European Journal of Radiology Open 3 (2016) 8–11

Contents lists available at ScienceDirect

European Journal of Radiology Open

journal homepage: www.elsevier.com/locate/ejro

The relationship of ADC values of renal parenchyma with CKD stage and serum creatinine levels

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ARTICLE INFO

Article history:
Received 3 July 2015
Received in revised form 22 October 2015
Accepted 26 October 2015
Available online 9 December 2015

Keywords:
ADC
MRI
Chronic kidney disease

ABSTRACT

Purpose: To evaluate the relationship of apparent diffusion coefficient (ADC) values of renal parenchyma with chronic kidney disease (CKD) stage and serum creatinine levels.
Materials and methods: One hundred and ten patients who had undergone magnetic resonance imaging of the upper abdomen for different reasons were retrospectively studied. A region of interest (ROI) was placed on the renal parenchyma for measurement of ADC values of both kidneys, without any preference for cortex or medulla. Three circular ROIs were placed-one each in the upper pole, interpolar region and lower pole of both kidneys. The mean ADC values were recorded for each patient and the relationship between ADC values and stage of CKD and serum creatinine levels were evaluated.
Results: Statistically significant difference was determined between the ADC values of the cases according to CKD stages ($p < 0.001$). Paired comparisons performed to determine the group that caused the difference revealed that median ADC values of healthy subjects who formed the control group was statistically significantly higher than that of the cases with stage 3, stage 4 and stage 5 CKD (p: 0.008; p: 0.008; and p: 0.002, respectively). Sensitivity and specificity were found to be 75.44% and 69.81%, respectively in detecting stage 3, stage 4 and stage 5 CKD among the cases with ADC values of 1151 and lower.
Conclusion: ADC values can play a role in the evaluation of renal dysfunction. However, population-and protocol-based cut-off ADC values are needed to identify renal dysfunction and to distinguish between different stages of CKD.

1. Introduction

Chronic kidney disease (CKD) is being recognized as a worldwide leading public health problem [1]. Along with the high cost and poor outcomes, there is a rising incidence and prevalence of kidney failure all over the world [2]. Serum markers such as creatinine and blood urea nitrogen level, and estimated glomerular filtration rate (eGFR) are useful parameters for estimating renal function [3]; however, blood tests depend on age and body mass index and cannot be used to evaluate single kidney function.

Because of the limitations of serum markers, imaging techniques gain importance in the evaluation of renal function [4]. Functional renal imaging methods, such as diffusion-weighted magnetic resonance imaging (DW-MRI), which is used to show the Brownian motion of the spins in biological tissues and to distinguish between normal and abnormal structures of tissues better, has been shown to be a promising technique in the evaluation of renal function [5]. The apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DW-MRI images, and represents the water diffusion in the extracellular and extravascular space and capillary perfusion [6]. To date, there have been few studies investigating the relationship between ADC values and different stages of CKD. Various cut off ADC values have been identified by different researchers [7–11].

The aim of our study was to retrospectively evaluate the relationship of ADC values of renal parenchyma with CKD stage and serum creatinine levels.

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http://dx.doi.org/10.1016/j.ejro.2015.10.002

2. Materials and methods

One hundred and ten (45 men, 65 women; mean age 61.58 ± 13.25 years; range, 19–85 years) patients who had undergone abdominal MRI for different reasons and whose serum creatinine levels had been measured within two weeks from imaging between September 2014 and February 2015, were retrospectively studied. The study protocol was approved by the Ethics Committee of our hospital. Patients were classified into five stages of CKD based on disease severity, according to the K/DOQI CKD (kidney disease outcomes quality initiative) classification [12]. Stage 1: eGFR; ≥90 mL/min/1.73 m^2 (kidney damage with normal or increased eGFR). Stage 2: eGFR; 60–89 mL/min/1.73 m^2 (kidney damage with a mild reduction in eGFR). Stage 3: eGFR; 30–59 mL/min/1.73 m^2 (moderate reduction in eGFR). Stage 4: eGFR; 15–29 mL/min/1.73 m^2 (severe reduction in eGFR). Stage 5: eGFR; < 15 mL/min/1.73 m^2 (kidney failure). GFR was calculated using Japanese eGFR equation based on serum creatinine level: eGFR (mL/min/1.73 m^2) = 194 × plasma creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 if female) [13]. All data including demographic information, clinical, and laboratory findings were obtained from the medical records of the patients. Patients were excluded from the study if they had a single kidney, severe parenchymal atrophy, large solid/cystic lesion in the kidney, autosomal dominant polycystic kidney disease, acute renal failure, unacceptable image quality, and insufficient medical information.

All MRI examinations were performed with a 1.5-T scanner (Avanto, Siemens Healthcare, Germany). All MRI scans were obtained with the following parameters: Repetition time (TR); 1580 ms, echo time (TE); 60 ms, slice thickness; 1–5 mm, receiver bandwidth; 1158 kHz/pixel, field of view (FOV); 40 cm, matrix size; 164 × 159. All MRI scans were independently evaluated by four experienced radiologists who were blinded to the clinical and laboratory findings. ADC value of the kidneys was calculated with diffusion gradient *b*-values of 0 and 400 s/mm^2. In the axial ADC map, a region of interest (ROI) was placed for measurement of ADC values on the renal parenchyma of both kidneys, without any preference for cortex or medulla (Fig. 1). Three circular ROIs of size 1 cm^2 were placed-one each at the upper pole, interpolar region, and lower pole of both kidneys—and 6 total ROIs from bilateral kidneys were averaged for each patient. Creatinine was calculated using the standard laboratory assay. The mean ADC values were recorded for each patient and the relationship of ADC values with CKD stage and serum creatinine levels were evaluated.

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistics are presented as mean, standard deviation, median, minimum, maximum, frequency and ratios. Kruskal–Wallis test was used to compare the variables between the groups, and Mann–Whitney *U* test was used as post-hoc test. ROC curve analysis and sensitivity, specificity, PPV, NPV and accuracy values were used to determine cut-off values. Spearman's rank correlation coefficient was used to determine the association between variables. Significance was evaluated at a *p* value <0.05.

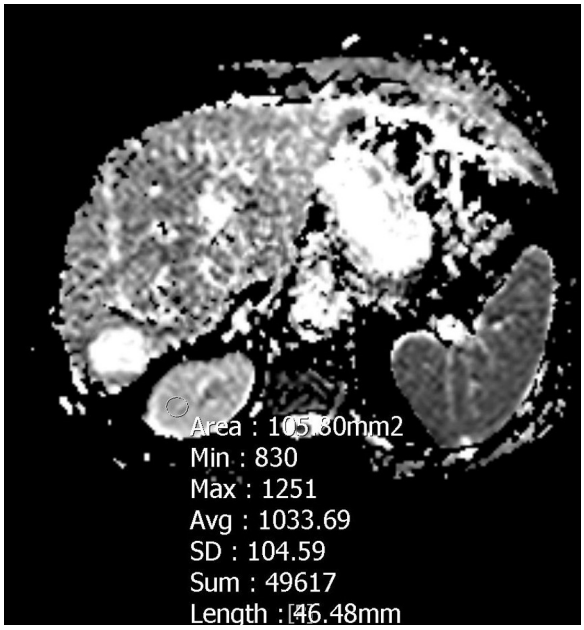

Fig. 1. ADC map of a patient. Sample of measurement technique.

3. Results

ADC values of the cases ranged between 839 and 1508 units, with a mean ADC value of 1156.34 ± 122.909 units. Of the cases, 13.6% (*n* = 15) were healthy subjects; whereas, 4.5% (*n* = 5) had stage 1, 30.0% (*n* = 33) had stage 2, 39.1% (*n* = 43) had stage 3, 5.5% (*n* = 6) had stage 4, and 7.3% (*n* = 8) had stage 5 CKD. Statistically significant difference was determined between ADC values of the cases according to CKD stages ($p < 0.001$). Paired comparisons performed to determine the group that caused the difference revealed that median ADC values of healthy subjects who constituted the control group was statistically significantly higher than that of the cases with stage 3, stage 4 and stage 5 CKD (*p*: 0.008; *p*: 0.008; and *p*: 0.002, respectively). It was found that median ADC values of the cases with stage 1 CKD were statistically significantly higher than that of the cases with stage 5 CKD (*p*: 0.013), and the median ADC values of the cases with stage 2 CKD were significantly higher than

Table 1
ADC values of different stages of CKD patients and healthy group.

	ADC			[a]*p*	[b]Post-hoc
	Min–max	Mean ± SD	Median (Q1–Q3)		
Healthy group	1082–1508	1237.13 ± 134.15	1219 (1126–1285)	<0.001**	H > G3**, G4**, G5**
Stage 1	1092–1212	1178.00 ± 50.39	1199 (1133.5–1212)		G1 > G5*
Stage 2	936–1484	1198.94 ± 98.34	1207 (1130.5–1251)		G2 > G3**, G4**, G5**
Stage 3	991–1465	1139.16 ± 97.61	1119 (1071–1167)		G3 > G4*, G5*
Stage 4	839–1272	1021.00 ± 149.95	1008 (904.25–1122.75)		
Stage 5	880–1163	1009.38 ± 123.58	998.5 (892.5–1127.75)		

Q1: First quartile.
Q3: Third quartile.
[a] Kruskal–Wallis test.
[b] Mann–Whitney *U* test.
* $p < 0.05$.
** $p < 0.01$.

Table 2
Relationship between serum creatinine level and ADC values.

		Creatinine
ADC	R	−0.316
	P	0.001**

r: Spearman correlation coefficient.
** $p < 0.01$.

that of the cases with stage 3, stage 4 and stage 5 CKD (p: 0.002; p: 0.008; p: 0.001, respectively). Median ADC values of the cases with stage 3 CKD were significantly higher than that of the cases with stage 4 and stage 5 CKD (p: 0.025 and p: 0.031, respectively). No statistically significant difference was determined between the other groups in terms of ADC values ($p > 0.05$) (Table 1).

In the ROC analysis performed to determine a cut-off point for ADC value between the control, stage1 and stage 2 CKD groups and stage 3, stage 4 and stage 5 CKD groups; sensitivity, specificity, positive predictive value and negative predictive value were found to be 75.44%, 69.81%, 72.88% and 72.55%, respectively in detecting stage 3, stage 4 and stage 5 CKD among the cases with an ADC value of 1151 and lower. The area under the ROC curve was calculated to be 75.2% and standard error was 4.7%.

A statistically significantly negative correlation by 31.6% was found between serum creatinine values and ADC values of the cases (r: − 0.316; p: 0.001) (Table 2).

4. Discussion

Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique that relies on changes in the diffusion properties of water molecules in tissues. DW-MRI is commonly accepted in neuroradiology for detecting early cerebral ischemia and characterization of cerebral tumors and infections [14]. In recent years, technological advances and improvements such as the development of dedicated surface coils and high amplitude gradients in MRI technique have drawn increasing interest in the potential clinical role of DW-MRI in non-invasive evaluation of extracranial organs [15]. As CKD is a growing health problem, physicians must be equipped to diagnose this patient population [16]. However, there are typically no clinical signs or symptoms for the early diagnosis of CKD patients especially early stages [17]. In the United States, based on data from the 1999–2006 National Health and Nutrition Examination Survey (NHANES) study, an estimated 11.1 percent (22.4 million) of adults have early stage CKD (CKD stages 1–3). Among adults with CKD stages 1–3, approximately half have either stage 1 or 2 CKD, and half have stage 3 CKD [18]. An additional 0.8 million U.S. adults have CKD stage 4, and more than 0.3 million have stage 5 CKD and receive hemodialysis [19]. As the main renal functions are associated with diffusion of water such as glomerular filtration, tubular reabsorption, and secretion; DW-MRI can play an important role in the evaluation of renal function [20]. Recently, the role of ADC values in the evaluation of kidney function has become a subject of multiple researches [7–11]. However, only a few cut-off ADC values have ever been reported to determine renal dysfunction.

Namimoto et al. [21] reported that ADC values in both the cortex and the medulla of the kidneys of acute and chronic kidney disease patients were significantly lower than the values in normal population. Xu, et al. [9] found a liner correlation between renal ADC values and stages of CKD ($r = -0.492$, $P = 0.000$) using b-values ranging from 0 to 500 s/mm^2. The authors indicated that the ADC values of kidneys were significantly lower than normal at most stages of CKD, except CKD 1; however, they did not report the difference between the ADC values of different stages of CKD. Goyal, et al. [11] reported that the mean ADC values of different stages of CKD were significantly different from each other and showed a decreasing trend with increasing stage using b-values ranging between 0 and 500 s/mm^2. They found that mean ADC values for stage- 3; stage- 4, and stage- 5 was 2.2964 ± 0.1243 ($\times 10^{-3}$ mm^2/s), 1.8413 ± 0.2117 ($\times 10^{-3}$ mm^2/s), and 1.5218 ± 0.1853 ($\times 10^{-3}$ mm^2/s), respectively. The difference was statistically significant between stage- 3 and stage- 4 disease, as well as between stage- 4 and stage- 5 disease ($P = 0.003$ and 0.05, respectively). They did not have any patient with stage-1 and -2 CKD; therefore, the difference between ADC values of stage-1 and stage-2 CKD was not evaluated. For similar cut-off GFR values, Toya, et al. [10] found a significant difference between stage-4 and -5 CKD using b-values of 50 and 1000 s/mm^2. However, they did not find a difference between stage-3 and -4 CKD. Different from most of the previous researches, stage 1 and stage 2 CKD patients were included in our study. We found a significant linear correlation between renal parenchymal ADC values and different stages of CKD patients using b-values of 0 and 400 s/mm^2. The mean ADC values showed a decreasing trend with increasing CKD stage ($p \leq 0.001$). However, lower cut-off values were obtained in our study than that in the other studies reported in the literature. This may be explained by the fact that the ADC values were measured in the renal parenchyma without any preference for cortex or medulla in our study, as it might be difficult to correctly position the ROI in these areas, as in the study performed by Goyal et al. [11]. Calculated ADC measurements depend on the b value, and lack of consensus has made it difficult to compare cut-off values of different studies and to determine standardized ADC values for different stages of CKD [10]. Similar to our study, Xu, et al. [9] and Goyal, et al. [11] found a negative correlation between renal parenchyma ADC values and serum creatinine levels.

Our study has some limitations. First, ADC values were measured manually. Manual measurements involve a degree of subjectivity. Therefore, automated ROI delineation methods with better accuracy are needed. Second, ADC values depend on the b values, and lack of consensus has made it difficult to compare the results of different studies and to generate standardized ADC values for CKD. Serum creatinine levels can also be affected by some factors such as dehydration, edema, infections, and drugs.

We conclude that ADC values can play a role in the evaluation of renal dysfunction. Cut off values that we obtained may be useful for stage 3 CKD patients that classified in early stages of disease and respond to treatment. However, population-and protocol-based (static magnetic fields, gradients, coils, b factors, use of acceleration techniques, etc.) cut-off ADC values are needed to identify renal dysfunction and to distinguish between different stages of CKD, especially early stages of the disease (CKD stages 1–3). Therefore, larger scale MRI studies are needed for confirmation.

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