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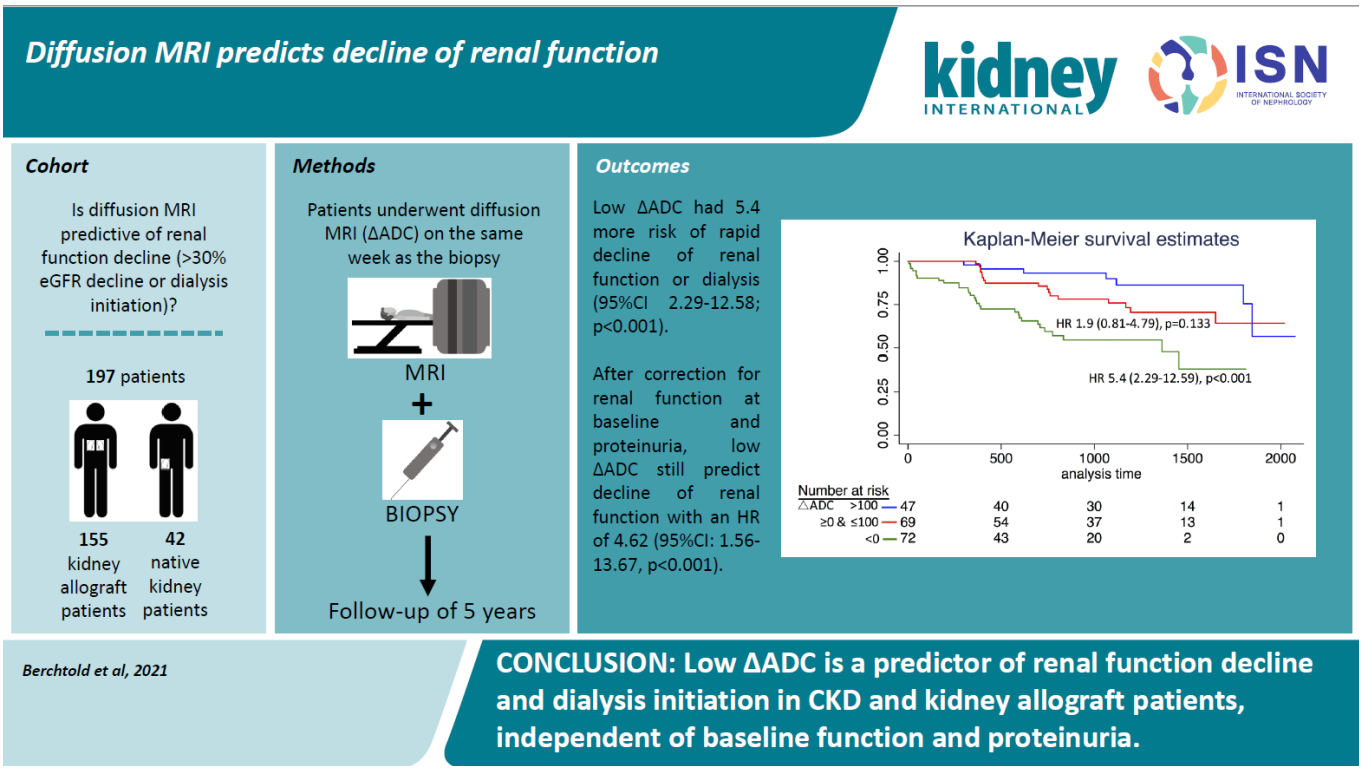
VISUAL ABSTRACT



Diffusion-MRI predicts decline of renal function in CKD and kidney allograft patients

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ABSTRACT

Kidney cortical interstitial fibrosis is highly predictive of renal prognosis and is currently assessed by the evaluation of a biopsy. Diffusion-weighted magnetic resonance imaging is a promising non-invasive tool to evaluate kidney fibrosis. We recently adapted a diffusion-weighted imaging sequence, allowing for the discrimination between the kidney cortex and medulla. The cortico-medullary difference in apparent diffusion coefficient (ΔADC) correlated to histological interstitial fibrosis. The aim of this study was to assess whether ΔADC as measured with diffusion-weighted magnetic resonance imaging is predictive of renal function decline and dialysis in CKD and kidney allograft patients.

We performed a prospective study including 197 patients. We measured ΔADC in 43 CKD patients (eGFR 55ml/min/1.73m^2) and 154 kidney allograft patients (eGFR 53ml/min/1.73m^2). Patients underwent a renal biopsy and diffusion-weighted magnetic resonance imaging, within 1 week of biopsy. Follow-up was 2.2 years in median. During follow-up, laboratory parameters were measured. Primary outcome was defined as rapid decline of renal function (eGFR decline >30% or dialysis initiation) during follow up.

Patients with low ΔADC (<0 x10^{-6}mm^2/s) had 5.4 times more risk of rapid decline of renal function or dialysis (95%CI: 2.29-12.58; p<0.001). After correction for renal function at baseline and proteinuria, low ADC still predict renal function loss with an HR of 4.62 (p<0.001, 95% CI 1.56-13.67).

We demonstrate in this study that low ΔADC is a predictor of renal function decline, and dialysis initiation in CKD and kidney allograft patients, independent of baseline renal function and proteinuria.

Keywords: Chronic kidney disease, MRI, prognostic tool

TRANSLATIONAL STATEMENT

Prediction of renal prognosis is a crucial parameter in order to individualize treatment and follow up in patients with chronic kidney disease. Our data suggest that diffusion MRI may contribute to prediction of renal function decline and dialysis initiation in CKD and kidney allograft patients, independent of baseline renal function and proteinuria. We propose that diffusion MRI could be used in addition to biochemical parameters to predict the individual outcome and tailor follow up of a given patients with renal disease, in native and allograft kidneys.

INTRODUCTION

Prediction of renal impairment is a crucial parameter in order to individualize treatment and follow up in patients with chronic kidney disease (CKD). Tools using biological parameters such as estimated renal function (eGFR) and proteinuria can help in this prediction [1]. Although very valuable, these tools probably lack some personalized aspects of kidney disease. Renal lesions assessed by biopsies are predictive of the renal evolution, independently of renal function, and are usually more informative on individual prognosis than biochemical parameters only [2]. However renal biopsies present a sampling bias, and carry some risks and can therefore not be performed in all patients, nor repeatedly to serve as a prognostic tool. A need exists for non-invasive methods to evaluate renal parenchyma, but also to predict the individual renal evolution.

Diffusion-weighted magnetic resonance imaging (DWI) is an imaging method sensitive to the Brownian motion of water molecules in the tissue that can be used to assess tissue structure in multiple organs [3]. The apparent diffusion coefficient (ADC) obtained from diffusion-weighted magnetic resonance imaging (MRI) has emerged over the past years as an important measure to evaluate kidney interstitial fibrosis (IF) non-invasively [4]. A negative correlation between ADC and the renal fibrosis assessed by biopsy has been reported by several groups [5-9]. As supported by a recent meta-analysis, DWI may be a promising tool to diagnose and classify early CKD diseases [10]. However, whether DWI could also predict the renal function evolution is currently not known. In the 122 participants of the CKD Optimal Management with Binders and Nicotinamide trial, baseline ADC was associated with a decrease in eGFR over time in the 1-year observation period [11]. In a 5-year follow-up of 91 patients with various stage of CKD, the eGFR decline was not associated with the baseline ADC but with the baseline eGFR [12]. The difference between both these studies may be related to the patient population and study design as well as the MR methodology used. Substantial improvement in the assessment of renal fibrosis by DWI can be obtained by using the cortico-medullary difference of ADC (ΔADC) instead of cortical or renal ADC [13]. Subtracting the medullary from the cortical ADC in each patient allows for lower interindividual variability of the measured index. ΔADC was better correlated to interstitial fibrosis (IF) than any other histological parameters, including inflammation [5]. When ΔADC measurements were repeated in a CKD patient, ΔADC variation over the time was better associated to IF and tubular atrophy progression than eGFR, which is

a relatively late marker of parenchymal kidney loss [14].

In this study, we thus assessed the role of diffusion derived ΔADC in the prediction of renal evolution in a mixed cohort of 197 patients with either native kidney patients or kidney allograft patients followed during 5 years. During follow-up, laboratory parameters (creatinine and proteinuria) were measured.

METHODS

Patients

We designed a prospective study, including adult kidney allograft recipients and CKD patients. Every patient ≥18 years of age followed in our hospital, and planned for a kidney biopsy for clinical purposes from August 2013 to October 2018, was eligible for enrolment in studies assessing the role of MRI in noninvasive kidney diagnosis as previously described[5, 13]. Exclusion criteria were the presence of a pacemaker or other magnetic resonance incompatible device, pregnancy, claustrophobia and patient refusal. MRI was scheduled on the same day as the biopsy whenever possible, or within 1 week. In all patients, additional fasting serum and urine were collected and stored at -80°C. Patients were then followed at least yearly by the physicians of the outpatient clinic of Nephrology our hospital. The study was approved by our local ethical committee for human studies (CER 11-160) and performed according to the Declaration of Helsinki principles. All the patients were contacted to provide written informed consent to participate in this prospective study. None of the patients was from a vulnerable population and all patients provided written informed consent, which was freely given. In the present study, all patients included in our initial study and having benefitted from research MRI were included and their follow up analyzed (figure 1).

Laboratory measurement

Baseline characteristics, including medical history, comorbidities and treatment, were collected through patient records. Patients' blood pressure, weight and size were measured routinely during follow-up visits. Serum creatinine and other standard laboratory values were measured during routine follow-up visits or hospitalizations. Standard biochemical analyses were performed in the hospital laboratory using routine automated analyzers. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). Creatinine was measured by Jaffe kinetics using Isotopic Dilution Mass Spectroscopy (IDMS)-traceable methods. When 24-hour urine protein was not available, the protein to creatinine ratio was used to estimate proteinuria.

Outcomes

The primary outcome was a decline of e-GFR of > 30% or renal replacement therapy [15, 16]. For participants who died, the last available eGFR was used to assess the primary outcome.

Histological fibrosis quantification

Renal fibrosis was assessed quantitatively on the kidney biopsy specimen by the Pathology Department of our hospital, using Masson's trichrome-stained kidney sections. The expert pathologist (S.M.) was blinded to the other results, including eGFR and MRI. Expert evaluation of fibrosis is recommended to evaluate IF and is reproducible [17]. This is the current gold standard in most pathology services [18, 19]. The severity of renal fibrosis was scored from 0% to 100% for each patient and reported on the clinical biopsy report independently of our study. 0% to 100% of renal fibrosis refers to the percentage of cortical interstitial fibrosis (extent of fibrosis in the cortical tissue present in the renal biopsy) assessed in a semi-quantitative manner by the pathologist using the trichrome staining. To verify the reproducibility of this evaluation, 60 random sections were evaluated blindly by two experienced nephrologists (SdS and LB). This repeated fibrosis evaluation displayed a good correlation to pathological evaluation (Intraclass correlation coefficient (ICC) 0.92; 95% CI 0.87–0.95). Furthermore, renal fibrosis was quantified using the Banff criteria in renal allograft patients: ci (IF) and ct (tubular atrophy) with a minimal score of 0 and maximal score of 6. Due to a good correlation between the two methods ($r=0.86$; $P<0.001$), we used subjective histological renal fibrosis as a continuous variable (0–100%) for all analyses.

MRI

Patients were scanned on a Prisma 3T MR (Siemens AG, Erlangen, Germany) with the standard 32-element spine coil and the 18-element phased-array abdominal coil. MRI protocol parameters are summarized in Table 1 [5]. The analysis of the MRI images was blinded to all other markers. Regions of interest (ROI) were determined on the T1 map (about $1cm^2$ for the cortex and $20mm^2$ in 3 medullae zones) as previously described [13, 20] and copy on the ADC map, produced by the Siemens MR system, which uses a monoexponential fitting model. This model was used based on previous studies [5, 21]. ΔADC, the corticomedullary differences was used to reduce inter subject variability and provide an MRI index of fibrosis. ΔADC was calculated as (cortical ADC – medullary ADC). ΔADC was separated in 3 subgroups based on

previous study [13, 21]. All focal pathological areas (cyst, scar and hematomas) were avoided in the ROI placement aiming to cover a large and representative part of the cortex and medulla. Reproducibility has been assessed in our protocol [13]. Strong reproducibility of ADC in the cortex and medulla was found between two readers. For each patient independently, all ICC were superior to 0.91 [95% CI:0.92–0.99] for ADC cortex, ADC medulla and ΔADC. Correlation coefficients between the two readers were $R^2 = 0.96$ for the ADC evaluation in the cortex, $R^2 = 0.97$ in the medulla and $R^2 = 0.95$ for the ΔADC ($p < 0.05$).

Table 1: Parameters for RESOLVE DWI MRI

Parameters for RESOLVE DWI MRI	
Resolution (mm^3)	2x2x5
Echo time(ms)	68
Repetition time (ms)	>2000 = respiratory gated
Acceleration factor (GRAPPA)	3
Bandwidth (Hz/pixel)	960
Readout segments	5
Echo spacing (ms)	0.69
Flip angle	180
b-values (s/mm^2)	0, 50, 100, 150, 200, 250, 300, 500, 700, 900
Diffusion gradient scheme	Bipolar
Respiratory gating	Belt

Statistical analysis

Continuous variables are expressed as mean +/- SD, or median and interquartile range, according to the distribution. Categorical variables are expressed as numbers and percentages. The statistical significance was determined as a $p< 0.05$, and all tests were two-sided. To test the hypothesis that MRI and clinical parameters tests could predict decline of renal function or new dialysis, we performed log-rank tests for trend comparing for each variable the risk of renal function lost. Time-to-event data were evaluated with the use of Kaplan Meier estimates and Cox proportional-hazard models. Survival curves were compared using Log-Rank test. Hazard ratios, 95% confidence intervals and P values were calculated with the use of Cox models. Proportionality of hazard was graphically verified by plotting log minus log of survival against time. The selection of covariates (eGFR and proteinuria) in multivariable analyses was based on prior knowledge from the scientific. The discriminative performance of clinical parameters (eGFR and proteinuria) and ΔADC to predict decline of renal function was assessed by a composite score. For a specific patient, the composite score is calculated as the sum of the regression coefficients corresponding to his/her characteristics (Table 5). The higher the prognostic index, the higher the level of risk predicted by the model. The 3-year free-eGFR decline survival according to the value of a predictor (composite score or proteinuria) was assessed by using a non-parametric method based on Kaplan-Meier's approach and nearest neighbor's approach [22] with the package prodlim for R (version 2019.11.13)[23].

Statistical analyses were performed using STATA 13.1 (StataCorp, College Station, TX, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study population

From August 2013 to October 2018, we included 197 CKD patients, mainly Caucasian (90%) and male (68%) with a mean age of 54(+/- 14) years old, undergoing kidney biopsy for clinical reasons. Of the 197 patients, 154 (78%) were kidney allograft patients and 43 (22%) were native kidney patients (Figure 1 and supplementary Figure S1).

Baseline characteristics are presented in Table 2. Biopsy indications were made by the nephrologist in charge of the patients, as clinically justified, and independently of this study. For native kidney disease, most of the indications were an abnormal urinary microscopy and proteinuria and/or acute or chronic renal dysfunction. For allograft patients, biopsy indications were routine biopsies (at 1 year, after steroid withdrawal), elevation of creatinine levels and apparition of proteinuria or de novo donor-specific antibodies. MRI was done within one week of the biopsy. ΔADC was available in 188 of the 197 total patients.

Table 2: Baseline characteristics of the study population (n=197): clinical parameters, medication, laboratory measurements, biopsy diagnosis and chronic histological lesions at the time of inclusion.

Characteristics	Total (n=197)	Native (n=43)	Allograft(n=154)
Clinical parameters			
Age, years	54 ± 14	52 ± 15	55 ± 13
Male, n (%)	134 (68%)	31 (74%)	103 (66%)
Body mass index, kg/m^2	25.6 ± 4.2	25.9 ± 4.6	25.5 ± 4.1
Caucasian, n (%)	178 (90%)	34 (81%)	144 (93%)
Medication, n (%)			
ACEi/ARB	94 (47.7%)	28 (65.1%)	66 (42.9%)
Calcium channel blockers	147(74.6%)	3 (7.0%)	144 (93.5%)
Diuretics	30 (15.2%)	18 (41.9%)	12 (7.8%)
Beta-blockers	85 (43.2%)	12 (27.9%)	73 (47.4%)
Statins	92 (47.2%)	18 (41.9%)	74 (48.7%)
Calcium supplementation	105 (53.3%)	9 (20.9%)	96 (62.3%)
1.25OH-vitamin D supplementation	17 (8.6%)	0 (0%)	17(11.0%)
25OH-vitamin D supplementation	142 (72.1%)	18 (41.9%)	124(80.5%)
Anticalcineurin	-	-	144 (93.5%)
Mycophenolate mofetil	-	-	123 (79.9%)
Corticosteroids	-	-	113 (73.9%)
Others (Azathioprine, m-Tor inhibitor, …)	-	-	14 (9.0%)
Laboratory measurements			
Creatinine, micromol/l	125 [99 –154]	133 [99 - 201]	123 [101-150]
eGFR ml/min per 1.73m^2 *	53.8 ± 24	55.1 ± 33.4	53.4± 20.7
Hemoglobin, g/l (n=187)	126.6 ± 21.2	119.6± 25.3	128.5± 15.6
Calcium, mmol/l (n=154)	2.34±0.14	2.26 ± 0.16	2.36± 0.13
Phosphate, mmol/l (n=165)	1.07 ±0.35	1.17± 0.38	1.04± 0.33
Magnesium, mmol/l	0.7±0.22	0.83 ± 0.17	0.6 ± 0.22
25-hydroxyvitamin D, nmol/l	69.4 ± 25.3	39.7 ± 20.3	74.6 ± 22.4
Parathyroid hormone, pmol/l	8.4 [5.6 – 12.3]	7 [4.6 – 9.1]	8.9 [5.8 ± 12.6]
Albumin, g/l	63.4 ± 25.3	39 ± 6.5	74.6 ± 22.3
Urine protein/créatinine, g/g	0.16 [0.1- 0.35]	0.92 [0.53 -1.65]	0.16 [0.1- 0.32]
Clinical Aetiology of the CKD, n (%)			
Hypertension/nephron-angiosclerosis	31 (15.7%)	8 (19.1%)	23 (14.9%)
Diabetes	12 (6.1%)	6 (14.3%)	6 (3.9%)
ADPKD	29 (14.7%)	0 (0%)	29 (18.7%)
IgA	46 (23.4%)	8 (19.1%)	38 (24.5%)
Alport / thin membrane disease	4 (2.0%)	1 (2.4%)	3 (1.9%)
Membranous Nephropathy	9 (4.6%)	4 (9.5%)	5 (3.2%)
Lupus Nephritis	11 (5.6%)	5 (11.9%)	6 (3.9%)
Pauci-immun nephropathy	3 (1.5%)	2 (4.8%)	1 (0.7%)
MPGN	6 (3.1%)	1 (2.4%)	5 (3.2%)
MGRS	1 (0.5%)	0 (0%)	1 (0.7%)
Primary FSGS	6 (3.1%)	1 (2.4%)	5 (3.2%)
Amyloidosis (AA / AL)	3 (1.5%)	1 (2.4%)	2 (1.3%)
Intersitial nephritis / sarcoidosis /IgG4	6 (3.1%)	2 (4.8%)	4 (2.6%)
Reflux / CAKUT	7 (3.6%)	0 (0%)	7 (4.5%)
Cortical necrosis (septic shock, hemorrhage)	3 (1.5%)	0 (0%)	3 (1.9%)
Other (cardiomegalic, tubulopathy, primary hyperoxaluria,…)	6 (3.1%)	2 (4.8%)	4 (2.6%)
Unknown	14 (7.1%)	2 (4.7%)	12 (8.4%)

Biopsy Indication, n (%)			
Proteinuria or active sediment	45 (23.0%)	33 (80.5%)	12 (7.8%)
Creatinine elevation	36 (18.4%)	8 (19.5%)	28 (18.1%)
Donor specific antibodies	14 (7.1%)	-	14 (9.0%)
Protocol biopsy	81 (41.3%)	-	81 (52.3%)
After rejection treatment	16 (8.2%)	-	16 (10.3%)
Other (BK virus, before change of immunosuppression)	4 (2.0%)	-	4 (2.6%)
Biopsy findings, n (%)			
Cellular rejection	6 (3.1%)		6 (3.9%)
Humoral rejection	12 (6.1%)	-	12 (7.8%)
Tubular lesions	17 (8.6%)	-	17 (11.0%)
Interstitial nephritis	3 (1.5%)	1(2.4%)	2(1.3%)
Arteriolopathy / atheriolosclerosis	18 (9.1%)	0 (0%)	18 (0.7%)
Chronic allograft nephropathy	4 (2.0%)	-	4 (2.6%)
Normal kidney / No abnormality	38 (19.3%)	-	38 (24.5%)
Anticalcineurin toxicity	24 (12.1%)	-	24 (15.5%)
IgA nephropathy	23(11.7%)	5 (11.9%)	18 (11.6%)
Alport / thin membrane disease	2 (1.0%)	2 (4.8%)	0 (0%)
Membranous nephropathy	4 (2.0%)	0 (0%)	4 (9.5%)
Lupus Nephritis	5 (2.5%)	5 (11.9%)	0 (0%)
Pauci-immune nephritis	2 (1.0%)	1 (2.4%)	1 (0.7%)
Minimal change disease	1 (0.5%)	0 (0%)	1 (0.5%)
MPGN	1 (0.5%)	0 (0%)	1 (0.7%)
MGRS	2 (1.0%)	1 (2.4%)	1 (0.7%)
Thrombotic microangiopathy	3 (1.5%)	0 (0%)	3 (1.9%)
Diabetic nephropathy	9 (4.6%)	8 (19.1%)	1 (0.7%)
FSGS / vascular	16 (8.1%)	10 (23.9%)	6 (3.9%)
Others (oxalate, amyloidosis, …)	7 (3.6%)	7(16.3%)	0 (0%)
Fibrosis in %	28% ± 19	39% ± 26	25% ± 16
BANFF score			
IF/TA (ci+ct), min 0 – max 6 (n)			
0			18 (12%)
1			14 (9%)
2			60 (39%)
3			7 (5%)
4			44 (29%)
5			2 (1%)
6			7 (5%)

Values reported as numbers and %, mean+/- SD or median with interquartile ranges, as appropriate.

*eGFR was calculated according to the CKD-EPI.

One biopsy may have more than one diagnosis.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; FSGS, focal segmental glomerulosclerosis.

Univariable and multivariable analysis of predictors of renal function decline

In this cohort, median follow-up time from biopsy was 2.2 years (IQR: 1.1-3.7). Diagnosis of rapid decline of renal function was defined as eGFR decline >30% ml/min/1.73m^2 or initiation of dialysis during follow up [15, 16]. Rapid decline of renal function occurred in 54 patients after a median time of 1.1 years (IQR: 0.9-2.1). Median follow-up in the non-rapid decline of renal

function patients was 2.9 years (IQR: 1.8-4.0). During the follow-up, 11 patients died including 5 patients classified as rapid decline of renal function before their death. The 6 remaining patients were considered non-rapid decline of renal function responder based on the last available eGFR.

Recognized clinical predictors of rapid decline of renal function such as sex, age, eGFR and proteinuria were included in a Cox survival analysis. By univariate analysis, eGFR at baseline and proteinuria were associated with rapid decline of renal function (Table 3 and supplementary figure S2). Moreover, a negative ΔADC was associated by univariate analysis with rapid decline of renal function (HR 5.4; 95%CI 2.29-12.58; p<0.001) (Table 3 and Figure 2). This result was confirmed both in kidney allograft patient (HR 3.88; 95%CI 1.81-10.9; p=0.003) and CKD patients (HR 4.7; 95%CI 1.45-15.5; p=0.01) (supplementary table S1). A decrease of ΔADC was more associated (HR 5.4 versus 0.70) to rapid decline of renal function than cortex ADC (cortex ADC >1735 & ≤1891 $x10^{-6}mm^2/s$: HR 0.70, 95%CI: 0.37-1.33; p=0.273; cortex ADC >1891 $x10^{-6}mm^2/s$: HR 0.39; 95%CI 0.19-0.78, p=0.008). In Figure 3, two representative examples are shown: two patients presented with a creatinine of 110-120umol/l of creatinine and no proteinuria at baseline. Patient 1 displayed a positive ΔADC and had a good evolution at 3 years follow-up (creatinine level of 119umol/l) whereas patient 2 displayed a negative ΔADC and had an increase of creatinine to 178umol/l at 4 years follow-up. Thus, our tool may identify patients with a worse prognosis despite similar baseline clinical characteristics.

By multivariable analysis, a negative ΔADC, low eGFR and high proteinuria were independently associated with rapid decline of renal function (Table 4). The hazard ratio was the highest for a negative baseline ΔADC. In another multivariable analysis, absolute cortex ADC value was not associated with rapid decline of renal function (Supplementary table S2).

Table 3: MRI and Clinical predictors of decline of renal function by univariable analysis

	Hazard ratio (95%CI)	p-value
Univariable Model		
ΔADC *(*x10^{-6}mm^2/s*)*		
>100	Reference	
≥0 & ≤100	2.0 (0.81-4.79)	0.133
<0	5.4 (2.29-12.58)	<0.001
Gender		
- Male	Reference	
- Female	1.4 (0.83-2.45)	0.201
Age (per 10years)	1.03 (0.85-1.26)	0.730
eGFR		
≥60ml/min/1.73m^2	Reference	
≥30 & <60ml/min/1.73m^2	0.99 (0.52-1.89)	0.975
<30ml/min/1.73m^2	7.87 (3.86-16.03)	<0.001
Proteinuria		
<0.3gr/24h	Reference	
≥0.3&<3.0gr/24h	2.8 (1.51-5.47)	0.001
≥3.0gr/24h	5.7 (2.49-13.0)	<0.001

Table 4: MRI and clinical predictors of decline of renal function by multivariable analysis

	Coefficient	Hazard ratio (95%CI)	p-value
Multivariable Model			
ΔADC ≥0 & ≤100 *(*x10^{-6}mm^2/s*)*	0.66	1.93 (0.67-5.49)	0.217
ΔADC <0 *(*x10^{-6}mm^2/s*)*	1.53	4.62 (1.56-13.67)	0.006
eGFR ≥30 & <60ml/min/1.73m^2	0.01	1.01 (0.48-2.12)	0.973
eGFR <30ml/min/1.73m^2	0.97	2.63 (1.05-6.61)	0.039
Proteinuria ≥0.3&<3.0gr/24h	1.09	2.97 (1.44-6.13)	0.003
Proteinuria ≥3.0gr/24h	1.0	2.71 (1.07-6.87)	0.036

To be able to classify patients according to their clinical and MRI risk profile, we constructed a composite score including ΔADC, eGFR and proteinuria. The composite score is the sum of the regression coefficient (Table 5).

Table 5: The composite score

- MRI value: ΔADC (x10^{-6}mm^2/s)	
>100	+0
0 - ≤100	+0.66
< 0	+1.53
- eGFR (ml/min/1.73m^2)	
≥ 60	+0
≥30 - <60	+0.01
<30	+0.97
- Proteinuria (g/24h)	
<0.3	+0
≥0.3 - <3.0	+1.09
≥3.0	+1.0

The composite score ranged from 0 to 3.5 (supplementary table S3). The higher the score, the higher the risk of renal function decline: from 6.6% for a score of 0 to 74.5% for a score of 3 (Figure 4A).

We determine 3 levels of risk based on the composite score value. Values less than 0.80 correspond to a 3-year risk less than 20% (low risk category), values between 0.81 and 2.00 to a risk between 20 and 50% (intermediate risk category) and values greater than 2.00 to a risk of 50% or higher (high risk category). In these categories, the observed 3-year risk of decline of renal function (Figure 5A) matched with the predicted risk based on the composite score values (Figure 5 B).

The relationship between each component of the composite score and the 3-year free-decline survival are shown in Figure 4B_C_D. The risk estimation based on proteinuria only increases importantly when proteinuria increases from 0 to 3 gr/24h but remains around 60% for proteinuria values higher than 3gr/24h (Figure 4D). eGFR displayed also a threshold effect at approximately 45 ml/min/1.73 m^2. Only our combined risk score only displayed a mostly linear relationship to actual survival.

Proteinuria is a major predictive factor for CKD prognosis. To better determine the potential value of our composite score, we studied its performance in comparison to proteinuria. Taking into account only the predictive value of proteinuria, patients with lower than 0.17 gr/24 hours, have a low risk of progression of 20%. However, in this subgroup, ΔADC varied importantly across patients (ΔADC: from -184 to 296 $x10^{-6}mm^2/s$). Therefore, despite a low proteinuria, the composite score also varied importantly: from 0 to 2.50 (corresponding respectively to a 3-year risk based on composite score of 6.6% and 51.8%). Thus, the risk assessment based on proteinuria and based on the composite score lead to different risk classification in some patients. Of the 95 patients classified at low risk by proteinuria, 50 (%) were classified at intermediate risk by the composite score and 43 (%) were still classified at low risk and 2 at high risk. The difference of survival between these 2 groups of patients was confirmed to be statistically significant (log rank test p =0.04).

To further determine whether the composite score increased performance to predict rapid decline of renal function compared to proteinuria alone we compared the observed survival with the survival predicted by proteinuria or the composite score. As shown in Figure 6, the observed survival was closer to the survival predicted by the composite score than to the survival predicted by the proteinuria. In low risk patients at 3 years, proteinuria predicts a risk of 14.2% whether the composite score predict a risk of 9.4% for an observed risk of 7.5%. At 4 years, proteinuria predicts a risk of 20.53%, the composite score predicts a risk of 9.4% and

the observed risk is 7.5%. In intermediate risk patients at 3 years, proteinuria predicts a risk of 14.2% and the composite score a risk of 24.7% for a risk observed of 24.5%. At 4 years, proteinuria predicts a risk of 19.9% at 4 years, the composite score of 33.5% and the risk observed is 37%.

As described in previous studies, ΔADC correlated with IF (r=-0.56, p<0.001) (supplementary figure S3). IF was associated with rapid decline in renal function (Fibrosis >25% & ≤50%: HR 1.95; 95%CI 1.05-3.64, p=0.035; fibrosis >50% HR 7.82 95%CI 3.90-15.69, p<0.001). Adding fibrosis to the multivariable analysis did not improve the prediction of the model (supplementary table S4).

DISCUSSION

In a mixed population of 197 patients including 154 kidney allograft patients and 43 patients with chronic kidney disease followed for 5years (median of 2.2 years), a negative ΔADC value was predictive of a worse renal outcome. This predictive value was observed both in patients with native kidney disease and in kidney allograft recipients, and was independent of baseline age, sex, eGFR and proteinuria.

Our results are in apparent disagreement with the recent study by Sugiyama et al who did not observe a correlation of e-GFR decline with cortical ADC over a 5 year period in a single-center, longitudinal, retrospective observational design of 91 patients [12]. The CKD stage of the patients could not explain the difference as the baseline eGFR was close (eGFR 53.8 ± 24 ml/min/1.73m^2 in our study versus 49.2 ± 28.9 ml/min/1.73m^2 in Sugiyama's study. Neither could the inclusion of both native and kidney transplant recipients in our study as our results are still valid in the subgroup of patients with native kidneys. Important methodological difference between both studies may explain the different results. First, Sugiyama's study was conducted on a 1.5T MR system whereas our study was performed on a 3T MR system equipped with the strongest clinical gradients available on the market. The strength of both the static magnetic field and gradients has been well recognized as a key factor in the improvement of diffusion MRI. Furthermore, we used a RESOLVE diffusion sequence based on segmented acquisition rather than the single shot approach of Sugiyama et al according to the best overall performance of this sequence for prostate and renal imaging [20, 24]. The RESOLVE sequence allows a much shorter echo train with reduced signal blurring due to T2* decay [25] and yields

better correlation of ADC and renal fibrosis than traditional single shot EPI MR sequences [21]. Finally, the increased image quality of the RESOLVE diffusion sequence allows a combined ADC measurement from both the cortex and medulla namely the cortico-medullary ADC difference (ΔADC) which corrects for some extend inter-individual ADC variations that are known for absolute ADC values [5, 13]. We have shown previously that ΔADC was reproducible and better associated to IF in CKD patients than cortical ADC alone [13, 14]. In the present study, ΔADC also outperformed ADC for prediction of renal function evolution, and was more robust in multivariable analysis. Therefore, we believe that the technical improvements used in our study are the main explanation of the different results from Sugiyama's study. The recent study of Srivastava et al [11] performed also on a 3T MR system confirmed an association between e-GFR decline and cortical ADC and supports our results. In their study, albuminuria abrogated the predictive value of cortical ADC. Similar results were observed in our study with ADC but not ΔADC which remained an independent predictor of renal function evolution. These observations call for a better uniformization of diffusion MRI techniques to allow an optimal use of this technique in the clinical setting with the systematic use of the cortico-medullary difference for the measure of ADC.

Histologically, interstitial fibrosis (IF) is the parameter displaying the best association to renal function, and also has the largest predictive value for renal function evolution [19]. Since ADC and ΔADC are surrogate for IF, it is not surprising that they also predict renal function evolution. Correcting for IF decreased slightly the independent predictive value of ΔADC (from 4.69 to 4.32), but did not abrogate it. This result suggests that diffusion MRI is also dependent on factors other than interstitial fibrosis. It may indeed be affected by inflammation for example and renal perfusion, as well as other unknown parameters [26]. It may also suggest that the MRI assessment of IF is different to the one performed by biopsy given the largest sample of cortex analyzed using MRI. ΔADC is therefore a good predictor of renal function evolution, since it may cumulate the effects of several parameters involved in CKD progression, such as capillary rarefaction, perfusion and fibrosis for example.

Previous studies have shown that BOLD-MRI could also predict the evolution of renal disease in native kidneys. Given our observations, the value of BOLD-MRI for prognosis assessment in kidney allograft recipients would be valuable. Moreover, the added value of multiparametric MRI for renal prognosis would be of interest.

One limitation of our study is its monocentric design. Another limitation is the follow-up in median of 2.5 year and not 5 years but we included a mixed population of patients (CKD and kidney allograft patients) and the number of patients included is high. We used only one modality of MRI, multiparametric-MRI could be of interest for further studies. We use a mono-exponential fit for the analysis of our data as our previous study shown a better correlation of ΔADC than ΔD obtained from IVIM [21]. Moreover ΔADC can be measured directly from the Siemens ADC maps of the RESOLVE sequence and could therefore improve the reproducibility of our results by other groups. However evaluation of more advanced diffusion model on our data could be of interest in further studies. A last limitation is that we included fewer patients with emergency biopsies and AKI given the design of our study.

Altogether, we show here that ΔADC is predictive of kidney outcome independently of biochemical parameters. Diffusion MRI may be of value in better assessing the individual renal prognosis, also in patients in whom biopsy is difficult, or not clearly indicated. We showed that baseline ΔADC was predictive of a worst evolution, independently of biochemical parameters including eGFR. We propose that ΔADC could be used in addition to biochemical parameters to predict the individual outcome and tailor follow up of a given patients with renal disease, in native and allograft kidneys.

DISCLOSURE STATEMENT

None declared.

SUPPLEMENTARY MATERIAL

Supplementary Tables

Supplementary Table S1: MR and Clinical predictors of decline of renal function by univariable analysis in CKD and kidney allografts patients

Supplementary table S2: MR (cortex ADC), clinical and histological (fibrosis) predictors of decline of renal function by multivariable analysis in CKD and kidney allograft patients

Supplementary table S3: Composite score distribution

Supplementary table S4: MR, clinical and histological (fibrosis) predictors of decline of renal function by multivariable analysis in CKD and kidney allograft patients

Supplementary Figures

Supplementary Figure S1: detailed flow chart

Supplementary Figure S2: Kaplan-Meier curves of survival stratified according to (A) sexe, (B) age, (C) renal function, (D) proteinuria.

Supplementary figure S3: Supplementary figure 3: Correlations between MRI indices and fibrosis. Scatter plots of ΔADC (A), cortex ADC (B) and medulla ADC versus IF. Each symbol represents one patient. The continuous line indicates least-square linear regression. Correlation coefficient (r) and significance (p) are displayed in each scatter plot.

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AUTHORS' CONTRIBUTIONS

L.B., SdS, J.-P.V. and LAC contributed to the study design, data acquisition, statistical analysis and manuscript writing; P.-Y.M. contributed to study design and manuscript revision; MK, IA, D.L and S.M. contributed to data acquisition and manuscript revision; CC contributed to statistical analysis and manuscript revision.

FIGURE LEGENDS

Figure 1: Flowchart illustrating patient recruitment.

Figure 2: Kaplan-Meier curves of survival stratified according to ΔADC.

Figure 3: Two examples of patients with baseline characteristics (ΔADC value, creatinine, eGFR and proteinuria), MRI images (ADC and T1 maps; blue arrows - medulla, green arrows - cortex) and the evolution of creatinine and eGFR during the follow up.

Figure 4: Free GFR decline survival at 3 years based on (A) composite score combining ΔADC, eGFR and proteinuria. Free GFR decline survival based on (B) ΔADC, (C) eGFR and

(D) proteinuria.

Figure 5: Kaplan-Meier curves of free decline stratified according to the level of risk based on the composite score value (based on ΔADC, eGFR and proteinuria).

Figure 6: Survival in patients with (A) low risk composite score and (B) intermediate composite score. Black line is the observed survival, grey circle (dotted line) the survival predicted by proteinuria and black square (dotted line) predicted by the composite score.