Received: 2019.09.22

Accepted: 2019.12.05

Published: 2020.03.03

Diffusion Weighted Magnetic Resonance Imaging in the Assessment of Renal Function and Parenchymal Changes in Chronic Kidney Disease: A Preliminary Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BDEF 1 Katarzyna Sułkowska
DEF 1 Piotr Palczewski
BE 2 Agnieszka Furmańczyk-Zawiska
BE 2 Agnieszka Perkowska-Ptasińska
CD 1 Damian Wójcik
CD 1 Wojciech Szeszkowski
AD 2 Magdalena Durlik
AE 1 Marek Gołębiowski
AD 3 Piotr Małkowski

1 Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland
2 Department of Transplantation Medicine and Nephrology, Transplantation Institute, Medical University of Warsaw, Warsaw, Poland
3 Department of Surgical and Transplantation Nursing and Extracorporeal Therapies, Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Katarzyna Sułkowska, e-mail: k.sulkowska@outlook.com
Source of support: Departmental sources

Background: The aim of this study was to evaluate the feasibility of using intravoxel incoherent motion (IVIM) imaging for noninvasive assessment of pathologic changes in chronic kidney disease (CKD).

Material/Methods: Thirty-four patients with CKD and 20 healthy volunteers were examined on a 1.5 T magnetic resonance imaging (MRI) unit. The examination consisted of morphologic sequences and diffusion-weighted echo-planar sequence with 10 b values. Diffusion parameters were calculated with the use of mono- (apparent diffusion coefficient, ADC) and bi-exponential model: pure diffusion coefficient (D) and perfusion fraction (Fp). Blood samples to assess the serum creatinine level were taken immediately before examination. Ultrasound guided biopsies were performed in less than 30 days from MRI and were scored by an experienced nephropathologist. Parametrical unpaired *t*-test and ROC curve analysis were used to investigate differences in diffusion parameters in relation to estimated glomerular filtration rate (eGFR). Pearson's correlation coefficients were calculated to assess relationship between diffusion parameters and laboratory and histopathological markers of renal damage. *P*-value <0.05 indicated statistical significance.

Results: Both ADC and D correlated positively with eGFR (respective *r* 0.74 and 0.72), however D showed a more significant correlation with histopathology: while D correlated negatively with parameters reflecting chronic glomerular (*r* -0.48) and tubulo-interstitial changes (*r* -0.47), ADC correlated only with interstitial infiltrations (*r* -0.44). Flow-related diffusion parameters showed high standard deviation.

Conclusions: IVIM imaging is sensitive to functional and morphologic changes in CKD. The separation of influence of Fp from true diffusion improves the assessment of chronic changes in renal parenchyma.

MeSH Keywords: Diffusion Magnetic Resonance Imaging • Fibrosis • Glomerular Filtration Rate • Pathology • Renal Insufficiency, Chronic

Full-text PDF: <https://www.annalsoftransplantation.com/abstract/index/idArt/920232>

2391 4 3 32

Background

An ultrasound-guided percutaneous renal biopsy (PRB) remains the gold standard in the diagnosis of renal parenchymal disease [1]. However, invasiveness of PRB limits its frequent repetition, for instance for the monitoring of progression of chronic kidney disease (CKD) [2]. Therefore, non-invasive tests that may be used as an alternative marker of renal parenchymal damage are sought [3]. Recent years have witnessed a growing interest in the application of diffusion weighted magnetic resonance imaging (DW-MRI) for the assessment of renal pathology. This MRI technique is based on measuring the motion of the water molecules in the tissues and as being devoid of ionizing radiation and intravenous contrast medium administration, is completely non-invasive. The combination of magnetic field gradients and radiofrequency pulses used in diffusion-weighted sequences results in moving water particles producing lower signal than stationary molecules. Both the Brownian motion and organized motion in vascular bed (tissue perfusion) contribute to the signal loss [4]. The changes in tissue micro-architecture, either with respect to the blood vessel density, the addition or removal of structural inhibitors to water movement or the ratio of extracellular extravascular to intracellular space (for instance increased cellularity), influence the signal measured in DW-MRI [4]. Apparent diffusion coefficient (ADC), a product of mono-exponential fitting of diffusion-dependent signal decay curves that reflects total diffusivity of renal tissue has been shown to correlate with renal function and histopathologic markers of renal fibrosis both in animal model and in patients with CKD [5–10]. Alternatively, decay curves may be analyzed using biexponential fitting according to Le Bihan's concept of intravoxel incoherent motion (IVIM). By providing 3 distinct diffusion parameters, this model enables the differentiation between diffusion in extra- and intravascular space: D (pure molecular diffusion parameter) reflects true diffusion in extravascular space, while D^* (perfusion related diffusion parameter) and F_p (perfusion fraction) represent a faster diffusion component, mainly tissue perfusion [11]. It has been suggested that biexponential model may allow more accurate measurements of diffusion parameters in organs with high tissue perfusion, such as kidneys [12]. In theory, it could also provide a better understanding of renal pathology by distinguishing changes in microcirculation and interstitium. Recent publications using an IVIM model showed encouraging results as for the correlation of diffusion parameters with renal function and histopathology [13,14]. However, at the same time doubts were raised whether a more complex biexponential fitting provides a real advantage over simple and robust mono-exponential fitting in assessment of renal functional impairment and a previously established correlation of diffusion parameters with renal fibrosis was questioned by an animal study [15,16]. Since most of the human studies correlated diffusion parameters

with global load of parenchymal changes calculated with different scoring systems and not with individual histopathologic parameters, our understanding of the relation of diffusion parameters to complex pathologic changes in CKD seems far from perfect. Therefore, the purpose of our study was to perform an in-depth analysis of the behavior of diffusion parameters in patients with CKD and to assess their feasibility for evaluation of renal parenchymal damage.

Material and Methods

This prospective study was approved by our institutional review board with a demand of a written informed consent to be submitted by all participants.

Study population

The study population consisted of 34 patients with CKD (17 female patients, average age 44 ± 13 years). On the day of MRI, blood and urine samples were collected from all participants. For each individual estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) formula. The patients were assigned Kidney Disease Improving Global Outcomes (KDIGO) stage based on their eGFR at the time of MRI and divided in 3 groups: mild (stage G1 and G2, 10 patients), moderate (stage G3a and G3b, 10 patients), and severe CKD (stage G4 and G5, 14 patients) [17]. The exclusion criteria for this study were: a recent parenchymal post-biopsy hematoma, renal artery stenosis, hydronephrosis, active urinary tract infection, undergoing dialysis, and solid renal lesion. The reference values of diffusion parameters in healthy kidneys were obtained previously by examining healthy volunteers with exactly the same imaging protocol [18]. In the cited study, we applied only a mono-exponential fitting, therefore we reused the acquired data to establish the referential values of IVIM diffusion parameters.

Magnetic resonance imaging

Prior to examination no special preparations of participants were taken. MRI was performed with a 1.5 T imager (Ingenia, Philips, the Netherlands) with a posterior and anterior body coil (dS Torso coil). Morphologic evaluation of the kidneys consisted of coronal T2 sequence (TR-1.8 s; TE-80 ms; FA-90°, slice number-22, slice thickness-5 mm), coronal T1 sequence (TR-10ms; TE-10ms; FA-15°; slice number-22; slice thickness-5 mm), and transverse in-phase, out-of-phase, and fat and water-saturated m-Dixon sequence (6 ms TR, 2.3 ms TE, 15° FA, number of sections – 95, section thickness – 4 mm). DWI was acquired using multislice EPI sequence with diffusion gradient in 3 orthogonal axes, in coronal plane, with field of view 400×40, matrix of 116×116, time to echo 71 ms, and minimal TR of 2000 ms.

Figure 1. Example of signal intensity measurements for the left kidney for each b value.

A SENSE parallel imaging technique was used (acceleration factor=4, applied in the antero-posterior direction). Diffusion gradient b values were grouped in 2 sets – low (0, 10, 20, 40, 60, 150) and high (300, 500, 700, 900) b values as proposed by Thoeny et al. and the NEX for each b value was 1 [19]. The entire sequence consisted of 22 slices. The patients were free-breathing, and a respiratory sensor placed on the upper abdomen was used to trigger the acquisition of images in the end-expiration. The acquisition time was 7 ± 3 minutes.

IVIM calculations

All diffusion parameters were calculated only for the whole kidney as most of the patients had no cortico-medullary differentiation on morphological sequences ($n=23$, 67%). For both mono- and bi-exponential model signal intensities for each b value were measured in both kidneys by manually delineated ROIs encircling the whole mid-coronal kidney section on diffusion-weighted images (Figure 1). Renal cysts and areas of parenchymal scarring were excluded from ROIs. The values of signal intensities from ROIs were averaged and incorporated into the locally developed script written in Matlab (R2014b, Mathworks, Natick, USA) and fitted in 2 ways [20]:

- 1) ADC was calculated using a standard mono-exponential model expressed by equation:

$$S_b/S_0 = \exp(-b \times \text{ADC}) \quad [11]$$

where S_b is a signal intensity acquired with a given b-value and S_0 is the signal intensity at b-value=0 s/mm²,

- 2) IVIM parameters were calculated using biexponential model defined by:

$$S_b/S_0 = F_p \times \exp(-b \times D^*) + (1 - F_p) \times \exp(-b \times D) \quad [11]$$

where S_b is the signal intensity acquired with the given b-value, S_0 is the signal intensity at b-value=0 s/mm², D is the diffusion constant of “pure” diffusion, D^* is the diffusion constant of pseudo-diffusion (capillary microperfusion contribution), and F_p is the perfusion fraction. A direct fit approach based on the Levenberg-Marquardt minimization algorithm was used [21,22]. Initial values of D and D^* were set a priori to 0.001 and 0.01 mm/s², respectively.

Histopathological assessment

The cause of kidney insufficiency was established based on PRB in all patients. The pathologic diagnoses are presented in Table 1. In 31 patients, ultrasound-guided PRB was performed in less than 30 days from MRI (18 ± 4 days) and the results of those biopsies were used for histopathologic correlation. In 15

Table 1. Pathology diagnoses and values of markers of renal function and diffusion parameters in the study population.

Patient's number	Demographic/clinical data				Biopsy results	Histopathology				MRI		
	Age	Sex	eGFR [ml/min/ 1.73 m ²]	KDIGO class		Glome- rular index	Tubulo- interstitial index	Global index	Intersti- tial infiltra- tions	ADC [*]	D [*]	Fp [%]
1	61	F	94	1	Membranous nephropathy	1	1	3	0	1.8	1.8	41
2	34	M	88	2	Unspecified glomerular lesions	1	2	4	1	2.12	1.68	34
3	60	F	87	2	Membranous nephropathy	1	0	1	0	1.8	1.7	12.5
4	31	F	79	2	IgA nephropathy	2	3	5	1	2.1	2.1	15
5	30	F	79	2	IgA nephropathy	1	2	3	1	2.05	1.8	24
6	54	M	77	2	Membranous nephropathy	1	2	5	1	1.9	1.88	13.5
7	69	M	74	2	FSGS	2	11	13	4	1.77	1.5	25
8	28	M	72	2	IgA nephropathy	1	3	7	1	2.29	2.1	17.2
9	33	M	68	2	Pauci-immune focal and segmental N GN	1	4	5	1	1.97	1.8	22
10	28	M	64	2	IgA nephropathy	3	5	8	2	2.06	1.85	20.5
11	59	F	46	3a	Membranoproliferative glomerulonephritis	1	3	4	1	1.78	1.7	10
12	44	M	45	3a	Minimal change nephropathy	1	0	1	0	1.53	1.45	10.5
13	44	F	44	3b	IgA nephropathy	3	9	15	3	1.76	1.75	11
14	51	M	41	3b	FSGS	2	3	6	1	2.15	2	18.5
15	61	M	38	3b	Membranoproliferative glomerulonephritis	5	5	10	2	1.94	1.7	26.5
16	58	F	35	3b	Filbrillary glomerulonephritis	4	5	11	2	1.58	1.3	24
17	32	F	33	3b	FSGS	5	8	16	3	1.91	1.2	47
18	56	F	31	3b	Membranopro-liferative- glomerulo-nephritis	1	4	5	1	1.7	1.7	8
19	60	F	29	4	IgA nephropathy	2	4	6	1	2	1.6	29
20	35	F	26	4	Unspecified glomerular lesions	1	3	6	1	1.83	1.7	14
21	55	F	25	4	FSGS	3	3	6	1	2	1.7	20
22	60	M	24	4	IgA nephropathy	4	8	14	3	2	1.6	29
23	67	F	24	4	Amyloidosis	3	8	13	3	1.84	1.7	14
24	36	F	23	4	IgA nephropathy	4	5	9	2	2	1.85	27.5
25	45	M	22	4	Thrombotic microangiopathy	1	7	11	3	1.62	1.4	19

Table 1 continued. Pathology diagnoses and values of markers of renal function and diffusion parameters in the study population.

Patient's number	Demographic/clinical data				Biopsy results	Histopathology				MRI		
	Age	Sex	eGFR [ml/min/1.73 m ²]	KDIGO class		Glomerular index	Tubulo- interstitial index	Global index	Inter- stitial infiltrations	ADC [*]	D [*]	Fp [%]
26	32	M	21	4	Thin basement membrane nephropathy	5	8	15	3	1.58	1.25	31
27	39	M	20	4	Membranoproliferative glomerulonephritis	2	7	9	2	1.73	1.4	29
28	31	F	18	4	Crescentic glomerulonephritis	5	7	12	1	1.71	1.4	47
29	26	F	15	4	Thrombotic microangiopathy	4	9	16	3	1.63	1.7	11
30	62	M	15	4	Pauci-immune focal and segmental N GN	2	5	7	1	1.63	1.7	11
31	25	M	13	5	IgA nephropathy	5	9	14	3	1.46	1.25	18

eGFR – estimated glomerular filtration; KDIGO – kidney disease improving global outcomes; Glomerular index – sum of points for completely or partially sclerosed glomeruli and mesangial matrix increase; Tubulo-interstitial index – sum of points for interstitial fibrosis, tubular atrophy and casts; Global index – sum of glomerular index, tubule-interstitial index and vessel lesions; ADC – apparent diffusion coefficient; D – pure diffusion coefficient; Fp – perfusion fraction, Pauci-immune focal and segmental; NGN – pauci-immune focal and segmental necrotizing glomerulonephritis; FSGS – focal segmental glomerulosclerosis. [*] – [$\times 10^{-3} \text{ mm}^2/\text{s}$].

Figure 2. Pathology image in a patient in severe stage of chronic kidney disease secondary to IgA nephropathy. AFOG (Acid Fuchsin Orange G) staining, original magnification 10 $\times$. Glomeruli with focal global sclerosis (arrow), tubular atrophy (circle), interstitial infiltration (x).

Figure 3. Pathology image in a patient in severe stage of chronic kidney disease. AFOG (Acid Fuchsin Orange G) staining, original magnification 10 $\times$. Glomeruli with segmental sclerosis (arrow), tubular atrophy (circle), interstitial infiltration (x).

patients, the MRI-biopsy interval was less than a week and among those patients 13 had a biopsy on a day of MRI (after MRI to avoid a possible influence of post-biopsy hematoma on diffusion measurements).

The processing of renal tissue for light microscopic evaluation was performed in a routine manner. The tissue was embedded in paraffin blocks and cut to 3 to 5 μm thick sections, transferred to slides, deparaffinized and rehydrated, and finally

stained. In all cases, all tissue compartments were evaluated in several stainings: hematoxylin and eosin, trichrome, periodic acid–Schiff, silver methenamine, acid fuchsin orange G, and orcein. All slides were read by a single experienced nephropathologist. The lesions in glomeruli, parenchyma, and vessels were scored separately. Depending on the intensity of sclerosis, glomeruli were divided into either completely (focal global sclerosis) or partially sclerosed (segmental sclerosis) (Figures 2, 3). Glomerulosclerosis (focal and segmental) and

Table 2. Histopathologic evaluation of changes in CKD.**A.** Basic parameters.

Parameters	Score
Glomerular sclerosis <ul style="list-style-type: none"> • Focal global sclerosis • Segmental sclerosis 	1–5 points 1 point for <20% affected glomeruli; 2 points for 21–40%; 3 points for 41–60%; 4 points for 61–80%; 5 points for >80% affected
Mesangial matrix increase	
Interstitial infiltrations Tubular atrophy Fibrosed crescents Arteriolosclerosis Casts Interstitial fibrosis	0–4 points 0 – none, 1 – minimal, 2 – mild, 3 – moderate, 4 – severe

B. Combined indices.

Parameters	Description
Glomerular index <ul style="list-style-type: none"> • Focal global sclerosis • Segmental sclerosis • Mesangial matrix increase 	<ul style="list-style-type: none"> • Combined parameter reflecting chronic changes in glomeruli • Sum of points awarded for the percentage of sclerosed glomeruli and mesangial matrix increase
Tubulo-interstitial index <ul style="list-style-type: none"> • Interstitial fibrosis • Tubular atrophy • Casts 	<ul style="list-style-type: none"> • Combined parameter reflecting chronic changes in tubules and interstitium • Sum of points for interstitial fibrosis, tubular atrophy and casts
Global index <ul style="list-style-type: none"> • Glomerular index • Tubulo-interstitial index • Arterial vessel lesions 	<ul style="list-style-type: none"> • Chronic changes in all compartments: glomeruli, tubules, interstitium and vessels • Sum of glomerular index, tubulo-interstitial index and vascular lesions (arteriosclerosis, hyalinosis)

mesangial matrix increase in the glomeruli were assessed in a 5-point scale (1 point for <20% affected glomeruli; 2 points for 21% to 40% affected glomeruli; 3 points for 41% to 60% affected glomeruli; 4 points for 61% to 80% affected glomeruli; and 5 points for >80% glomeruli). A 4-point semiquantitative scale (0-none, 1-mild, 2-moderate, 3-severe) was used to grade the remaining lesions: interstitial infiltrations, interstitial fibrosis, tubular atrophy, fibrous crescents, arteriosclerosis and casts. Finally, combined indices reflecting chronic changes were calculated by adding the scores for chronic lesions in each of tissue compartments (Table 2).

Statistical analysis

Statistical analysis was performed using Statistica software (version 13.0; Statsoft, Inc., Tulsa, OK, USA) and MedCalc Statistical Software (version 18.11.3.; MedCalc Software bvba, Ostend, Belgium). Mean values and standard deviations of ADC, D, D*, and Fp were calculated. D* was rejected from further analysis

due to excessive variability suggesting low reliability of estimates. The assumptions of normality and homogeneity of variances were verified with normality test and Levene's test. Pearson's correlation coefficients were calculated by bivariate correlation to investigate the relationship between diffusion parameters and SCr, eGFR, and histopathologic parameters. All *P* values <0.05 were taken as statistically significant.

Results

The results of measurements of SCr/eGFR and diffusion parameters in individual patients and sub-groups of our study population are presented in Tables 1 and 3, respectively.

Both ADC and D correlated with markers of renal function: negatively with SCr (respective *r*: –0.68 and –0.60) and positively with eGFR (*r* 0.74 and 0.72) (Table 4). Perfusion fraction did not correlate significantly with neither eGFR nor SCr (*r* –0.004

Table 3. ADC, D, and Fp values, SCr level, and eGFR in the study population.

	SCr [mg/dl]	eGFR [ml/min/1.73 m ²]	ADC [×10 ⁻³ mm/s ²]	D [×10 ⁻³ mm/s ²]	Fp [%]
Volunteers	0.86±0.12	98±14	2.06±0.17	2.03±0.22	20±7
Mild CKD	1±0.15	78±9.35	1.99±0.17	1.82±0.18	22±9
Moderate CKD	1.56±0.22	40±8.8	1.77±0.16	1.59±0.23	20±12
Severe CKD	3.17±1.06	21±4.7	1.75±0.17	1.52±0.2	23±12

ADC – apparent diffusion coefficient; D – pure diffusion coefficient; Fp – perfusion fraction; SCr – serum creatinine; eGFR – estimated glomerular filtration rate; CKD – chronic kidney disease.

Table 4. Correlation between diffusion parameters, markers of renal function, and histopathological parameters.

Parameters	ADC		D		Fp	
	r	p	r	p	r	p
SCr	-0.68	0.000*	-0.60	0.000*	-0.24	0.204
eGFR	0.74	0.000*	0.72	0.000*	-0.004	0.980
Focal global sclerosis	-0.22	0.221	-0.52	0.003*	0.36	0.044*
Segmental sclerosis	-0.04	0.808	-0.12	0.495	0.18	0.314
Mesangial matrix increase	0.06	0.736	0.03	0.867	-0.10	0.576
Interstitial infiltrations	-0.44	0.013*	-0.38	0.038*	0.00	0.998
Interstitial fibrosis	-0.15	0.399	-0.16	0.377	-0.08	0.658
Tubular atrophy	-0.23	0.21	-0.4	0.01*	0.10	0.57
Arteriolosclerosis	-0.20	0.274	-0.25	0.181	-0.11	0.529
Casts	-0.38	0.03*	-0.35	0.05	0.30	0.87
Fibrosed crescents	-0.2	0.27	-0.22	0.23	0.3	0.08
Glomerular index	0.2	0.277	-0.48	0.006*	0.39	0.032*
Tubulo-interstitial index	-0.33	0.074	-0.47	0.007*	0.17	0.356
Global index	-0.22	0.230	-0.50	0.004*	0.37	0.039*

ADC – apparent diffusion coefficient; D – pure diffusion coefficient; Fp – perfusion fraction; r – Person's correlation coefficient; SCr – serum creatinine; eGFR – estimated glomerular filtration rate; * indicates statistically significant correlations.

and -0.24), at the same time showing a high standard deviation (up to 50% of the average value). While ADC and D decreased with deteriorating renal function, mean values of Fp showed inconsistent behavior: they were higher in mild CKD than in volunteers and patients with moderate CKD and highest in patients with severe CKD.

Both ADC and D showed a weak negative correlation with the presence of interstitial infiltrations ($r = -0.44$, $P = 0.013$, 0.038). D correlated with several chronic lesions: it showed a moderate negative correlation with all combined indices of chronicity and 2 basic parameters: focal global sclerosis

($r = -0.52$, $P = 0.003$) and tubular atrophy ($r = -0.4$, $P = 0.01$). Besides of weakly correlating with casts ($r = -0.38$, $P = 0.03$), ADC failed to reach a statistically significant correlation with any other chronic changes. Fp showed a weak positive correlation with focal global sclerosis ($r = 0.36$, $P = 0.044$), glomerular index ($r = 0.39$, $P = 0.032$), and global index ($r = 0.37$, $P = 0.039$) (Table 4).

Discussion

The purpose of this study was to assess the correlation of diffusion parameters acquired with DW-MRI with laboratory

and histopathologic markers of renal parenchymal damage in CKD. The main findings of our study are: 1) the correlation of global diffusivity (ADC) and pure molecular tissue diffusion (D) with laboratory markers of renal function and 2) the correlation of D with histologic parameters of chronicity. At the same time, we observed that perfusion fraction (Fp) displayed an opposite behavior to D reaching the highest values in severe CKD and showing positive correlation where D correlated negatively (Table 4).

In agreement with previous publications, we found a significant correlation between both ADC and D and laboratory markers of renal function [5,8,9,23]. However, ADC and D differed significantly concerning their correlation with histopathologic findings. While both ADC and D showed weak negative correlation with inflammatory infiltrates, D showed moderate negative correlation with the overall load of chronic changes and with focal global sclerosis in particular (Table 4). From a clinical standpoint, the correlation with chronic changes is more meaningful, since chronic changes defined as interstitial fibrosis (IF), tubular atrophy (TA), and depletion of capillaries are associated with irreversible injury that accumulates over time leading to impairment of renal function [24,25]. Numerous papers have demonstrated a prognostic value of IFTA for progression towards end stage renal disease [26–28]. A probable explanation for a better performance of D lies in the influence of flow-related parameters on ADC. There is a convincing evidence that both vascular and tubular flow influence renal Fp values and that it may translate on ADC [29–32]. Wittsack et al. who used temporally resolved ECG-gated DWI demonstrated that Fp values differ significantly between minimum and maximum renal blood flow and that ADC follows the behavior of Fp and may be biased by changes in renal blood flow [30]. Ebrahimi, who used porcine model of renal artery stenosis-induced renal fibrosis, correlated diffusion parameters with MDCT renal perfusion and observed that while MDCT-derived GFR was reduced in the fibrotic and elevated in the contralateral kidneys, flow-related diffusion parameters were elevated

in both the stenotic and contralateral kidneys [32]. Data from MDCT perfusion strongly suggested that elevation of Fp reflected increased tubular flow due to compensatory hyperfiltration. In our study, the tightest correlation between a diffusion parameter and a histopathologic parameter was found between D and focal global sclerosis. Fp showed positive correlation with this parameter, which may suggest that increase in renal flow (either vascular or tubular) was compensatory to the loss of functioning glomeruli caused by their sclerosis. Likewise, when D showed a moderate correlation with indices of chronic changes, a weak negative correlation of Fp with those indices was also observed.

Our study has limitations. One limitation is an overrepresentation of IgA nephropathy that may have influenced our results and hindered the comparison between the groups of patients with different pathologies. Next, our patients were examined only at a single time point. Longitudinal studies are needed to assess the sensitivity of diffusion parameters to changes in the intensity of parenchymal damage over time.

Conclusions

Both structural changes in renal parenchyma and compensatory vascular/tubular flow alternations influence renal diffusion parameters. Despite those complex interactions, the biexponential analysis of DWI-MR signal allows for a non-invasive assessment of parenchymal damage and glomerular loss in CKD. Renal function monitoring with laboratory tests is simple and cost-effective, however, a repetition of renal biopsy to monitor parenchymal changes is not advisable due to possible complications. Provided that further research confirms that parameters acquired with DW-MRI may be used in a comparable manner to histopathologic scores to assess the risk of progression to end stage renal disease and help in optimal timing of transplantation, DW-MRI may become a valuable adjunct to a standard clinical assessment.

References:

- Fiorentino M, Bolignano D, Tesar V et al: Renal biopsy in 2015 – from epidemiology to evidence-based indications. *Am J Nephrol*, 2016; 43: 1–19
- Whittier WL: Complications of the percutaneous kidney biopsy. *Adv Chronic Kidney Dis*, 2012; 19: 179–87
- Mullen W, Delles Ch, Mischak H: Urinary proteomics in the assessment of chronic kidney disease. *Curr Opin Nephrol Hypertens*, 2011; 20: 654–61
- Thoeny HC, De Keyser F: Extracranial applications of diffusion-weighted magnetic resonance imaging. *Eur Radiol*, 2007; 17: 1385–93
- Thoeny HC, De Keyser F, Oyen RH, Peeters RR: Diffusion-weighted MR imaging of kidneys in healthy volunteers and patients with parenchymal diseases: Initial experience. *Radiology*, 2005; 235: 911–17
- Xu X, Fang W, Ling H et al: Diffusion-weighted MR imaging of kidneys in patients with chronic kidney disease: initial study. *Eur Radiol*, 2010; 20: 978–83
- Togao O, Doi S, Kuro-o M et al: Assessment of renal fibrosis with diffusion-weighted MR imaging: Study with murine model of unilateral ureteral obstruction. *Radiology*, 2010; 255: 772–80
- Li Q, Li J, Zhang L et al: Diffusion-weighted imaging in assessing renal pathology of chronic kidney disease: A preliminary clinical study. *Eur J Radiol*, 2014; 83: 756–62
- Zhao J, Wang ZJ, Liu M et al: Assessment of renal fibrosis in chronic kidney disease using diffusion-weighted MRI. *Clin Radiol*, 2014; 69: 1117–22
- Xu X, Palmer SL, Lin X et al: Diffusion-weighted imaging and pathology of chronic kidney disease: Initial study. *Abdom Radiol*, 2018; 43: 1749–55
- Le Bihan D, Breton E, Lallemand D et al: Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology*, 1988; 168: 497–505
- Zhang JL, Sigmund EE, Chandarana H et al: Variability of renal apparent diffusion coefficients: Limitations of the monoexponential model for diffusion quantification. *Radiology*, 2010; 254: 783–92

13. Mao W, Zhou J, Zeng M et al: Intravoxel incoherent motion diffusion-weighted imaging for the assessment of renal fibrosis of chronic kidney disease: A preliminary study. *Magn Reson Imaging*, 2018; 47: 118–24
14. Mao W, Zhou J, Zeng M et al: Chronic kidney disease: Pathological and functional evaluation with intravoxel incoherent motion diffusion-weighted imaging. *J Magn Reson Imaging*, 2018; 47: 1251–59
15. Ding J, Chen J, Jiang Z et al: Assessment of renal dysfunction with diffusion-weighted imaging: Comparing intra-voxel incoherent motion (IVIM) with a mono-exponential model. *Acta Radiol*, 2016; 57: 507–12
16. Boor P, Perkuhn M, Weibrech M et al: Diffusion-weighted MRI does not reflect kidney fibrosis in a rat model of fibrosis. *J Magn Reson Imaging*, 2015; 42: 990–98
17. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: Clinical practice guideline for the evaluation and management of chronic kidney disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf
18. Sutkowska K, Palczewski P, Duda-Zysk A et al: Diffusion-weighted MRI of kidneys in healthy volunteers and living kidney donors. *Clin Radiol*, 2015; 70: 1122–27
19. Thoeny HC, Zumstein D, Simon-Zoula S et al: Functional evaluation of transplanted kidneys with diffusion-weighted and BOLD MR imaging: Initial experience. *Radiology*, 2006; 241: 812–21
20. Sutkowska K, Palczewski P, Wojcik D et al: Intravoxel incoherent motion imaging in monitoring the function of kidney allograft. *Acta Radiol*, 2019; 60: 925–32
21. Madsen K, Nielsen H: Nonlinear least squares problems. In: Introduction to optimization and data fitting. Informatics and mathematical modelling. Kongens Lyngby: Technical University of Denmark, 2010; 113–40
22. Nielsen H: separable nonlinear least squares. Report IMM-REP-2000-01. Informatics and mathematical modelling. Kongens Lyngby: Technical University of Denmark, 2000; 1–16
23. Namimoto T, Yamashita Y, Mitsuzaki K et al: Measurement of the apparent diffusion coefficient in diffuse renal disease by diffusion-weighted echoplanar MR imaging. *J Magn Reson Imaging*, 1999; 9: 832–37
24. Liu Y: Renal fibrosis: New insights into the pathogenesis and therapeutics. *Kidney Int*, 2006; 69: 213–17
25. Farris AB, Alpers CE: What is the best way to measure renal fibrosis? A pathologist's perspective. *Kidney Int Suppl*, 2014; 4: 9–15
26. Rijnink EC, Teng YKO, Wilhelmus S et al: Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol*, 2017; 12: 734–43
27. Mise K, Hoshino J, Ueno T et al: Clinical and pathological predictors of estimated GFR decline in patients with type 2 diabetes and overt proteinuric diabetic nephropathy. *Diabetes Metab Res Rev*, 2015; 31: 572–81
28. Lv J, Shi S, Xu D et al: Evaluation of the Oxford Classification of IgA nephropathy: A systematic review and meta-analysis. *Am J Kidney Dis*, 2013; 62: 891–99
29. Lemke A, Laun FB, Simon D, Stieltjes B, Schad LR: An *in vivo* verification of the intravoxel incoherent motion effect in diffusion-weighted imaging of the abdomen. *Magn Reson Med*, 2010; 64: 1580–85
30. Wittsack HJ, Lanzman RS, Quentin M et al: Temporally resolved electrocardiogram-triggered diffusion-weighted imaging of the human kidney: Correlation between intravoxel incoherent motion parameters and renal blood flow at different time points of the cardiac cycle. *Invest Radiol*, 2012; 47: 226–30
31. Sigmund EE, Vivier PH, Sui D et al: Intravoxel incoherent motion and diffusion-tensor imaging in renal tissue under hydration and furosemide flow challenges. *Radiology*, 2012; 263: 758–69
32. Ebrahimi B, Rihal N, Woollard JR et al: Assessment of renal artery stenosis using intravoxel incoherent motion diffusion-weighted magnetic resonance imaging analysis. *Invest Radiol*, 2014; 49: 640–46