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The role of diffusion-weighted imaging in the diagnosis of early kidney damage

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ABSTRACT

Objectives: This study aimed to determine a threshold value for distinguishing early-stage chronic kidney disease (CKD) from moderate and advanced stages as well as patients with early-stage CKD from those with normal renal function using apparent diffusion coefficient (ADC) and normalized ADC values.

Methods: This retrospective study enrolled 257 patients. Diffusion-weighted images were obtained with a set of b = 50,400,800 values. In each patient, six ADC values were measured from upper, middle, and lower areas of both kidneys, and three ADC values were measured from the spleen. Patients with CKD were classified into five subgroups and healthy patients were classified into two subgroups according to their glomerular filtration rate (GFR).

Results: The renal ADC values were found to be positively correlated with GFR (r = 0.790, $p < 0.001$) and negatively correlated with creatinine levels (r = − 0.709, $p < 0.001$). The mean ADC values of the stage 1 and 2 CKD groups were found to be significantly higher than those of advanced-stage CKD groups ($p < 0.001$), and these values were significantly lower in the stage 1 and 2 CKD groups than in the healthy group ($p < 0.001$). With a cut-off value of ≥ 1.791 for ADC, the sensitivity was 76.5% and the specificity was 85% while distinguishing between patients with early- and advanced-stage CKD.

Conclusion: Renal and normalized ADC values are strongly correlated with CKD stages, and with the use of appropriate threshold values, the difference between early and advanced stages of CKD can be predicted.

Keywords: Diffusion-weighted imaging, apparent diffusion coefficient, chronic kidney disease

Chronic kidney disease (CKD) is a progressive illness that causes decrease in renal function as well as subsequent kidney tissue damage and uremia [1]. The main goal in managing CKD is to slow down the progression of CKD through early diagnosis and appropriate treatment selection based on the underlying pathology [2]. Another parameter that affects the treatment approach is the stage of CKD. Serum creatinine and blood urea nitrogen (BUN) levels as well as estimated glomerular filtration rate (eGFR) are the most commonly used markers during the follow-up of patient with CKD and evaluation of renal function [3]. As serum creatinine level begins to rise when the loss of renal function exceeds 50%, it is not a reliable marker for the early diagnosis of CKD [4]. GFR, which provides information about renal function, is calculated by measuring 24-hour urinary and serum creatinine clearance. In general, serum creatinine clearance-based eGFR levels are calculated according to the Cockcroft-Gault formula and are used for CKD

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staging. However, in cases where eGFR is > 60 mL/min/1.73 m^2, the dietary measures to be adopted during the disease is relatively uncertain. Although serum markers help assess overall renal function, they do not provide information about the morphology of the kidney and whether there is a difference between the two kidneys. Ultrasonography (US) examination is insufficient to detect early changes in renal function and is generally used in diagnosis when morphological and anatomical changes are evident. With the use of imaging techniques, such as intravenous pyelography (IVP), computed tomography (CT), or magnetic resonance imaging (MRI), it is possible to obtain information about functions of the kidneys as well as their morphological structure using contrast material. However, especially in patients with reduced renal functions, there is a risk of nephrotoxicity with IVP and CT urography and systemic nephrogenic fibrosis with MR urography. Therefore, the use of these imaging techniques is limited in such patients [5]. Scintigraphy is widely accepted and provides a quantitative result in the evaluation of kidney functions; however, the magnitude of the radiation exposure and low spatial resolution are its important disadvantages. Therefore, there is a need for a noninvasive and quantitative radiological method to detect kidney damage at an early stage. Currently, the diffusion-weighted imaging (DWI) technique, which basically reveals the Brownian motion of water molecules in biological tissues, as well as microcirculation and diffusion are used appropriately without contrast material. In this technique, diffusion in biological tissues can be expressed quantitatively by measuring the apparent diffusion coefficient (ADC). Promising results have been obtained in some studies on this subject [6-8].

In this study, we aimed to investigate the relationship between conventional ADC values obtained using DAG/DWI MR and normalized ADC values (nADC) obtained by using the spleen as a reference organ, with CKD stage, eGFR and serum creatinine level, and to compare them with previous studies.

METHODS

Patient Selection

Overall, 243 patients with CKD who underwent MRI of the upper abdomen for any reason at our hospital between 2018 and 2022 were included in this study; in addition, 100 patients without a history of CKD were included in the control group. Of 243 patients with CKD, 86 were excluded because of the following reasons: apparent atrophic renal parenchyma or absence of organs to be examined (n = 34); absence of serum biomarkers concomitant with MRI scan (n = 24); dense artifacts that may interfere with MRI measurements or inadequate image quality (n = 22); and presence of a mass lesion or multiple cysts of immeasurable extent in the renal parenchyma (n = 6). Accordingly, 157 patients with CKD and 100 patients without a history of CKD (control group) were included in this study. The study protocol was approved by the research ethics committee of our hospital, and the requirement of informed consent from the patients was waived. Patients in the CKD group were classified into five subgroups based on the severity of the disease according to the Kidney Disease Outcomes Quality Initiative (K/DOQI CKD) guidelines [9]: Stage 1: eGFR ≥ 90 mL/min/1.73 m^2 (kidney damage with normal or elevated eGFR), Stage 2: eGFR = 60-89 mL/min/1.73 m^2 (kidney damage with mild decrease in eGFR), Stage 3: eGFR = 30-59 mL/min/1.73 m^2 (moderate decrease in eGFR), Stage 4: eGFR = 15-29 mL/min/1.73 m^2 (severe decrease in eGFR), and Stage 5: eGFR < 15 mL/min/1.73 m^2 (renal failure). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula as follows: eGFR cr = 142 × min (S cr /κ, 1) α × max (S cr /κ, 1) − 1,200 × 0.9938 Age × 1.012 [if female] [10]. Patients in the control group were classified into two subgroups: those with eGFR ≥ 90 mL/min/1.73 m^2 (n = 59) and those with eGFR = 60-89 mL/min/1.73 m^2 (n = 41).

MRI Technique and Analysis

MRI and DWI examinations of the patients were performed using a sixteen-channel body coil and a 1.5 T MR device (Optima MR360 Advance, GE Medical Systems, Milwaukee, Wisconsin, USA).

First, coronal T2-weighted single-shot fast spin-echo (SSFSE) (TR = 1800 ms, TE = 70 ms, flip angle = 90°, field of view = 40 × 40 cm, matrix = 200 × 192, breath holding), axial T2-weighted single-shot fast spin-echo (SSFSE) (TR = 1700 ms, TE = 110 ms, flip angle = 90°, field of view = 40 × 40 cm, matrix = 320 × 224, breath holding), axial fs-FSE T2-weighted (TR = 2200 ms, TE = 85 ms, thickness = 5.5 mm, pitch = 1 mm,

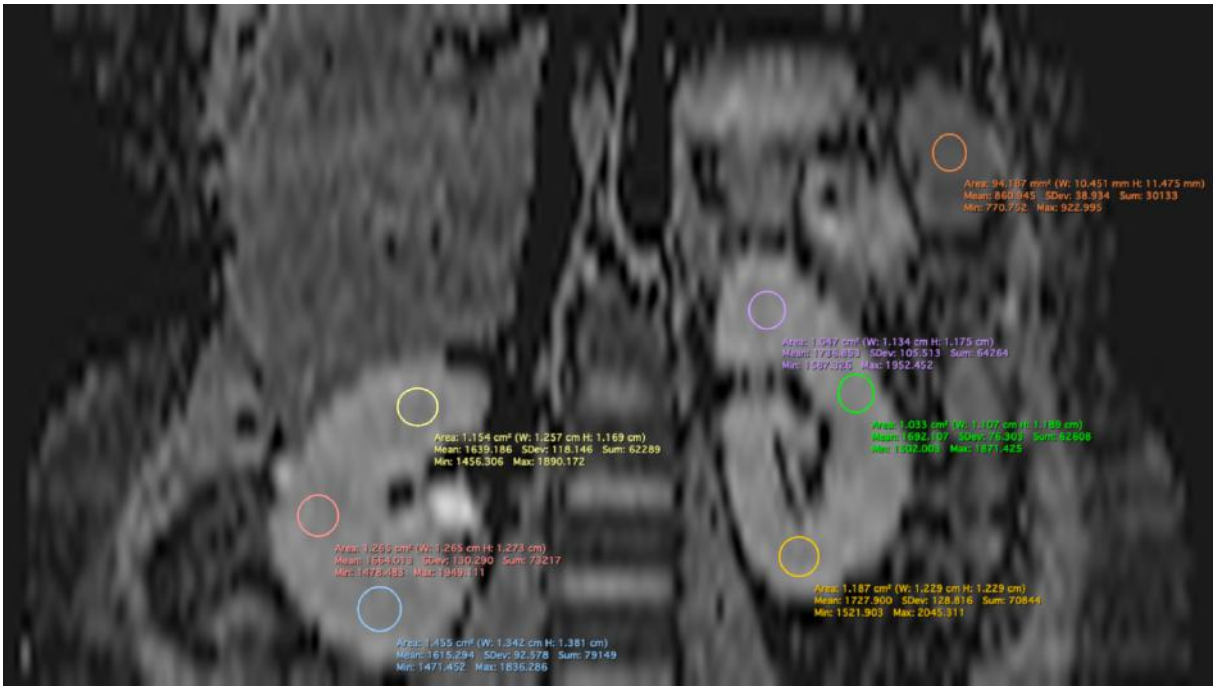

Fig. 1. ADC measurement sites in both kidney parenchyma are shown.

rotation angle = 90°, matrix = 320 × 224, mean number = 1), axial fat-suppressed FIESTA (TR = 4.2 ms, TE = 2.1 ms, thickness = 5.5 mm, pitch = 1 mm, flip angle = 75°, matrix = 192 × 288, mean number = 1), and axial 3D DualEcho (TR = 6.4 ms, TE = 2.1 and 4.3 ms, thickness = 5.5 mm, spacing = 1 mm, flip angle = 12°, matrix = 320 × 224) sequences were obtained. Subsequently, axial DWI was analyzed using a single-shot echo-planar imaging array (TR = 5,000 ms, TE = 75 ms, field of view = 41 × 41 cm; matrix = 160 × 160, NEX = 2, slice thickness = 5.0 mm, slice space = 1.0 mm, b-values 50, 400 and 800 s/mm2, acquisition time = 100 sec). The DWI sequence was triggered by breathing using the navigator-trigger prospective acquisition correction technique (PACE), and the position of the diaphragm was periodically evaluated using navigator echoes. ADC maps were created on a different workstation (Advantage workstation 4.4-GE Medical Systems) using a software (FuncTool). The images of patients were obtained using picture archiving and communication system, and evaluation was made at the workstation after the images were transferred. In the axial ADC map, a region of interest (ROI) ranging from 60 to 100 mm^2 was placed in the renal parenchyma of both kidneys for the measurement of ADC values without any preference for cortex or medulla. Overall, six ROIs were placed in the renal parenchyma of each patient, including one each in the upper pole, interpolar space, and lower pole of each kidney (Fig. 1). The mean values and standard deviations for each kidney and each patient were analyzed separately. In addition, three ROIs were placed in the parenchymal region in the upper and lower poles of the spleen and at the hilum level on the ADC map in each patient, and the mean values were calculated. In each patient, nADC was calculated by dividing the mean ADC values obtained from the renal parenchyma by the mean ADC value obtained from the spleen parenchyma.

Statistical Analysis

SPSS version 23.0 was used for the analysis of the collected data. After analyzing the normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests, descriptive statistical values, such as frequency and percentage, were used for categorical variables, and mean and standard deviation (SD), were used for the continuous variables. The Pearson's chi-square or Fisher's exact test was used for comparison between the categorical groups. For nonparametrically distributed data, the Kruskal-Wallis test was used to compare more than two groups; subsequently, the Mann-Whit-

ney U test was used to identify differences between the groups. Correlations between continuous variables were analyzed using the Pearson's correlation analyses. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the curve for determining the cut-off value to be used to distinguish between Stage 1-2 and Stage 3-5 CKD groups. In addition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained according to the cut-off value calculated in both groups. The variability in ADC values measured from three different areas in both kidneys was evaluated using the intraclass correlation coefficient (ICC). The interpretation of the degree of fit for different ICC values is as follows: ICC ≤ 0.20, poor; 0.2 < ICC ≤ 0.4, poor-to-moderate; 0.4 < ICC ≤ 0.6, moderate; 0.6 < ICC ≤ 0.8, substantial; and ICC ≥ 0.8, almost perfect [11]. Multiple linear regression analysis was performed to examine the effect of serum creatinine level, GFR, BUN, and patient age on ADC value. During comparison between more than two groups, $p < 0.005$ was considered significant after Bonferroni correction, and $p < 0.05$ was considered significant in all other statistical tools.

RESULTS

This study included 157 patients with CKD of different stages and 100 patients without CKD or any other known chronic disease affecting the renal parenchyma. Of these, there were 84 (53.5%) females and 73 (46.5%) males in the CKD group, whereas there were 69 (69%) females and 31 (31%) males in the healthy group. The mean age of the participants was 53.6 ± 9.0 (range, 18-79) years in the CKD group, whereas it was 48.4 ± 11.0 (range, 18-78) years in the healthy group. The mean creatinine value was 1.78 ± 1.6 mg/dL (range, 0.5-9.4) in the CKD group and 0.79 ± 0.4 mg/dL (range 0.5–1.0) in the healthy group. The mean ADC value for the right and left kidney in patients with impaired renal function was found to be 1.831 ± 0.133 and 1.835 ± 0.127 (×10−3mm^2/s), respectively, and it was 1.833 ± 0.129 (×10−3mm^2/s) when both kidneys were considered. The mean ADC value was 2.115 ± 0.115 (× 10 − 3mm^2/s) in the healthy control group, and it was significantly higher than that in the Stage 1 and 2 CKD groups ($p < 0.001$). Patients with renal dysfunction were classified according to the K/DOQI CKD classification, and demo-

Table 1. Demographic, biochemical and imaging findings of groups formed according to eGFR levels.

	Group 1 (n = 38)	Group 2 (n = 45)	Group 3 (n = 37)	Group 4 (n = 20)	Group 5 (n = 17)
Age (years), mean (min, max)	38.5 (18.0-69.0)	59.7 (19.0-76.0)	57.9 (18.0-79.0)	55.4 (35.0-68.0)	60.1 (46.0-74.0)
Gender (female), n (%)	23 (60.5)	23 (51.1)	20 (54.1)	9 (45.0)	9 (52.9)
Mean ADC values					
Right Kidney (×10^{-3} mm^2/s)	1.957 ± 0.114	1.868 ± 0.101	1.799 ± 0.092	1.706 ± 0.049	1.669 ± 0.054
Left Kidney (×10^{-3}mm^2/s)	1.955 ± 0.110	1.871 ± 0.102	1.810 ± 0.065	1.713 ± 0.044	1.672 ± 0.058
Mean (×10^{-3} mm^2/s)	1.956 ± 0.110	1.869 ± 0.100	1.804 ± 0.075	1.709 ± 0.046	1.670 ± 0.056
Spleen (×10^{-3} mm^2/s)	0.836 ± 0.059	0.863 ± 0.077	0.858 ± 0.069	0.865 ± 0.032	0.856 ± 0.049
Normalised ADC	2.348 ± 0.194	2.179 ± 0.188	2.115 ± 0.190	1.978 ± 0.088	1.956 ± 0.105
BUN (mg/dL)	22.3 ± 7.541	34.9 ± 10.159	45.9 ± 12.964	85.3 ± 28.882	138.3 ± 52.107
Creatinin (mg/dL)	0.83 ± 0.146	1.01 ± 0.163	1.43 ± 0.323	2.69 ± 0.718	5.60 ± 1.705
eGFR (mL/min/1.73 m^2)	102.9± 9.446	75.0 ± 8.079	50.2 ± 7.158	25.550 ± 4.322	10.41 ± 3.202

eGFR = Estimated glomerular filtration rate, ADC = Apparent diffusion coefficient, BUN = Blood urea nitrogen, Group 1 = eGFR; ≥ 90 mL/min/1.73m^2, Group 2 = eGFR; 60-89 mL/min/1.73 m^2, Group 3 = eGFR; 30-59 mL/min/1.73 m^2, Group 4 = eGFR;15-29 mL/min/1.73 m^2, Group 5 = eGFR; < 15 mL/min/1.73 m^2.

Table 2. Agreement o ADC values measured from three separate areas in the right and left kidney.

Variable	ADC value ICC (95% CI)		ICC	*p value*
	Lower limit	Upper limit		
Right Kidney	0.973	0.982	0.978	**< 0.001**
Left Kidney	0.980	0.987	0.984	**< 0.001**

ADC = Apparent diffusion coefficient, ICC = intraclass correlation coefficient, CI= confidence interval

graphic, laboratory, and ADC measurement data for each group were evaluated in terms of mean value and SD (Table 1). In these patients, the compatibility of three ADC measurements from each kidney was evaluated using ICC, and the result was found to be almost perfect ($p < 0.001$) (Table 2). Serum creatinine level, GFR, BUN, and age were identified as independent determinants of ADC values measured in patients with renal dysfunction, and these were analyzed using stepwise multiple linear regression method. The established regression model revealed statistical significance ($F = 66.219$, $p < 0.001$). Of the independent determinants, a significant linear regression relationship was observed only between the eGFR level and ADC value ($p < 0.001$) (Table 3). In the same group, the correlation between the ADC values and eGFR, creatinine, and BUN levels was evaluated. ADC was found to be positively correlated with eGFR ($r = 0.790$, $p < 0.001$) and negatively correlated with creatinine and BUN levels ($r = -0.709$, $p < 0.001$; $r = -0.704$, $p < 0.001$, respectively). Moreover, a statistically significant difference was found in comparison using Kruskal–Wallis test in terms of mean ADC values and nADC coefficient of groups representing different stages of CKD (x2: 88.963, $p < 0.001$; x2: −65.085, $p < 0.001$, respectively) (Table 4). In the pairwise comparison of five different groups of patients with CKD using the Mann–Whitney U test, there was no significant difference between the groups representing Stage 4 and 5 kidney diseases ($p = 0.067$); however, the difference between the other groups was statistically significant ($p < 0.001$) (Table 5). A statistically significant difference was found in pairwise comparisons between the Stage 1-2 CKD and healthy groups, which were divided into two groups in terms of eGFR levels ($p < 0.001$) (Table 5). Regarding the ROC analysis performed to determine a cut-off value to distinguish moderate and severe stages from early stages and the control group from the CKD group, while detecting Stage 1 or 2 CKD in patients with an ADC value of ≥ 1791, sensitivity, specificity, PPV, and NPV were found to be 76.3%, 85%, 89.2%, and

Table 3. Multiple linear regression analysis of ADC values with , eGFR, serum creatinine levels, BUN and age.

Variable	Unstandardized		Bootstrapping BCa 95% CI		Standardized		R^2	$F_{(4-152)}$	*p value*
	B	SE_B	Lower limit	Upper limit	*β*	*t*			
(Constant)	1.672	0.049	1.574	1.770		33.856			**< 0.001**
Age	-0.001	0.000	-0.002	0.001	-0.069	-1.255			0.211
eGFR	0.003	0.000	0.002	0.004	0.759	8.414	0.582	66.219	**< 0.001**
BUN	0.001	0.000	-0.001	0.001	0.062	0.727			0.468
Creatinin	-0.006	0.007	-0.020	0.008	-0.072	-0.811			0.418

ADC = Apparent diffusion coefficient, eGFR = Estimated glomerular filtration rate, BUN = Blood urea nitrogen.

Table 4. Comparison of the mean ADC and nADC values of groups representing the five stages of CKD established according to the K/DOQI CKD classification

Variable	ADC ($\times 10^{-3}$ mm^2/s) mean ± SD	Mean rank	X^2 *p value*	nADC mean ± SD	Mean rank	X^2 *p value*
Group 1 (n = 38)	1.956 ± 0.110	120.87		2.348 ± 0.194	118.74	
Group 2 (n = 45)	1.869 ± 0.100	94.40		2.179 ± 0.188	86.14	
Group 3 (n = 37)	1.804 ± 0.075	69.92	88.963 **< 0.001**	2.115 ± 0.190	73.28	65.085 **< 0.001**
Group 4 (n = 20)	1.709 ± 0.046	31.15		1.978 ± 0.088	36.75	
Group 5 (n = 17)	1.670 ± 0.056	20.71		1.956 ± 0.105	33.41	

ADC = Apparent diffusion coefficient, nADC = Normalised apparent diffusion coefficient, CKD = Chronic kidney disease, K/DOQI = kidney disease outcomes quality initiative, SD = standard deviation, Group 1 = eGFR; ≥ 90 mL/min/1.73 m^2, Group 2 = eGFR; 60-89 mL/min/1,73 m^2, Group 3 = eGFR; 30-59 mL/min/1.73 m^2, Group 4 = eGFR; 15-29 mL/min/1.73 m^2, Group 5 = eGFR;< 15 mL/min/1.73 m^2

*Kruskal Wallis H

Table 5. ADC values of CKD patients at different stages and healthy group

Groups	n	Mean ADC	Mean Rank	Sum of Ranks	*U*	*r*	*p value*
Group1 vs 2	38	1.956	52.76	2005.00	446.000	-0.42	**< 0.001**
	45	1.869	32.91	1481.00			
Group 2 vs 3	45	1.869	49.02	2206.00	494.000	-0.35	**0.002**
	37	1.804	32.35	1197.00			
Group 2 vs 4	45	1.869	42.00	1890.00	45.000	-0.71	**< 0.001**
	20	1.709	12.75	255.00			
Group 3 vs 4	37	1.804	36.05	1334.00	109.000	-0.58	**< 0.001**
	20	1.709	15.95	319.00			
Group 4 vs 5	20	1.709	22.00	440.00	110.000	-0.30	0.067
	17	1.670	15.47	263.00			
Group 1 vs N1	38	1.956	25.14	956.00	215.000	-0.68	**< 0.001**
	59	2.144	64.36	3797.00			
Group 2 vs N2	45	1.869	26.67	1200.00	165.000	-0.71	**< 0.001**
	41	2.073	61.98	2541.00			

ADC = Apparent diffusion coefficient, CKD = Chronic kidney disease, Group 1= eGFR; ≥ 90 mL/min/1.73 m^2, Group 2 = eGFR; 60-89 mL/min/1,73 m^2, Group 3 = eGFR; 30-59 mL/min/1.73 m^2, Group 4 = eGFR; 15-29 mL/min/1.73 m^2, Group 5 = eGFR; < 15 mL/min/1.73 m^2, N1 = Control group (eGFR > 90 ml/min/1.73m^2), N2 = Control group (90 < eGFR < 60 mL/min/1.73m^2).

It was considered statistically significant for $p < 0.005$ with Bonferroni correction.

Table 6. Comparison of area under curve (AUC) to predict the CKD stage and patients with normal renal function

	AUC (95%CI)	Cut-off levels	Sensitivity	Specificity	PPV	NPV	*p* value
CKD Stage 1-2							
ADC ($\times 10^{-3} mm^2/s$)	0.872 (0.817-0.927)	1.791	0.763	0.850	0.892	0.689	**< 0.001**
nADC	0.798 (0.728-0.869)	2.155	0.803	0.728	0.735	0.797	**< 0.001**
Normal renal function							
ADC ($\times 0^{-3} mm^2/s$)	0.940 (0.913-0.968)	1.944	0.740	0.954	0.940	0.790	**< 0.001**
nADC	0.883 (0.840-0.926)	2.296	0.697	0.877	0.830	0.771	**< 0.001**

CKD = Chronic kidney disease, PPV = Positive predictive value, NPV= Negative predictive value, ADC =Apparent diffusion coefficient, nADC= Normalised apparent diffusion coefficient.

68.9%, respectively. Moreover, the area under the ROC curve was found to be 87.2% (Table 6).

DISCUSSION

The results of the present study indicated that the ADC values measured from the renal parenchyma and the normalized ADC coefficient obtained using the spleen as a reference organ can effectively represent the stages of CKD. DWI is based on the principle of detecting the random motion (Brownian motion) occurring as a result of the induction of basic water molecules, and the degree of diffusion in an organ is quantitatively expressed using ADC [12]. There are many factors that affect the diffusion-weighted images of the kidneys. These include the water content of the kidneys, renal perfusion, blood flow and blood flow volume of the kidney, the amount of intrarenal tubular flow, and the water content of the tubules [12-14]. Therefore, each factor that causes a change in DWI affects the quantitative indicator ADC. In the early stages of CKD, especially in Stage 1, minor changes are commonly seen in terms of the structure and function of the kidney. At this stage, detection of the disease is crucial because early treatment can prevent or decrease the rate of possible functional and structural loss [2, 15, 16]. In our study, we found that the mean renal ADC and nADC values of patients with Stage 1 CKD differed significantly from those with Stage 2 CKD and healthy controls with an eGFR of ≥ 90. Similarly, there was a significant difference between Stages 2-3 and 3-4 in terms of mean ADC and nADC values. However, there was no significant difference between Stages 4 and 5 in terms of mean ADC and nADC values. This may be due to the following reaons: small number of patients with CKD Stages 4 and 5, functional and structural changes in the renal parenchyma, and case-by-case perfusion differences. Emre *et al*. compared creatinine clearance and renal ADC values in a retrospective study that involved 62 patients with CKD, and they found a significant difference between ADC values of Stage 1 and 2 CKD groups; notably, this finding was similar to that of our study [17]. Moreover, Emre *et al*. revealed significant differences between all stage groups in terms of mean ADC values. In a recent study by Arora *et al*. [18] that compared 60 patients with CKD to 60 healthy individuals without a history of CKD and high creatinine levels, the mean ADC values significantly differed in the CKD group at different stages. In addition, they found that the mean ADC values in the CKD group were significantly lower than those in the healthy control group. Şafak *et al*. [19] examined 110 patients, including 95 patients with CKD and 15 healthy volunteers, in terms of ADC values and serum creatinine and eGFR levels. They found that the mean ADC values of Stage 1-2 groups were significantly higher than

those of Stage 3-5 groups, and these values were significantly lower in the CKD group than in the healthy group. Carbone *et al*. [20] examined the relationship between renal ADC values and CKD stages in 14 patients (including 9 with CKD and 5 healthy controls). Although no significant difference was found between the Stage 1-2 and 2-3 groups in terms of mean ADC values, they found that mean ADC values of Stage 3-4 groups were significantly different from healthy and Stage 1-2 groups. This result that indicates significant difference between the early-stage and healthy groups but no difference within the early-stage groups in terms of mean ADC values could be attributed to the relatively small sample size and the relative uncertainty of Cockcroft–Gault formula at GFR > 60/mL/min/1.73 m^2. Decreased water diffusion and possibly reduced perfusion owing to renal function loss and structural deterioration in early-stage renal parenchymal disease may explain the lower ADC values in these patients. In addition, in cases of glomerulosclerosis and tubular atrophy, wherein the movement of water molecules in the intracellular and extracellular components is restricted, a decrease in diffusion and ADC values can be expected.

Serum creatinine level and the degree of correlation between creatinine clearance and renal ADC values are among the most frequently investigated topics in the relevant literature. In our study, we found a significantly strong correlation between eGFR, serum creatinine level, and BUN and ADC levels, as indicators of creatinine clearance ($p < 0.001$). In a study by Namimoto *et al*. that examined 34 patients, a significant correlation was found between serum creatinine levels and ADC values measured in the renal cortex [21]. Similarly, in a study by Xu *et al*. [22], the kidneys of patients with mild, moderate, and severe renal impairment as well as those of healthy volunteers were evaluated. Based on the b-values ranging from 0 to 500 s/mm^2 in these four groups, they found a positive correlation between measured ADC values and GFR and a negative correlation between ADC values and serum creatinine level. They also found a positive correlation between CKD stages and renal ADC. Goyal *et al*. [23] examined 22 patients with renal dysfunction and 66 patients with preserved kidney function, and they reported that the mean ADC values obtained using b = − 0 – 500 s/mm^2 values differed significantly in different stages of CKD, and the ADC levels tended to decrease with increasing stage of CKD. In the same study, they found a negative correlation between the ADC value and serum creatinine level and a positive correlation between the ADC value and GFR level. In a meta-analysis published by Haitian *et al*. [24] in 2018, DWI was reported as a useful method for demonstrating renal function; moreover, the meta-analysis reported that there was a significant correlation between GFR level and ADC and that DWI can distinguish patients with early-stage CKD from those with normal renal function. The main reason for the decrease in ADC levels in renal parenchymal damage can be explained by decreased diffusion of water and decreased perfusion. This could explain why the measured mean ADC values were significantly lower in patients with impaired renal function than in those with normal renal function.

Accurate prediction of renal damage and thereby CKD stages is critical for early prediction of outcome and provision of individualized treatments [2]. Studies have particularly focused on the distinction of early stages from moderate and severe stages of CKD. In our study, we performed ROC analysis to differentiate between early-stage CKD and moderate-to-severe-stage CKD. We found that CKD stages 3 and higher could be predicted with 76.3% sensitivity and 85% specificity for measurements below the cut-off value of 1.791 (× 10 − 3mm^2/s) for ADC. While predicting CKD stages 3 and higher, the sensitivity was 80.3% and the specificity was 72.8% with the measurements below the cut-off value of 2.155 (× 10 − 3mm^2/s) for nADC. We found that individuals with normal renal function can be differentiated from patients with dysfunction with 69.7% sensitivity and 87.7% specificity for measurements above the cut-off value of 1.944 (× 10 − 3mm^2/s). Notably, Arora *et al*. [18] found the cut-off value of 2.000 (× 10 − 3mm^2/s) as an indicator of renal dysfunction. They reported that with the currently used cut-off value, the sensitivity is 56% and the specificity is 91%. However, in their study, the cut-off value was not calculated to distinguish the early stages from the moderate and advanced stages. Some studies have reported similar threshold ADC values for patients with normal renal function [25-27]. In studies evaluating normal and impaired renal functions, the mean ADC values measured for both normal kidneys and different stages of CKD differed [6, 8, 19, 20, 23, 28]. This difference may be due to different pa-

rameters in the MR devices used for imaging, the device being of 1.5 or 3 Tesla, the selection of different b-values, and the heterogeneity of the patient population included in the study. In particular, the selected b-value has a direct effect on the used measurements. ADC values measured at low b-values are prone to perfusion, and this leads to an increase in ADC values. With higher b-values, the effect of perfusion is strongly suppressed, and the measured ADC values reflect tissue diffusion more accurately [29]. However, as b-value increases, image quality may decrease due to TE elongation, T2-weight dominance, and weaker signal strength. In a study involving 100 patients, Kim *et al*. [30] calculated the mean ADC values from the liver, spleen, pancreas, and kidney parenchyma using six different combinations of b = 0.50,400,800 s/mm^2 and nADC values using the spleen as a reference organ. In their study, they reported higher ADC values at lower b-values (b2 = 0.800 and b4 = 0,50,800 s/mm^2) and significantly lower ADC values at higher b-values (b5 = 50,800 and b6 = 50,400,800 s/mm^2). They calculated the mean nADC value of the kidney parenchyma as 2.310 when a set of b = 50,400,800 s/mm^2 was used. In our study, we found the nADC value to be 2.155 in CKD group and 2.512 in the control group, with a set having the same b-values (b = 50,400,800 s/mm^2).

Limitations

Our study had some limitations. First, ADC measurements from the kidney and spleen parenchyma were performed by manual ROI insertion, and this method can lead to some inaccurate measurements. Second, the study did not consider some parameters, such as edema or dehydration, water restriction, or diuretic use, before imaging. Hence, the ADC values measured in patients with water restriction and diuretic use may differ. Finally, the sample size of the study is relatively small; therefore, the results may contain a certain margin of error.

CONCLUSION

In conclusion, DWI is a useful method to evaluate renal function, differentiate patients with early-stage CKD from those with normal renal function, and perform staging, treatment, and follow-up of patients with CKD. The use of the ADC and nADC cut-off values may be beneficial in distinguishing healthy individuals from patients with CKD and early-stage CKD from moderate-to-advanced CKD.

Authors' Contribution

Study Conception: ŞK; Study Design: ŞK; Supervision: ŞK; Funding: ŞK; Materials: ŞK; Data Collection and/or Processing: ŞK; Statistical Analysis and/or Data Interpretation: ŞK; Literature Review: ŞK; Manuscript Preparation: ŞK and Critical Review: ŞK.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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