated with eGFR, while FA values in the medulla were negatively correlated with the urinary albumin/creatinine ratio, urinary alpha-1 microglobulin/creatinine ratio, and urinary transferring/creatinine ratio. ADC values in the renal cortex and medulla showed a trend towards an increase in the DM group compared with the control group.

CONCLUSIONS: Renal DTI is a promising method for assessing early renal function changes in DM patients.



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## Introduction

Diabetic kidney disease (DKD) is a common microvascular complication of diabetes, and is the leading cause of chronic kidney disease (CKD).[1,2] The estimated glomerular filtration rate (eGFR) based on serum creatinine values, and the urinary albumin-to-creatinine ratio (UACR), are widely used to identify early kidney damage in diabetic patients. According to the Kidney Disease: Improving Global Outcomes (KDIGO) recommendation,[1,3] the CKD stages 1 and 2 are defined by evidence of "kidney damage" (usually albuminuria) with an eGFR of ≥60 ml/min/1.73 $m^2$, while CKD stages 3–5 are defined by a reduced eGFR (<60 ml/min/1.73 $m^2$) with or without evidence of kidney damage. According to KDIGO recommendations,[1] "kidney damage" typically manifests as albuminuria (UACR ≥30 mg/g) in CKD stage 1 and 2; however, there is increasing evidence of a decreased GFR in the absence of increased urine albumin excretion in many diabetic adult patients. For example, of 11,573 type 2 diabetic patients with estimated kidney function, CKD was identified in 17% of patients with normo-albuminuria (stage 3–5), while the estimated creatinine clearance was <60 ml/min in 20.5% of normo-albuminuric patients and in 30.7% of micro-albuminuric patients.[4] There is also evidence that in type 1 diabetic patients with persistent micro-albuminuria, screening with the albumin excretion rate alone misses >20% of progressive disease.[5] Thus, a large proportion of diabetic patients with completely normal urinary albumin excretion or micro-albuminuria can present with significant kidney dysfunction.

Except for albuminuria, "kidney damage" described in the KDIGO recommendations includes glomerular haematuria, other abnormalities of the urinary sediment, radiographic abnormalities, and other presentations. Thus, discovery of alternative biomarkers (e.g., more subtle radiographic abnormalities) that can identify patients in the early stages of CKD (stage 1 and 2) attributed to diabetes may facilitate the diagnosis and treatment of earlier stages of DKD.

Functional magnetic resonance imaging (fMRI) techniques can measure physiological markers in the kidney.[6,7] The renal structure consists of numerous tubules and vessels in the parenchyma, especially the medulla. These structures are oriented radially from the surface towards the pelvis, which may cause an anisotropic pattern of the molecular diffusion. Diffusion tensor imaging (DTI) is a comprehensive diffusion-weighted imaging (DWI)-related method used to evaluate the direction (fractional anisotropy, FA) and magnitude (apparent diffusional coefficient, ADC) of water molecule transport.[8] Indeed, DTI has been used to assess renal function and structure in healthy subjects,[9] in human patients with renal allografts,[10] renal fibrosis,[11] CKD,[12] and in rodent models.[13] A range of changes in FA and ADC values were reported between the normal and injured kidney, suggesting that DTI may be useful for evaluating renal microstructure; however, the utility of DTI in the diagnosis of early-stage DKD remains unclear. Thus, in the present study, the utility of the renal DTI technique was assessed for evaluating early-stage DKD in an adult cohort, and the correlation of DTI parameters with eGFR and urinary biomarkers.

## Materials and methods

### *Study population*

From September 2016 to September 2017, thirty-six Chinese diabetic patients (age range 25–60 years, median 51 years) and 26 healthy subjects (age range 27–60, mean 43 years) were enrolled in this study. Patients with diabetes were diagnosed according to the American Diabetes Association 2014 criteria.[5] Exclusion criteria were patients with primary hypertension or heart disease, primary kidney disease, rheumatologic disease, chronic liver disease, solid lesion in the kidney, and autosomal dominant polycystic kidney disease. This imaging study was approved by the institutional review board of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants provided written informed consent before the MRI examinations.

### *Serum and urinary biomarkers*

Laboratory tests were measured within 1 week from the MRI examination, including blood glycated haemoglobin (HbA1C), serum creatinine, uric acid, blood urea nitrogen, urinary creatinine, urinary micro-albumin, urinary alpha-1 micro-albumin, and urinary transferring. Patients were classified according to their eGFR (ml/min/1.73 $m^2$) based on the Kidney Disease Outcomes Quality Initiative (KDOQI) classification,[1] as follows: CKD stage 1, eGFR ≥90, kidney damage with normal or increased GFR; CKD stage 2, eGFR 60–89, kidney damage with mildly decreased GFR. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on serum creatinine level,[14] as follows:

Female:

$$\text{Cr} \leq 61.6\ \mu\text{mol/l for eGFR} = 144 \times (\text{Cr}/88/0.7)^{-0.329} \times (0.993)^{\text{age}};$$

$$\text{Cr} > 61.6\ \mu\text{mol/l for eGFR} = 144 \times (\text{Cr}/88/0.7)^{-1.209} \times (0.993)^{\text{age}};$$

Male:

$$\text{Cr} \leq 79.2\ \mu\text{mol/l for eGFR} = 141 \times (\text{Cr}/88/0.9)^{-0.411} \times (0.993)^{\text{age}};$$

$$\text{Cr} > 79.2\ \mu\text{mol/l for eGFR} = 141 \times (\text{Cr}/88/0.9)^{-1.209} \times (0.993)^{\text{age}}$$

Because of spotted urine samples, three urinary biomarkers (micro-albumin, alpha-1 micro-albumin, and transferring) were adjusted for variability in urine flow by dividing values by urine creatinine level.

### Imaging

All participants were asked to abstain from food for 4 h and water for 3 h (no more than 200 ml of water was allowed), and to stop taking diuretic drugs for 24 h, before MRI. All subjects were imaged using a clinical 3 T MRI system (Discovery 750; GE Healthcare, Waukesha, WI, USA) with an eight-channel phased-array body coil. An axial echo-planar DTI sequence was performed with the subject breathing freely, using two b-values (0, 800 s/mm$^2$), 30 different diffusion gradient directions, 28 cm field of view (FOV), 3000 ms repetition time (TR)/minimum echo time (TE), 128×128 matrix, 5 mm section thickness with a 1 mm gap, number of excitations (NEX)=2. Six saturated zones were used around the kidneys to reduce artefacts from the nearby gastrointestinal tract. The scanning time was approximately 2 minutes 40 seconds.

### MRI analysis

ADC maps and FA maps were generated automatically with DTI post-processing software in the workstation (Advantage Workstation software 4.6; GE Healthcare). Six round regions-of-interest (ROIs) were drawn on the anterior, middle, and posterior portions of the bilateral kidneys cortices and medulla near the level of the renal hilus. ROIs were first drawn on the b=0 s/mm$^2$ DTI images, and then were automatically transferred to the equivalent ADC maps and FA maps. Care was taken to exclude the renal sinus, visible blood vessels, and artefacts in the ROIs (Fig 1). ROIs were uniformly round (area of approximately 40–60 mm$^2$). Each sample was measured independently by two professional radiologists with 7 and 20 years of experience in abdominal imaging, who were blinded to the clinical data. DTI values of each ROI measured by these two radiologists were averaged to reduce the measurement error.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 24.0, IBM, Armonk, NY, USA) and the GraphPad Prism (version 5.0; Graph Pad Software, San Diego, CA, USA). Differences in gender between the diabetic group and the control group were tested by using the $\chi^2$ test. The Shapiro–Wilk test was applied to the other clinical data and the DTI-derived parameters for normality ($p<0.05$ indicates non-normal distribution). Normally distributed data were presented as mean ± standard deviation, while non-normally distributed data were presented as median (interquartile range).

Inter-rater agreement was assessed by the intraclass correlation coefficient (ICC), as previously reported.[15] Data were modelled using a two-way random model (absolute agreement type) as the same raters evaluated all of the data using the same methods, and as the raters were considered a subset of a larger set of raters. The ICC results were interpreted as follows: 0.75–1.00, 0.60–0.74, 0.40–0.59, and <0.40, indicating excellent, good, fair, and poor agreement, respectively.[15,16]

Differences in DTI parameters between the right and left cortices and medulla for each group were examined by using the paired *t*-test for normally distributed difference values, or by the Wilcoxon test for non-normally distributed difference values. Similarly, differences in the averaged DTI parameters in the cortex and medulla of the kidneys for each group were examined by using the paired *t*-test or Wilcoxon test accordingly. Differences in DTI parameters and other clinical data between the groups were examined using the independent-sample *t*-test for normally distributed values, and the Mann–Whitney *U*-test for non-normally distributed values. The correlations of renal ADC and FA values with serum and urine biomarkers were analysed using Spearman's or Pearson's correlation analysis, as appropriate. All statistical tests were two sided, and a *p*-value of <0.05 was regarded as statistically significant.

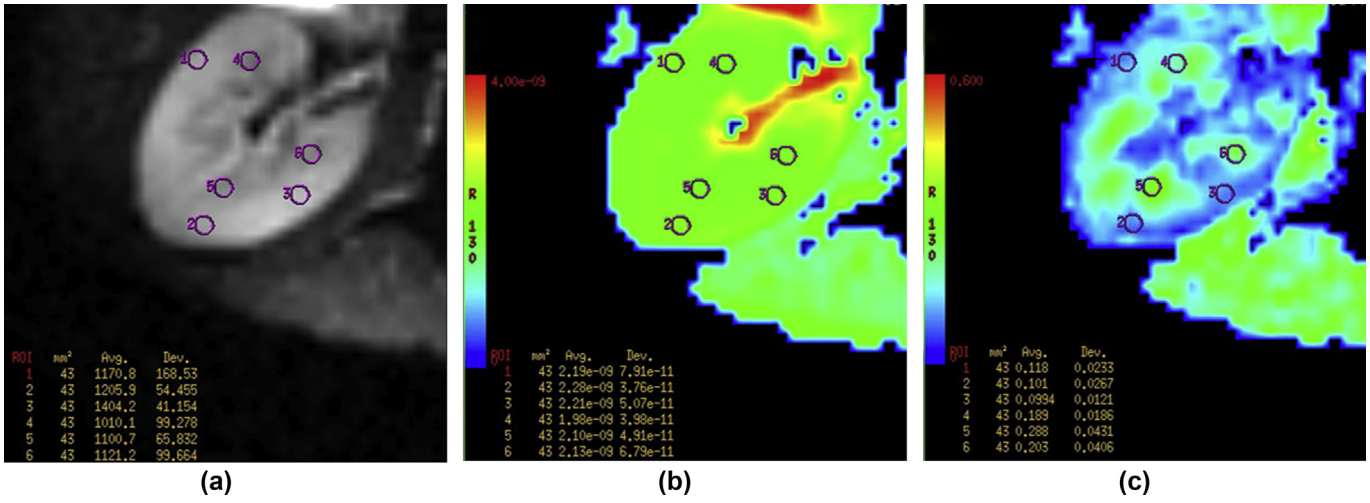


**Figure 1** Localisation of regions-of-interest in the right kidney: axial b0 map (a), ADC map (b), FA map (c) of the kidney shows localisation of the three single round ROIs at the anterior, middle, and posterior parts of the renal cortex and medulla.

## Results

The demographics and clinical characteristics of all subjects are shown in Table 1. Compared with controls, diabetic patients showed no changes in the concentration of uric acid, serum creatinine, blood urea nitrogen, or eGFR.

Based on the grading scale of ICC, inter-rater agreement was 0.728 and 0.759 for cortex and medullary ADC, respectively; 0.701 and 0.645 for cortex and medullary FA, respectively. There were no differences in the mean FA and ADC values between the left and right renal cortex and medulla in control group (cortical FA: $t$=0.064, $p$=0.949; cortical ADC: $t$=1.029, $p$=0.313; medullary FA: $t$=0.920, $p$=0.366; medullary ADC: $t$=−0.352, $p$=0.728) and the DM group (cortical FA: $t$=1.208, $p$=0.235; medullary FA: $z$=−0.079, $p$=0.937; medullary ADC: $t$=0.328, $p$=0.745), except for cortical ADC in the DM group ($z$=−2.209, $p$=0.027). ADC values in the renal cortex were significantly higher than those in the medulla in the control group (2.09±0.11 versus 1.83 ± 0.13, $t$=17.223, $p$<0.001) and diabetic group (2.11±0.14 versus 1.89±0.14, $t$=18.485, $p$<0.001). FA values in the renal medulla were also significantly higher than those in the cortex in the control group (0.18±0.03 versus 0.13±0.02, $t$=−11.509, $p$<0.001) and the diabetic group (0.16±0.02 versus 0.11±0.02, $t$=−15.430, $p$<0.001; Fig 2).

**Table 1**
Subjects characteristics.

| Characteristics | Control group | DM group | $p$-Value |
|---|---|---|---|
| Female/male | 12F/14M | 9F/27M | 0.106 |
| Age (years) | 43±7 | 51 (15) | 0.059 |
| BMI (kg/m$^2$) | 23±3 | 23±3 | 0.692 |
| UACR (mg/g) | Null | 18 (33) | Null |
| UA1MCR (mg/g) | Null | 14 (12) | Null |
| UTRFCR (mg/g) | Null | 8 (3) | Null |
| UA (μmol/l) | 318.88±84.32 | 334.08±102.50 | 0.538 |
| SCr (μmol/l) | 64.20±12.85 | 64.15±18.19 | 0.990 |
| BUN (mmol/l) | 4.95±1.19 | 5.29±1.26 | 0.290 |
| eGFR (ml/min/1.73 m2) | 109.30±10.18 | 109.52±20.03 | 0.955 |

Data are presented as mean±SD for normally distributed values, and median (interquartile range) for non-normally distributed value.
BMI, body mass index; UACR, urinary albumin/creatinine ratio; UA1MCr, urinary alpha-1 microglobulin/creatinine ratio; UTRFCr, urinary transferring/creatinine ratio; UA, uric acid; SCr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

The mean DTI values in the control and DM groups are shown in Fig 2 and Table 2. There were significant differences in FA values in the renal cortex and medulla between the control group and the diabetic group (Mann–Whitney $U$-test, cortical FA: z=−2.834, $p$=0.005; medullary FA: $t$=2.768, $p$=0.007); however, there were no differences in ADC values in the renal cortex and medulla between the two groups (cortical ADC: $t$=−0.664, $p$=0.509; medullary ADC: $t$=−1.774, $p$=0.081).

In the diabetic group, there was significant positive correlation of cortical ADC values with eGFR (Pearson's correlation coefficient $r$=0.387, $p$=0.020); of medullary FA values with eGFR (Pearson's correlation coefficient $r$=0.340, $p$=0.043); and of the cortical FA values with eGFR (Spearman's correlation coefficient $r$=0.354, $p$=0.034; see Fig 3). There were no correlations of medullary ADC with eGFR in the diabetic group (see Table 3).

In the diabetic group, there was a significant negative correlation of cortical FA values with UACR (Spearman's correlation coefficient $r$=−0.410, $p$=0.013); of cortical ADC values with the urinary alpha-1 microglobulin/creatinine

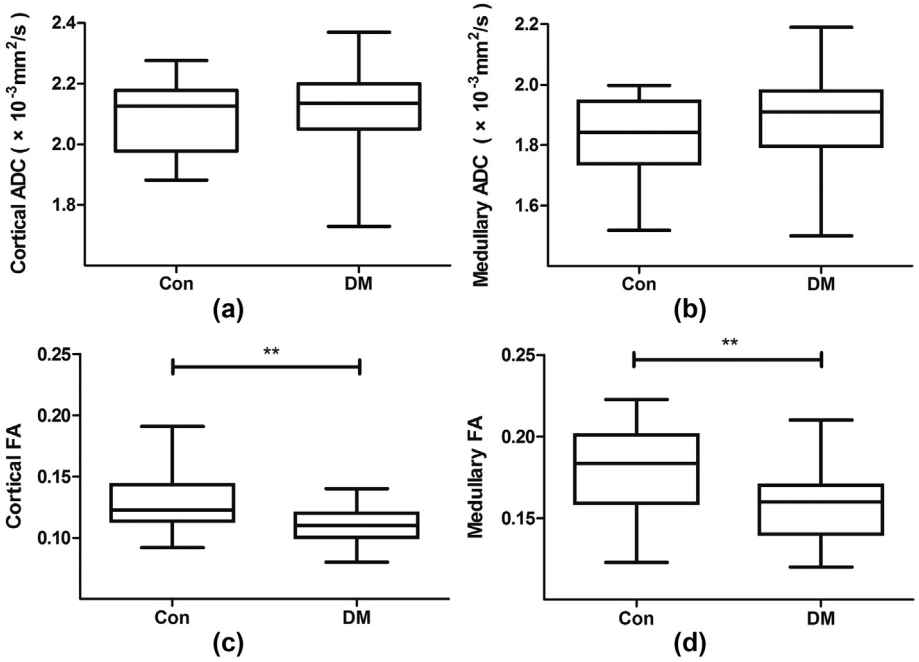


**Figure 2** Comparison of cortical ADC (a), medullary ADC (b), cortical FA (c), and medullary FA (d) values between two groups: control and diabetic patients (**p<0.01).

**Table 2**
Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of renal cortex and medulla.

| Group | n | Cortical ADC ($\times 10^{-3}$ m$^2$/s) | Medullary ADC ($\times 10^{-3}$ m$^2$/s) | Cortical FA | Medullary FA |
|---|---|---|---|---|---|
| Control | 26 | 2.09±0.11 | 1.83±0.13 | 0.13±0.02 | 0.18±0.03 |
| DM | 36 | 2.11±0.14 | 1.89±0.14 | 0.11 (0.02) | 0.16±0.02 |
| *p*-Value | | 0.509 | 0.081 | 0.005 | 0.007 |

Data are presented as mean ± SD for normally distributed values, and median (interquartile range) for non-normally distributed values.
DM, diabetes mellitus.

ratio (UA1MCR, Spearman's correlation coefficient $r=-0.384$, $p=0.021$); of cortical FA values with UA1MCR (Spearman's correlation coefficient $r=-0.383$, $p=0.021$); of cortical ADC values with the urinary transferrin/creatinine ratio (UTRFCR, Spearman's correlation coefficient $r=-0.377$, $p=0.023$); and between cortical FA values and UTRFCR (Spearman's correlation coefficient $r=-0.344$, $p=0.040$; see Table 3).

## Discussion

In the present study, a significant decrease was found in FA values in the renal cortex and medulla in early-stage CKD diabetic patients. Further, the FA values in the renal cortex and medulla were correlated with eGFR, while some DTI parameters of the renal cortex correlated with UA1MCR and UTRFCR; however, there was only a trend towards an increase in ADC values in the renal cortex and medulla in diabetic patients. These results suggest the presence of physiological dysfunction and pathological changes in the very early stage of diabetes, prior to eGFR decline or macroalbuminuria detection. There is some evidence that arterial spin-labelling MRI[17] and blood oxygenation level-dependent imaging[18] may be particularly sensitive for the detection of renal dysfunction in the early stages of diabetic nephropathy. Nevertheless, the present data suggest that DTI is a useful non-invasive technique for detecting subtle events during early diabetic renal damage, and for monitoring the effects of various interventions.

No differences were found in cortical and medullary DTI values between the bilateral kidneys, except for the cortical ADC in the diabetic group. Some previous reports also found differences in the DTI parameters of the left–right kidney to some extent.[19] As the eGFR reflects general renal function, the averaged DTI data from the bilateral kidneys were used in present study. Compared with the renal cortex, the renal medulla had higher FA values and lower ADC values in both the control group and the diabetic group. It is generally accepted that renal water transport is macroscopically oriented from the cortex to the renal pelvis, through a radial orientation of ducts (tubules and vessels). These blood and tubular flows are mainly in the renal medulla[9,20–25] resulting in high medullary anisotropy and increased FA values; however, the cause of the differences in the ADC values remains unclear.[26] Blood flow in the kidney is predominantly in the renal cortex, with only approximately 10% reaching the renal medulla.[27] Therefore, lower ADC values in the renal cortex mainly reflect the lower blood perfusion.

In the present study, the FA values in the renal cortex and medulla in CKD stage 1 and stage 2 diabetic patients were significantly decreased when compared with control subjects. Cortical and medullary FA values were also correlated positively with eGFR in the diabetic group. These findings are similar to that of Lu *et al.*,[28] where medullary renal FA values were correlated positively with eGFR during disease progression in early (eGFR >60) and late (eGFR <60) stage DKD patients. Cortical FA values were also reported to be lower in patients with allografts than in subjects with stable functioning healthy kidneys, while medullary FA decreased with eGFR as the allograft function declined.[29] Further, in a rat model of diabetic nephropathy, only cortical FA was significantly lower in the diabetic group compared with the control group, and was negatively correlated with the extent of glomerulosclerosis and tubular dilatation, while inner medulla FA was negatively correlated with tubulo-interstitial fibrosis. Swelling of renal tubular cells, degeneration of epithelial cells, increased thickness of basement membrane, glomerulosclerosis, tubular lumen expansion, tubular necrosis, and tubulo-interstitial fibrosis have been reported to develop progressively in the early stage of CKD. Thus, the decrease in FA values may reflect the severity of

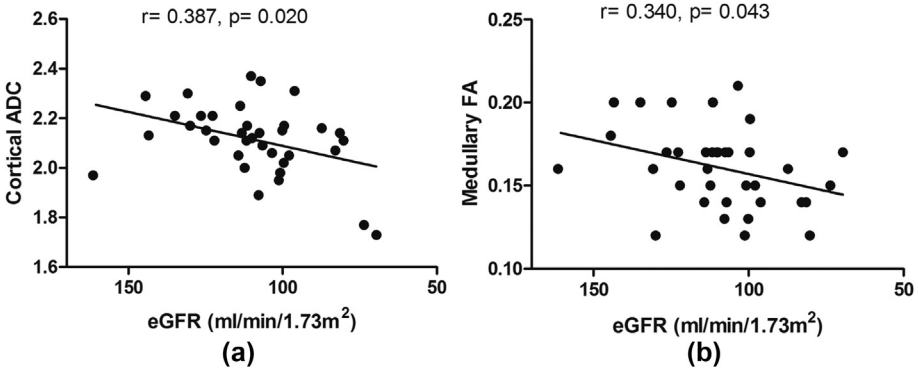


**Figure 3** The FA values of (a) renal cortex ($r=0.387$, $p=0.020$) and (b) medulla ($r=0.340$, $p=0.043$) correlate with eGFR in the diabetic group.

**Table 3**
Correlations of diffusion tensor imaging (DTI) parameters with estimated glomerular filtration rate (eGFR) and urinary biomarkers in diabetes patients ($n$=36).

| | | Cortical ADC ($\times 10^{-3}$ $m^2/s$) | Medullary ADC ($\times 10^{-3}$ $m^2/s$) | Cortical FA | Medullary FA |
|---|---|---|---|---|---|
| eGFR | $r$-Value (Pearson's correlation) | 0.387[a] | 0.132 | 0.354[a] | 0.340[a] |
| | $p$-Value | 0.020 | 0.443 | 0.034 | 0.043 |
| UACR | $r$-Value (Spearman's correlation) | −0.207 | −0.073 | −0.410[a] | −0.259 |
| | $p$-Value | 0.225 | 0.671 | 0.013 | 0.127 |
| UA1MCr | $r$-Value (Spearman's correlation) | −0.384[a] | −0.142 | −0.383[a] | −0.098 |
| | $p$-Value | 0.021 | 0.409 | 0.021 | 0.571 |
| UTRFCr | $r$-Value (Spearman's correlation) | −0.377[a] | −0.218 | −0.344[a] | −0.290 |
| | $p$-Value | 0.023 | 0.202 | 0.040 | 0.087 |

FA, fractional anisotropy; ADC, apparent diffusion coefficient; UACR, urinary albumin/creatinine ratio; UA1MCr, urinary alpha-1 microglobulin/creatinine ratio; UTRFCr, urinary transferring/creatinine ratio.
[a] Correlation is significant at the 0.05 level (two-tailed).

injury to the renal glomeruli and tubules in DKD patients.[20,30–33] Overall, these data suggest that, at the very early stages of renal impairment, a progressive decline in FA values occurs with gradual development of renal impairment.

Pathological albuminuria or micro-albuminuria is a widely used biomarker for acute and chronic kidney damage onset and progression; however, recent cohort studies evaluating the relationship of albuminuria changes with clinical outcomes report inconsistent findings.[4,34] For instance, Dwyer *et al.* found that a large proportion of type 2 diabetic patients with renal dysfunction showed completely normal urinary albumin excretion.[4] Thus, except for albuminuria, more sensitive and specific biomarkers, including UTRF and UA1M, are required for monitoring the development and progression of DKD, even in the very early stage.

UTRF is a low molecular weight protein with a low ionic load and can easily pass through the glomerular barrier. As increased UTRF was found in type 2 diabetic patients with normo-albuminuria, it was suggested to be a sensitive biomarker of early glomerular injury in DKD.[35] UA1M is a sensitive urinary biomarker of proximal tubular damage used to detect DKD, even before the emergence of micro-albuminuria.[34,36] The present study showed a negative correlation of cortical FA with the UACR of diabetic patients, similar to the finding reported by Razek *et al.*[37] In addition, both cortical FA and cortical ADC values were negatively correlated with UA1MCR and UTRFCR, respectively, in the diabetic group. This relationship between UACR/UA1M/UTRF and cortical DTI parameters suggests a role for renal DTI measurements in assessing early renal cortical injury status, as both the glomeruli and proximal tubulars are located in the renal cortex.

In the present study, there were no differences in ADC values between the control and diabetic group, as previously reported.[38] Nevertheless, there was an increasing trend of ADC values in the renal cortex and medulla in diabetic patients. In a DWI study of 62 CKD patients using three b-values (50, 500, 1000), the mean ADC values of the both kidneys in the stage 1 DKD patients were significantly higher than those in stage 2, 3, 4, and 5 patients.[39] According to intravoxel incoherent motion theory, ADC values are affected by pure water molecules diffusion, capillary perfusion, and tubular flow.[40,41] As a b-value of 800 s/mm$^2$ and the mono-exponential fitting model were used in the present study, the effect of perfusion should be remarkably removed. Thus, it could not be confirmed whether the trend towards an increase in ADC observed in diabetic patients reflects the residual effects of increased renal perfusion or increased real water molecules diffusion. Additional analysis of microvascular perfusion components with bi-exponential DWI analysis may demonstrate the characterisation of these subtle pathological processes.

The present study has several limitations. First, the sample size was relatively small, which may affect the statistical power. Previous studies have shown that renal ADC values are age and gender dependent.[27,42] Thus, further studies in a larger number of diabetic patients, including both sexes, should be performed to control for these biases. Second, the effect of hydration status on diffusion data is still controversial.[19,43] Although all subjects were asked to abstain from food and water for a similar time interval before MRI examination, the subjects were not uniformly hydrated. Third, the focus was mainly on the DTI markers for early DKD and did not include patients with stages 3–5. Thus, the relationship of DTI parameters with pathological findings needs further investigation.

In conclusion, the renal parenchyma DTI parameters, especially FA values, play an important role in the assessment of early DKD.

## Conflicts of interest

None declared.

## Acknowledgements

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