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

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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 extravascular and intravascular space, while D* (perfusion related diffusion parameter) and Fp (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. DWI was acquired using 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.
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:

\[ \frac{S_b}{S_0} = \exp \left( -b \times ADC \right) \]  

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/mm\(^2\),

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

\[ \frac{S_b}{S_0} = F_p \times \exp \left( -b \times D^* \right) + (1-F_p) \times \exp \left( -b \times D \right) \]  

where \( S_b \) is the signal intensity acquired with the given b-value, \( S_0 \) is the signal intensity at b-value=0 s/mm\(^2\), \( D \) 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/s\(^2\), 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
| Patient's number | Demographic/clinical data | Histopathology | MRI |
|------------------|---------------------------|----------------|-----|
|                  | Age | Sex | eGFR [ml/min/1.73 m²] | KDIGO class | Biopsy results | Glomerular index | Tubulo-interstitial index | Global index | Interstitial infiltrations | 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 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           | Filibrillary 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           | Membranoproliferative glomerulonephritis | 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 |
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).

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 | Histopathology | MRI |
|------------------|---------------------------|----------------|-----|
|                  | Age | Sex | eGFR [ml/min/1.73 m²] | KDIGO class | Biopsy results | Glomerular index | Tubulo-interstitial index | Global index | Interstitial 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 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. [*] – [x10⁻³ mm/s²].

**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×. 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×. Glomeruli with segmental sclerosis (arrow), tubular atrophy (circle), interstitial infiltration (x).
mesangial matrix increase in the glomeruli were assessed in a 5-point scale (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). A 4-point semi-quantitative scale (0–none, 1–minimal, 2–mild, 3–moderate, 4–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).

### Table 2. Histopathologic evaluation of changes in CKD.

#### A. Basic parameters.

| Parameters | Score |
|------------|-------|
| Glomerular sclerosis | 1–5 points |
| • Focal global sclerosis | 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 |
| • Segmental sclerosis | |
| Mesangial matrix increase | |
| Interstitial infiltrations | 0–4 points |
| Tubular atrophy | |
| Fibroed crescents | |
| Arteriolosclerosis | |
| Casts | |
| Interstitial fibrosis | |

#### B. Combined indices.

| Parameters | Description |
|------------|-------------|
| Glomerular index | Combined parameter reflecting chronic changes in glomeruli |
| • Focal global sclerosis | Sum of points awarded for the percentage of sclerosed glomeruli and mesangial matrix increase |
| • Segmental sclerosis | |
| • Mesangial matrix increase | |
| Tubulo-interstitial index | Combined parameter reflecting chronic changes in tubules and interstitium |
| • Interstitial fibrosis | Sum of points for interstitial fibrosis, tubular atrophy and casts |
| • Tubular atrophy | |
| • Casts | |
| Global index | Chronic changes in all compartments: glomeruli, tubules, interstitium and vessels |
| • Glomerular index | Sum of glomerular index, tubulo-interstitial index and vascular lesions (arteriosclerosis, hyalinosis) |
| • Tubulo-interstitial index | |
| • Arterial vessel lesions | |

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...
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, −0.38, 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 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]. Ebrahim, 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 alterations 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.

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