Value of Apparent Diffusion Coefficient (ADC) in the Assessment of Renal Insufficiency in Diabetic Patients

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ABSTRACT:

BACKGROUND:

diabetic nephropathy is being recognized as a worldwide public problem with high cost and poor outcomes, there is increase in the incidence and prevalence of renal failure all over the world. Functional renal imaging methods such as diffusion- weighted magnetic resonance imaging (DW-MRI), has been shown to be a promising technique in the evaluation of renal function

OBJECTIVE:

To study the value of apparent diffusion coefficient (ADC) in the detection and evaluation of diabetic nephropathy, correlating these values with the clinical stage of diabetic nephropathy and to compare these findings with diabetic patient without nephropathy.

PAT IENTS AND METHODS:

A cross sectional analytic study was conducted in MRI unit of Radiology department at Al-Imamein Al-Kadhimyain medical city through period form 1st oct.2017 to 30 of July 2018, 80 diabetic patients were classified according to GFR into two groups; group I 40 patients (diabetic patient with no nephropathy) group II 40 patients (diabetic patients with nephropathy). DWI (b value ,0 and 1000 s/mm2) was performed in two group of the study . The mean ADC value of renal cortex was calculated from three regions positioned in the upper, mid and lower third of the kidney. The Relationship between ADC value and stage of diabetic nephropathy were assessed.

RESULTS:

In comparing diabetic patients (with no nephropathy) with patient with diabetic nephropathy, there was significant decline in mean ADC value among patients with advanced stages of diabetic nephropathy($p< 0.001$). The mean ADC value with diabetic nephropathy was significantly lower among patients with type I DM ($P<0.001$).

CONCLUSION:

The magnetic resonance imaging-apparent diffusion coefficient value is an appropriate method for assessment and evaluation of diabetic nephropathy and is a reliable diagnostic tool for differentiation between diabetic nephropathy patients from diabetic patients with no nephropathy

KEYWORDS: apparent diffusion coefficient, diabetic nephropathy

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 150 per million populations, which is lower than that in the developed world. 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. Diabetic nephropathy is classically defined as a clinical syndrome characterized by persistent albuminuria, a relentless decline in glomerular filtration rate (GFR) progressing to end-stage renal disease, raised arterial blood pressure, and enhanced cardiovascular morbidity and mortality [(1)]. In diabetic patients, renal functional deterioration is the result of heterogeneous renal structural changes [(2)].

Serum creatinine (S.Cr), blood urea (BU), and estimated glomerular filtration rate (eGFR) derived from creatinine clearance are useful for

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monitoring renal function; however, these indirect measures of renal filtration are imperfect and cannot assess single kidney function [3]. 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 USG 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. Magnetic resonance imaging (MRI) has the unique ability to show both structure and function objectively without any radiation exposure to the patient. Functional MRI techniques such as diffusion-weighted imaging (DWI), blood oxygen level-dependent (BOLD) imaging, and contrast-enhanced MRI renography have potential utility in the evaluation of renal function [4]. Diffusion weighted (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. 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 [5, 6] renal parenchymal disease [7, 8] and renal infections [9].

AIM OF STUDY:

To study the value of ADC in the evaluation and detection of diabetic nephropathy, correlate these values with the clinical stage of diabetic nephropathy and compare these findings with diabetic patient without nephropathy.

PATIENTS AND METHODS

This cross sectional analytic study was conducted in the MRI unit of Radiology Department in Al-Imamain Al-Kadhmain Medical city/Baghdad/Iraq, through the period from 1st of October 2017 to 30th of July 2018.

Inclusion criteria: were adults (age >18 years), diabetes mellitus (DM) irrespective of the type for at least 2 years DM duration. Exclusion criteria: patients with congenital hypoplastic kidney, hydronephrosis, simple cysts larger than 3 cm in diameter or presence of more than three cysts, history of obstructive uropathy, pyelonephritis and any renal operation. None of the subjects had renal emphysema, which is a rare condition mostly seen in diabetic patients. Research approval was taken from Institutional Review Board/Al-Nahrain College of Medicine. An oral informed consent was taken from each patient.

A convenient sample of 80 diabetic patients was selected according to inclusion and exclusion criteria. The diabetic patients were classified according to glomerular filtration rate (GFR) into two groups; group I 40 diabetic patients with no nephropathy and group II 40 diabetic patients with nephropathy. The questionnaire included the followings: renal function test of diabetic patients (estimated Glomerular filtration rate (eGFR) is calculated by the abbreviated MDRD equation: 186 x (Creatinine/ 88.4) - 1.154 x (Age) - 0.203 x (0.742 if female) x (1.210 if black), Demographic characteristics of diabetic patients (age and gender), DM characteristics (type, duration and treatment type). Diabetic nephropathy was clinically categorized into five stages depending on the estimated GFR: Stage 1 with normal or high GFR (GFR > 90 mL/min), Stage 2 Mild CKD (GFR = 60-89 mL/min), Stage 3A Moderate CKD (GFR = 45-59 mL/min), Stage 3B Moderate CKD (GFR = 30-44 mL/min), Stage 4 Severe CKD (GFR = 15-29 mL/min) and 72) and Stage 5 End Stage CKD (GFR <15 mL/min.

The MRI examination was performed using a 1.5 Tesla system with an 8 Channel body array coil (Achieva, Philips medical system, Netherlands).

The maximum gradient amplitude and slew rate were 33 mT/m and 120 mT/m/s, respectively. Axial single-shot echo-planar DWI was performed during normal respiration using the following parameters: b value 0 and 1000 s/mm2; TR/TE 6000/81.8; bandwidth 250 kHz; number of excitations 6; slice thickness 6 mm; field of view 40 cm; matrix 128×128. Total scan time was 2 min and 24 s for the DWI image set. All images were reviewed on a workstation. The ADC maps were constructed using image analysis software. All MRI scans was evaluated independently by two experienced radiologists who were blinded to the clinical and laboratory findings. Each kidney was divided into three regions as upper, mid, and lower thirds. The mean ADCs were calculated with placement of at least three region-of-interest (ROI) ovoid circles (area 80-100 mm2) on the renal cortical areas in the ADC map images, each measurement was repeated 3 times and the average was taken.

Statistical analysis: the data of study participants were analyzed by application of Microsoft excel program and Statistical Package for Social Sciences (SPSS) version 23. Outcomes of analysis were arranged in scales variables (means and standard deviation) and in categorical variables. Chi square test was used for comparison between categorical data (Fishers exact test applied when expected variable was less than 20% of total). One way ANOVA analysis was used to compare between more than two means. The level of significance (p value) was set as ≤ 0.05.

RESULTS:

A total of 80 diabetic patients were included in this study with mean age of 54.9±10.2 years; Male were more than females with male to female ratio as 2.6:1. Most (85%) of diabetic patients were type 2 DM while type 1 represented 15% only. Mean DM duration was 10.7±6.9 years; 76.3% of them had duration of more than 5 years. The treatment types were oral agents (62.5%) and insulin (22.5%), while 15% of diabetic patients were not receiving any treatment.

Mean GFR of diabetic patients was 74.65±5.6 ml/min. Diabetic nephropathy patients were distributed according to GFR into 5 stages; stage I were 13 patients (32.5%), stage II were 9 patients (22.5%), stage III were 8 patients (20%), stage IV were 6 patients (15%) and stage V were 4 patients (10%).

The Mean GFR was significantly lower among patients with diabetic nephropathy ($p<0.001$). The mean MRI-ADC value of left kidney was significantly lower among patients with diabetic nephropathy ($p<0.001$).The mean MRI-ADC value of right kidney was significantly lower among patients with diabetic nephropathy ($p<0.001$).The mean average MRI-ADC value of both kidneys was significantly lower among patients with diabetic nephropathy ($p<0.001$). All these findings were shown in table 1.

Table 1: Distribution of GFR and MRI-ADC means according to study groups.

Variable	Study group		P value
	DM with no nephropathy	DM with nephropathy	
	Mean±SD	Mean±SD	
GFR (ml/min)	89.7±9.6	59.6±10.6	<0.001^S
ADC (left) (x10-3 mm2/s)	2.3±0.1	1.95±0.09	<0.001^S
ADC (right) (x10-3 mm2/s))	2.28±0.11	1.98±0.1	<0.001^S
ADC (average x10-3 mm2/s	2.29±0.1	1.97±0.1	<0.001^S

**One way ANOVA analysis, S=significant.*

When comparing the control group (diabetic patients without nephropathy) with patients with diabetic nephropathy, there was a significant decline in mean ADC value among patients with advanced stages of diabetic nephropathy ($p<0.001$). All these findings were shown in table 2.

Table 2: Distribution of MRI-ADC value according to controls and stages of diabetic nephropathy

Study groups	MRI-ADC (x10-3mm2/s) Mean±SD	P value
Controls	2.34±0.1	**<0.001S**
Stage I	2.28±0.1	
Stage II	2.1±0.12	
Stage III	1.95±0.14	
Stage IV	1.7±0.15	
Stage V	1.5±0.17	

**One way ANOVA analysis, S=significant.*

The mean MRI-ADC of patients with diabetic nephropathy was significantly lower among patients with type I DM (p<0.001). The mean MRI-ADC of patients with diabetic nephropathy was significantly lower among patients with longer DM duration (p<0.001). All these findings were shown in table 3.

Table 3: Distribution of MRI-ADC value according to the type and duration of DM

Variables		MRI-ADC(x10-3mm2/s) Mean±SD	P value
Type of DM	Type I DM	2.1±0.1	<0.001S
	Type II DM	2.22±0.11	
Duration of DM	≤5 years	2.32±0.1	<0.001S
	>5 years	1.93±0.12	

**Independent sample t-test, S=significant.*

The mean MRI-ADC of patients with diabetic nephropathy was significantly lower among patients with no DM treatment (p=0.04). All these findings were shown in table 4.

Table 4: Distribution of MRI-ADC value according to DM treatment.

Treatment groups	**MRI-ADC** (x10-3 mm2) **Mean±SD**	P value
Insulin	2.1±0.11	**0.04S**
Oral agents	2.28±0.1	
No treatment	1.9±0.13	

**One way ANOVA analysis, S=significant.*

DISCUSSION:

Diabetes mellitus is a common disease in Iraq with high prevalence of diabetic nephropathy reaching to 16.1% especially among type 2 DM [(10)]. The magnetic resonance imaging (MRI) techniques like diffusion-weighted imaging (DWI), blood oxygen level-dependent (BOLD) imaging, and contrast-enhanced MRI renography have a powerful ability in assessment of kidney functions [(11)].

Regarding stages of diabetic nephropathy, our study found nephropathy stages as I (32.5%), stage II (22.5%), stage III (20%), stage IV (15%) and stage V (10%). These findings are similar to results of Alwakeel et al [(12)] study in Saudi Arabia. The mean GFR of study participants was significantly lower among patients with diabetic nephropathy (p<0.001). This finding is consistent with results of Rigalleau et al [(13)] study in France which confirmed low GFR mean among patients with diabetic nephropathy that is used also in staging of nephropathy. Low GFR in rate of 1 ml/min/1.73 m2 /year for diabetic nephropathy is observed that is regarded as progressive

nephropathy, but rate of 5 ml/min/1.73 m2 year-1 is regarded as severe progressive nephropathy. Elevated hypertension and high proteinuria level are the main risk factors increased severity of diabetic nephropathy [14].

Present study revealed that diabetic patients had mean MRI-ADC value for right kidney was 2.1±1 x10-3 mm2/s and mean MRI-ADC of left kidney was 2.2±1.3 x10-3 mm2/s, while the mean average MRI-ADC value for both kidneys was2.05±1.2 x10-3 mm2/s. These findings are similar to ADC values reported by Ebrahimi et al [15] study in USA which documented lower MRI-ADC values for diabetic patients due to renal complications of diabetes. MRI-ADC means of study participants were significantly reduced among patients with diabetic nephropathy ($p<0.001$). This finding is in agreement with many previously reported studies like Inoue et al [16] study in Japan and Ries et al [17] study in France which reported significantly lower MRI-ADC values in patients with diabetic nephropathy in comparison to diabetic patients with no nephropathy and healthy population. Impaired kidney function could be acquired through abnormalities of chronic tubulointerstitial functions that lowers the renal water level and limited the fibrosis-mediated diffusion of water molecules. The MRI-ADC values are the reflection of different degrees of chronic tubule interstitial abnormalities attributed to declined renal oxygenation provokes nephropathy changes [18]. Low density of peritubular capillaries in diabetic nephropathy and non-diabetic nephropathy is due also to tubulointerstitial abnormalities that lead to parenchymal hypoxia [19]. Lu et al [20] study in USA suggested that medullary apparent diffusion coefficient and fractional anisotropy, quantified by kidney diffusion tensor imaging, may be potential imaging biomarkers for diabetic nephropathy.

In present study, there was a significant decline in mean MRI-ADC value among patients with advanced stages of diabetic nephropathy ($p<0.001$). This finding coincides with results of Çakmak et al [21] study in Turkey and Kaimori et al [22] study in Japan which found that MRI-ADC values were prominently decreased along with advanced stages of diabetic nephropathy. Toya et al [8] reported that MRI-ADC value was decreased with decrease of GFR but they did not revealed a significant correlation between ADC and GFR. However many authors had shown that MRI-ADC values of kidney were decreased in different forms of acute and chronic renal diseases with a significant relationship between MRI-ADC and GFR values [7, 23, 24]. In another Japanese study, the mean MRI-ADC for kidney cortex and the medulla of patients with chronic or acute kidney failure were effectively decreased than population with normal function kidneys[25]. Yalçin-Şafak et al [26] study revealed a highly significant decline in MRI-ADC values at stage V diabetic nephropathy in comparison to healthy individuals. As the MRI-ADC value is related directly to water molecular and capillary perfusion in tissues, Changes in MRI-ADC value inform Radiologists on microstructural changes in kidneys. Water level changes in kidney tissues in addition to kidney blood and tubular flow lead to changes in ADC values [27].

This study found that mean MRI-ADC of patients with diabetic nephropathy was significantly lower among patients with type I DM ($p<0.001$). This finding is consistent with results of Çakmak et al [21] study in Turkey which documented that tubulointerstitial lesions were more prevalent in type1 diabetes leading to lower MRI-ADC values in comparison to type 2 DM. In USA, current study conducted by Bjornstad et al [28] stated that earlier diabetic nephropathy was developed in type1 DM with more severe deterioration.

Our study found that mean MRI-ADC value of patients with diabetic nephropathy was significantly lower among patients with longer DM duration ($p<0.001$). This is similar to results of Nisar et al [29] study in Pakistan which stated that presence and severity of diabetic nephropathy were significantly related with higher HbA1c level and long duration of DM. Indeed, Lu et al [20] clarified the effect of long DM duration on decreasing MRI-ADC values among patients with diabetic nephropathy. Present study also showed that mean MRI-ADC of patients with diabetic nephropathy was significantly lower among patients with no DM treatment ($p=0.04$).

This finding is consistent with results of Inoue et al [16] study in Japan which documented that MRI-ADC value was affected by hyperglycemia among patients with diabetic nephropathy. Ries et al [17] stated that MRI-ADC is dependent on oxygen delivery to renal tissues and any metabolic changes in tissues will affect the MRI-ADC values.

CONCLUSIONS:

The magnetic resonance imaging-apparent diffusion coefficient value is an appropriate method for assessment and evaluation of diabetic nephropathy. It is a reliable diagnostic tool for differentiation between diabetic nephropathy patients from diabetic patients without nephropathy. The ADC is more likely to be affected by clinical type, duration and the type of treatment of diabetes mellitus.

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