Research Article

The Role of Diffusion-Weighted Magnetic Resonance Imaging in Assessment of Renal Dysfunction.

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Abstract
Background: Diffusion-weighted magnetic resonance imaging (DW-MRI) in renal diseases is an evolving field and its potential is yet to be fully realized. **Purpose:** To study the relationship between apparent diffusion coefficient (ADC) values of renal parenchyma and serum markers of renal function and stage of chronic kidney disease (CKD). **Materials and Methods:** A retrospective study included ٢٠ adult normal volunteers of both sexes as a control group and ٢٠ adult diabetic Patients with CKD collected from wards and clinics of El-Minia University Hospital and El-Minia General Hospital. The study was conducted in Al-Safwa Radiology center at the period from April ٢٠١٥ to March ٢٠١٦. Patients were classified into five stages of CKD based on disease severity. All patients underwent DW-MRI (at *b*-values of ٠ and ٥٠٠ s/mm ^{٢}). ADC values were determined for renal parenchyma and compared. Receiver operating characteristic (ROC) curves were drawn to establish cut-off ADC values. Pearson's correlation coefficient (*R*) was calculated between ADC and renal function parameters. **Results:** ADC values in patients with renal dysfunction were significantly lower than in patients with normal renal function (٢.١±٠.٣ vs. **٢.٤±٠.١**(×١٠$^{-٣}$mm^{٢}/s). There was significant inverse correlation between ADC and SCr/BU levels (P = ٠.٠٠١) , and significant linear correlation with (eGFR) (P = ٠.٠٠١). ADC values showed a statistically significant decreasing trend with increasing stage of CKD. **Conclusion:** ADC values may serve as an additional marker for the presence and degree of renal dysfunction.
Keywords: Apparent diffusion coefficient; chronic kidney disease; diffusion-weighted MRI; kidney; renal dysfunction.

Introduction
Chronic kidney disease (CKD) is a common global public health problem and the average incidence of end-stage renal disease in developing countries is ١٥٠ per million population, which is lower than that in the developed world.[١,٢]

Since renal parenchymal disease is accompanied by renal dysfunction, monitoring renal function permits assessment of disease progression, and periodic assessment of renal function is necessary for optimal management of a patient with suspected/proven renal disease. Serum creatinine (S.Cr), blood urea (BU), and estimated glomerular filtration rate (eGFR) derived from creatinine clearance are useful for monitoring renal function; however, these indirect measures of renal filtration are imperfect and cannot assess for early reversible renal damage and cannot be used to measure split renal function, i.e. function of each kidney separately. [٣,٤]

Keeping in view the limitations of serum markers, imaging may play an important role in the evaluation of renal parenchymal disease. Ultrasonography (US) and computed tomographic (CT) scan provide good anatomic images but limited functional information. Although US may show changes in renal echogenicity, it suffers from operator dependency and lacks objectivity. In addition to exposure to ionizing radiation, CT scan requires use of iodinated contrast material, which is undesirable in patients with renal dysfunction.[٥,٦]

Diffusion-weighted MRI (DW-MRI) is a non-invasive modality to characterize tissues based on Brownian motion of water

molecules within them. Apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI that combines the effects of capillary perfusion and water diffusion. DW-MRI in kidneys makes sense because of the organ's high blood flow and role in water filtration. [٧,٨]

DW-MRI in renal diseases is an evolving field and previous investigators have attempted to evaluate its utility in the characterization of focal renal lesions, [٩,١٠] renal parenchymal disease,[١١,١٢] and renal infections.[١٣,١٤] There is paucity of literature investigating the relationship between ADC values and eGFR as well as with different stages of CKD. [١٥,١٦]

The purpose of this study was to investigate the relationship between ADC values of renal parenchyma and serum markers of renal function and stage of CKD. We also intended to establish cut-off ADC values to identify renal dysfunction.

Patients and Methods

The study included ٢٠ adult normal volunteers of both sexes as a control group and ٢٠ adult diabetic Patients with CKD collected from wards and clinics of El-Minia University Hospital and El-Minia General Hospital. The study was conducted in Al-Safwa Radiology center at the period from April ٢٠١٥ to March ٢٠١٦. Patients were classified into stages based on disease severity, as per the K/DOQI CKD (kidney disease outcome quality initiative) classification [Table I]. eGFR was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation based on serum creatinine level and other readily available clinical parameters. All data including demographic information, clinical, and laboratory profile were collected by one author.

Table (I): KDOQI classification of CKD

Stage	Description	(GFR)
At increased risk	**Risk factors** for kidney disease (e.g., diabetes, high blood pressure, family history, older age, ethnic group)	More than ٩٠
١	Kidney damage with normal kidney function	٩٠ or above
٢	Kidney damage with mild loss of kidney function	٨٩ to ٦٠
٣a	Mild to moderate loss of kidney function	٥٩ to ٤٤
٣b	Moderate to severe loss of kidney function	٤٤ to ٣٠
٤	Severe loss of kidney function	٢٩ to ١٥
٥	Kidney failure	Less than ١٥

***** All GFR values are normalized to an average surface area (size) of ١.٧٣$m^{٢}$.

Conventional gray-scale ultrasonographic assessment.

All patients were examined in supine position. Additional scans in the lateral decubitus were useful in some situations. A coupling agent gel was used to ensure good acoustic contact between the transducer and the skin.

Examination was performed using different ultrasound scanners such as Toshiba Nemio XG, GE logiq P٣. These scanners drive convex probes produce a frequency of ٣.٧٥ MHz, also they were connected with printing facility through SONY video graphicprinter up-٨٩٠ MD.

Ultrasonographic examinations of both Kidneys were performed by the same radiologist concerning on renal size, cortical thickening, cortical echogenicity and corticomedullary differentiation.

Renal parenchymal echogenicity was graded using the normal liver or spleen as a reference (patients in the study had no known liver disease to not affect hepatic echogenicity). Normally the echogenicity of

the cortex of the right kidney is hypoechoic to the liver. Grade I nephropathy: the kidney parenchyma is isoechoic to the liver, but there is still cortiomedullary differentiation. Grade II nephropathy: the kidney

parenchyma is hyperechoic to the liver with preservation of corticomedullary differentiation. Grade III nephropathy: kidney appears hyperechoic but there is no corticomedullary differentiation **Mri .**

All patients underwent MRI on a ١.٥-T scanner Philips (Achieva) (maximum gradient strength ٣٣ mTm−١, maximum slew rate ١٢٢ mTm−١ s−١) using a phased array body coil with the patient in supine position.

The imaging protocol included axial and coronal sequences, which served as localizer for planning further sequences. Then conventional MRI sequences, T١W axial and T٢W axial and coronal sequences were acquired.

DW MR imaging

Respiratory triggered FS (spectral fat suppression) spin echo-echo planar imaging (SE-EPI) axial diffusion-weighted sequence at b-values of ٠ and ٥٠٠ s/mm^{٢} was done using parallel imaging.

The following parameters were used: EPI factor = ٩٥, TR/TE = ١٦٠٠/٦٢ ms, flip angle = ٩٠ degrees, slice thickness = ٧ mm, distance factor = ٣٠٪, number of averages = ٦, receiver bandwidth = ١٧٣٥ Hz/pixel, field of view = ٢٤٩ × ٣٨٠, matrix = ٩٤ × ١٩٢, acquisition time = ٢-٤ min (depending on patient's respiratory cycle).

The DW sequence was respiratory triggered using the navigator-triggered prospective acquisition correction technique (PACE) in which the diaphragmatic position is assessed periodically by navigator echoes. Trace DW images and ADC maps were derived automatically on a voxel-by-voxel basis. Good-quality DW images and ADC maps could be obtained in all the patients.

Image analysis

Regions of interest (ROIs) for quantitative measurement of ADC were placed on a commercial workstation (Ultima) by a single radiologist, blinded to the renal function parameters of the patients. To measure the ADC of renal parenchyma, circular ROIs of size ١cm^{٢} were placed on the renal parenchyma without any preference for cortex/medulla. ROIs were placed on the outer one third region of renal parenchyma, corresponding to the kidney contour [Figure١].

Three such ROIs were placed-one each in the upper pole, inter-polar region, and lower pole-and the mean of these three values was calculated. The ADC values were expressed as mean ± standard deviation in the form of A × ١٠$^{-٣}$ mm^{٢}/s.

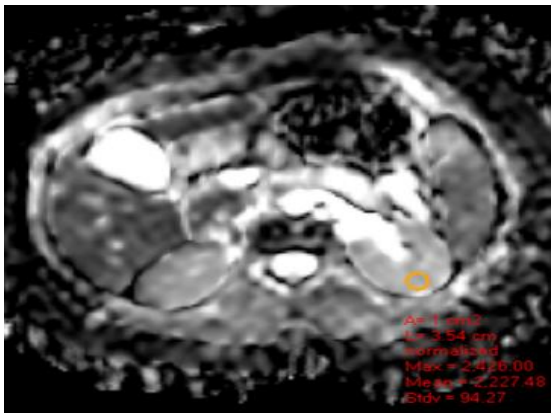

Figure ١: Axial apparent diffusion coefficient (ADC) map image (derived from DW-MRI) of a ٥٥ years old female with stage ٣ diabetic nephropathy. The circle depicts example of ROI placement in the inter-polar region of the left kidney. ROI revealed an

ADC value of ٢.٢٣×١٠–٣ mm٢/s.

Statistical analysis

It was performed using the SPSS software (version ١٩.٠; SPSS; Chicago, Illinois, USA). Mann-Whitney and Kruskal-Wallis tests were used to evaluate the difference between ADC values of two or more groups. Box- plots were drawn based on median and interquartile ranges to highlight the difference between the groups and variation within the groups.

Receiver operating characteristic (ROC) curves were drawn to find out area under the curve (AUC) for differentiation of two groups and cut-off ADC values were calculated so as to achieve the highest average sensitivity and specificity. To investigate the relationship between ADC values and S Cr/BU/eGFR, Pearson's correlation coefficient was calculated by bivariate correlation. All P values <٠.٠٥ were taken as statistically significant.

Results

Patient characteristics

A total of ٢٠ subjects (١٠ male, ١٠ female, .

mean age ٤٠.٠٥ years,age range ٢٢–٥٠ years) without diabetes mellitus or any renal diseases were enrolled as the control group and ٢٠ patients with diabetic nephropathy and no other systemic disease except diabetes mellitus (٩ males,١١ females, mean age ٥١.٢ years, age range ١٩-٧٠ years) were included in our retrospective study.

ADC values and renal function

The mean ADC value of renal parenchyma in patients with renal dysfunction was significantly lower than in patients with normal renal function (٢.١±٠.٣ vs. **٢.٤±٠.١**(×١٠$^{-٣}$mm^{٢}/s); *P* = ٠,٠٠١) [Figure ٢]. We performed ROC analysis for ADC in differentiating patients with renal dysfunction from those with normal functioning kidneys. For detection of renal dysfunction, AUC was ٠.٩٣ ± ٠.٠٤ and *P* = ٠.٠٠١. For a cut-off ADC value of ٢.٣ (×١٠$^{-٣}$mm^{٢}/s), sensitivity was ١٠٠٪, specificity was ٨٠٪, and ٩٥٪ confidence intervals (٠.٨٤-١). values below cut-off indicated renal dysfunction [Figure ٣].

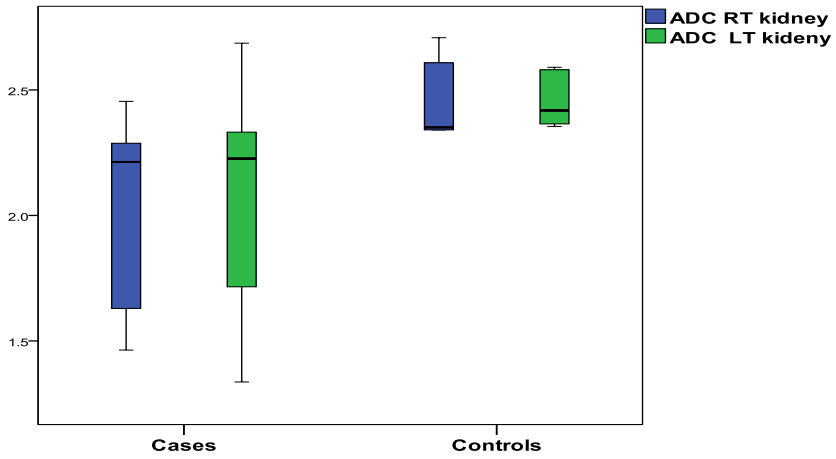

Figure ٢: Box-plot of mean renal parenchymal ADC of each kidney in patients with renal dysfunction and those with normal renal function showing lower ADC values associated with renal dysfunction.

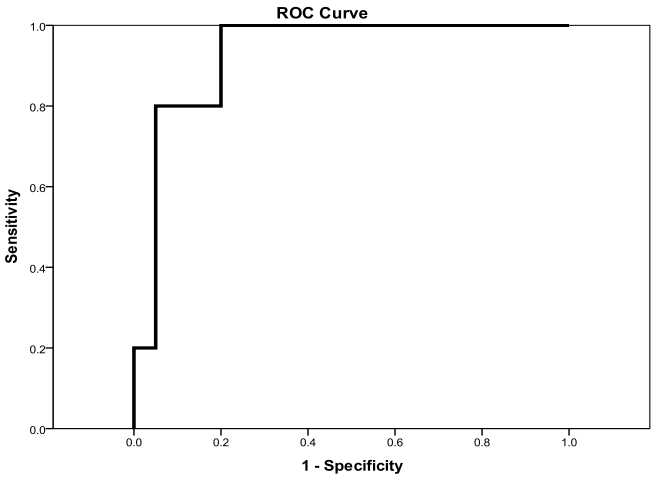

Figure ٣: ROC curve analysis of mean ADC values in detection of renal dysfunction.

ADC values and serum markers of renal function

There was a significant inverse correlation was found between ADC values of renal parenchyma and SCr/BU levels (P = ٠.٠٠١) [Figure ٤] [Figure ٥]. Also, a significant linear correlation was found between renal parenchymal ADC values and eGFR (P = ٠.٠٠١). [Figure ٦].

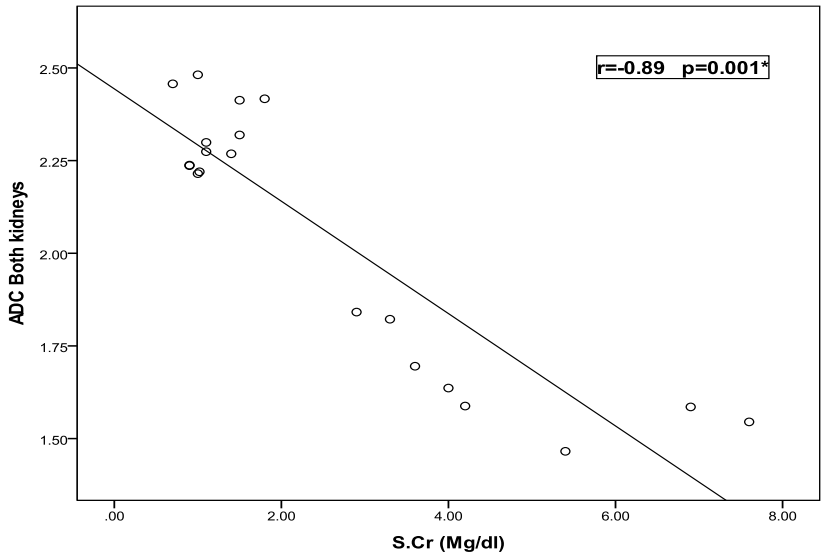

Figure ٤: Scatter plot with interpolation line showing inverse correlation between mean ADC values and serum creatinine among cases.

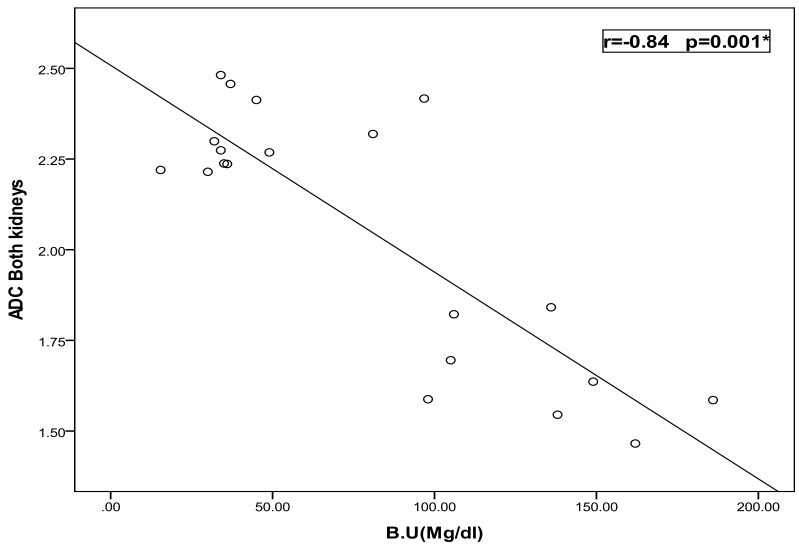

Figure ٥: Scatter plot with interpolation line showing inverse correlation between mean ADC values and blood urea among cases.

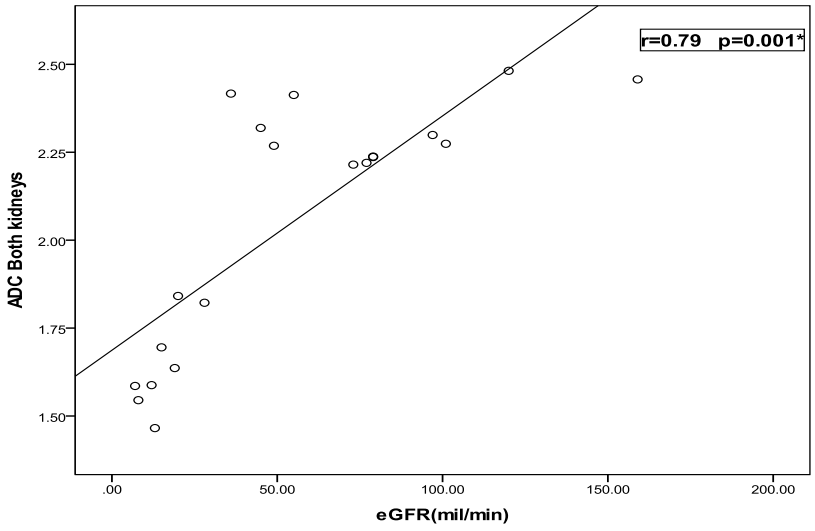

Figure ٦: Scatter plot with interpolation line showing linear correlation between renal parenchymal ADC and eGFR among cases.

ADC values and stages of CKD

The mean ADC values of different stages of CKD were significantly different from each other and showed a decreasing trend with increasing stage [Figure ٧]. The difference was more striking between stage ٣ and stage ٤. Significantly lower mean renal ADC values in stage ٣, stage ٤ and stage ٥ [٢.٣±٠.٠٧ (×١٠-٣mm٢/s) for stage ٣, ١.٧±٠.١ (× ١٠-٣mm٢/s) for stage ٤ and ١.٥ ± ٠.٠٥ (×١٠-٣mm٢/s) for stage ٥] compared to healthy control subjects (P = ٠.٠٠١) but no significant differences in earlier stages.

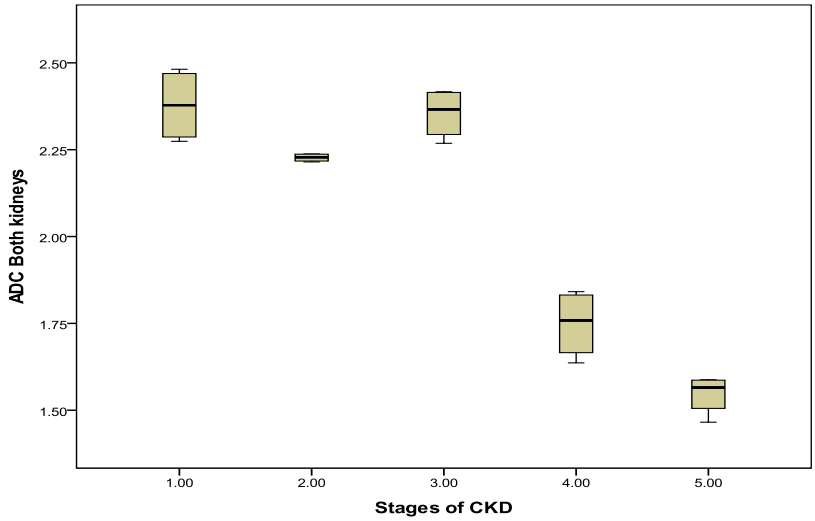

Figure ٧ : Box-plot of mean renal parenchymal ADC in different stages of CKD showing decreasing ADC values with increasing stage of CKD.

Discussion

The mean ADC value of renal parenchyma in patients with renal dysfunction was significantly lower than in patients with normal renal function (٢.١±٠.٣ vs. ٢.٤±٠.١ (×١٠$^{-٣}$mm^{٢}/s) ; P = ٠,٠٠١), Similar results have also been reported by previous investigators.Goyal, et al.,[١٧], Yoshikawa , et al.,[١٨], Namimoto, et al.,[١٩], Thoeny, et al.,[٢٠] , Xu,wang, et al.,[١٤]and Xu, Fang, et al.,[١٥]

Low ADC values in renal parenchymal disease can be explained by reduced perfusion as well as reduced water diffusion. Glomerulosclerosis, tubular atrophy, and interstitial fibrosis restrict the free movement of water molecules in both the extracellular and intracellular space, leading to lower ADC values.

We propose that population and equipment/protocol-based cut-off ADC values may serve as an additional marker for identifying renal dysfunction. For a cut-off ADC value of ٢.٣ ($\times ١٠^{-٣} mm^{٢}/s$), sensitivity was ١٠٠٪, specificity was ٨٠٪, and ٩٥٪ confidence intervals (٠.٨٤-١). values below cut-off indicated renal dysfunction, this matched with previous study. Goyal, et al.,[١٧]

A significant inverse correlation was found between ADC values of renal parenchyma and S Cr/BU levels (P = ٠.٠٠١). This is in concomitant with previous studies. Goyal, et al.,[١٧], Namimoto, et al.,[١٩] and Xu, Fang,et al.[٩]Also, a significant linear correlation was found between renal parenchymal ADC values and eGFR (P = ٠.٠٠١). This is in concordance with the results of Xu, wang, et al.,[٢١] who found a positive correlation between ADC and split renal GFR. Toya, et al.,[١٠] however, did not find any significant correlation between ADC values and eGFR.

The mean ADC values of different stages of CKD were significantly different from each other and showed a decreasing trend with increasing stage. For similar cut-off eGFR values, Toya, et al.,[١٠] found a significant difference between stage ٤ and stage ٥ but not between stage ٣ and stage ٤ disease.

On the other hand, in our study the difference was more striking between stage ٣ and stage ٤. Xu,Fang, et al.,[٩], found a mild negative correlation between ADC and stage of CKD; however, the difference between ADC values of different stages of CKD was not evaluated.

We also identified significantly lower mean renal ADC values in stage ٣, stage ٤ and stage ٥ [٢.٣±٠.٠٧ ($\times ١٠^{-٣} mm^{٢}/s$) for stage ٣, ١.٧±٠.١ ($\times ١٠^{-٣} mm^{٢}/s$) for stage ٤ and ١.٥ ± ٠.٠٥ ($\times ١٠^{-٣} mm^{٢}/s$) for stage ٥] compared to healthy control subjects (P = ٠.٠٠١) but no significant differences in earlier stages. This is in concordance with previous studies. Kadihan, et al.,[٢٢],Çakmak , et al.,[٢٣] , Goyal, et al.,[١٧]

Considering the inverse correlation of ADC values with SCr and BU, positive correlation with eGFR, and taking into account the observation that ADC values showed a statistically significant decreasing trend with increasing stage of CKD, we propose that ADC values may be employed to estimate and monitor the degree of renal dysfunction. Comparison with the baseline ADC values may enable non-invasive monitoring of parenchymal disease progression. Similar to eGFR, cut-offs may be established for ADC values for distinction between various stages of CKD.

There are several limitations of our study. First, the sample size of our study group was small. Cut-off ADC values were not calculated to distinguish among different stages because of the small number of patients in different stages of CKD. Second, we did not investigate the correlation of ADC values with the function of each kidney. We evaluated eGFR by individual patient not by each kidney.

Absence of histopathologic correlation may be another limitation; however, clinical staging is a widely accepted method for detection and prediction of diabetic nephropathy. Additionally, we ignored the influence of hypertension, since hyper-tension was reported to have no effect on renal ADC value, even though it causes end-organ damage.

We also acknowledge that a standardized protocol for renal DW-MRI has not yet been established and this contributes to variation in the absolute ADC values in different studies; nevertheless, the trends of ADC values are reproducible.

Conclusion

ADC values may serve as an additional paradigm to identify and estimate the degree of renal dysfunction. This may be especially useful in patients undergoing

DW-MRI for other purposes (where it may lead to incidental detection of renal dysfunction) as well as in established CKD patients to monitor disease progression. Assessment of renal dysfunction by DWI may help guide the decision to inject a gadolinium-based contrast into patients not previously known to have renal disease.

Population and protocol-based cut-off ADC values may be established to identify renal dysfunction and distinguish between different stages of CKD, and comparison with the baseline ADC values may enable detection of disease worsening/ improvement. The advantages of DW-MRI as indicator of renal function include short time of acquisition, non-invasive nature, and no exposure to ionizing radiation/ contrast material, whereas the drawbacks include availability and cost.

It must be borne in mind that DW-MRI is in no way a substitute to serum markers or renal scintigraphy for assessment of renal dysfunction; rather it is an additional tool, incorporation of which within existing MRI protocols provides additional functional information with minimal increase in imaging time. This functional information provided by DWI, along with morphological information of the kidneys, pelvicalyceal system (MRI urography), and renal vasculature (MRI angiography), may contribute toward making MRI a one-step modality for comprehensive renal evaluation.

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