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Multiparametric magnetic resonance imaging shows promising results to assess renal transplant dysfunction with fibrosis.

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Abstract

Here we assessed the diagnostic value of a quantitative multiparametric magnetic resonance imaging (mpMRI) protocol for evaluation of renal allograft dysfunction with fibrosis. Twenty-seven renal transplant patients, including 15 with stable functional allografts (eGFR mean 71.5 ml/min/1.73m²), and 12 with chronic dysfunction/established fibrosis (eGFR mean 30.1 ml/min/1.73m²) were enrolled in this prospective single-center study. Sixteen of the patients had renal biopsy (mean 150 days) before the MRI. All patients underwent mpMRI at 1.5T including intravoxel-incoherent motion diffusion-weighted imaging, diffusion tensor imaging, blood oxygen level dependent (BOLD R₂^{*}) and T₁ quantification. True diffusion D, pseudodiffusion D*, perfusion fraction PF, apparent diffusion coefficient (ADC), fractional anisotropy (FA), R₂^{*} and T₁ were calculated for cortex and medulla. T₁ was calculated as (100x(T₁ Cortex-T₁ Medulla)/T₁ Cortex). Test-retest repeatability and inter-observer reproducibility were assessed in four and ten patients, respectively. mpMRI parameters had substantial test-retest and interobserver repeatability (coefficient of variation under 15%), except for medullary PF and D* (coefficient of variation over 25%). Cortical ADC, D, medullary ADC and T₁ were all significantly decreased, while cortical T₁ was significantly elevated in fibrotic allografts. Cortical T₁ showed positive correlation to the Banff fibrosis and tubular atrophy scores. The combination of T₁ and cortical ADC had excellent cross-validated diagnostic performance for detection of chronic dysfunction with fibrosis. Cortical ADC and T₁ had good performance for predicting eGFR decline at 18 months (4 or more ml/min/

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Disclosures

All the authors declared no competing interests.

Supplementary Material

Supplementary information is available at *Kidney International's* website.

1.73m²/year). Thus, the combination of cortical ADC and T₁ measurements show promising results for the non-invasive assessment of renal allograft histology and outcomes.

Graphical Abstract

Keywords

renal allograft chronic dysfunction; renal allograft fibrosis; multiparametric MRI; apparent diffusion coefficient; T₁; eGFR slope

I. INTRODUCTION

Renal allograft interstitial fibrosis/tubular atrophy (IF/TA) can progress undetected, before elevation in serum creatinine (sCr), at which point irreversible damage may have occurred¹. The current reference standard for the diagnosis of IF/TA is histologic via percutaneous biopsy, which is invasive and suffers from risks of complications, inter-observer variability and sampling error^{2,3}. Early, non-invasive detection of IF/TA could improve risk stratification in renal transplantation, potentially preventing fibrosis progression by enabling personalization of immunosuppression.

Multiparametric magnetic resonance imaging (mpMRI), including intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI; assesses diffusion and perfusion⁴), diffusion tensor imaging (DTI; assesses tissue microstructure⁴), blood oxygen level dependent (BOLD; reflects oxygen bioavailability by measuring R₂* values⁵) and longitudinal relaxation time mapping (T₁ quantification, a marker of interstitial edema⁶), can provide insight into the structure and function of the kidney noninvasively without using gadolinium based contrast agents. These MRI techniques are feasible in renal allografts, and may provide information regarding renal parenchymal tissue structure including fibrosis^{7, 8}.

Here, we investigated a mpMRI approach in renal transplant patients with normal function or chronic dysfunction with established fibrosis to identify which mpMRI parameters, alone and in combination, provide the greatest value in the assessment of renal allograft dysfunction with fibrosis and for prediction of allograft outcome.

II. RESULTS

Clinical data

Fifteen patients with stable functional allografts and 12 patients with chronic dysfunction and established fibrosis were included in our sample (Table S1). Follow-up clinical data/eGFR was obtained in all 27 patients (median follow-up 560 days) after imaging. Since their index MRI (Table S1; 499±339 days), 2/12 patients with fibrosis were on hemodialysis, and

2/12 were relisted or eligible for relist (eGFR<20 ml/min/1.73m²). None of the 15 functional allografts had graft loss over 714±201 days since their MRI.

Inter-observer reproducibility, test-retest repeatability and interdependence of MRI parameters

Four functional allograft patients had re-test MRI exam within 28±12 days after initial MRI. mpMRI parameters had substantial interobserver and test-retest repeatability (Table S2 and S3), except for medullary perfusion fraction (PF) and medullary pseudo-diffusion coefficient D*. mpMRI parameters showed significant correlations between cortical and medullary values, and interdependence of ADC and IVIM-DWI parameters (Table S4). In the cortex, the IVIM true diffusion parameter D was independent of the perfusion parameters PF and D*, which were correlated to each other. The three IVIM parameters were correlated in the medulla. However, IVIM parameters and ADC did not correlate with T₁, FA or R₂*, demonstrating non-redundancy.

Cortico-medullary differentiation is reduced, diffusion parameters are decreased and T₁ is prolonged in fibrotic allografts

There was a trend of reduced renal volumes in dysfunctional compared to functional allografts (p=0.067) (Table 1). Cortical true diffusion coefficient D, and ADC, as well as medullary ADC were decreased in dysfunctional allografts (Fig. 1, Table 1). Cortical T₁ was prolonged (Fig. 1, Table 1) in dysfunctional vs stable function allografts with reduced absolute value of T₁ [100*(T₁ Cortex-T₁ Medulla)/T₁ Cortex].

mpMRI parameters correlate with biopsy assessments

A total of 16 biopsies were available for assessment (12/12 chronic dysfunction with fibrosis and 4/15 stable function allografts). The observation of prolonged T₁ in fibrotic allografts was supported by positive correlations (Fig. 2) of cortical T₁ with Banff ci- and ct-scores. Cortical FA was positively correlated to the i-IF/TA score (Fig. 2). Significant associations with other Banff subscores are shown in Fig. 3. Cortical mpMRI parameters did not correlate with digitized quantitative assessment of Masson's trichrome stained cortical fraction (p=0.1–0.99).

Diagnostic performance of mpMRI

Stable function vs. chronic dysfunction: The quantitative parameters cortical D, ADC, T₁ and T₁ distinguished stable function from chronic dysfunction allografts with fibrosis (AUCs >0.7), with the highest diagnostic performance observed for T₁ (Table 2, Fig. 4, AUC=0.86, p=0.001, sensitivity/specificity=0.75/0.86). Diagnostic performance of T₁ was improved by the combination with cortical ADC (AUC=0.94, p<0.001, sensitivity/specificity=0.83/0.93) in a binary logistic model (Table 2, Fig.4). Leave-one-out cross-validation of the logistic regression model combining T₁ and cortical ADC confirmed the high diagnostic performance (Fig. S1; cross-validated AUC=0.9).

Histologic variables: Among the biopsy cohort, mpMRI tended to distinguish moderate to severe IF (ci=2–3) from no or mild IF (ci=0–1) with AUCs>0.7, with the best AUC=0.83

observed for cortical T_1 , ($p=0.083$, sensitivity/specificity 0.83/0.99) (Fig. 4). No significant mpMRI models were identified for ct or ci+ct.

Prediction of eGFR decline: Cortical ADC (Fig. S2) and renal volume were associated with serum eGFR slope on follow-up, while cortical T_1 had moderate negative associations to eGFR-slope. Cortical ADC (AUC=0.76, $p=0.027$, sensitivity/specificity:0.77/0.8) and cortical T_1 (AUC=0.78, $p=0.018$, sensitivity/specificity: 0.99/0.63) were predictive of eGFR decline of >4 ml/min/1.73m²/year (Table 2, Fig. 4).

Graft survival: Univariate Cox proportional hazard analyses to predict graft loss and/or relist eligibility were performed for each of the clinical, imaging, and pathology variables (Table S5). Cortical T_1 , ADC and D^* predicted graft loss/relist independently of clinical/demographic characteristics, while medullary ADC predicted graft loss/relist independently of clinical/demographic and histopathologic characteristics (Table 3).

II. DISCUSSION

A multiparametric MRI approach has the unique potential to identify changes in renal tissue structure, perfusion and oxygen consumption that occur in parallel in renal fibrosis^{9, 10}. Previous validation studies showed the association of MRI parameters with renal allograft dysfunction and histopathology^{4, 6, 7, 9–11}, with few studies focusing on comparisons of diagnostic performance between techniques^{7, 12} or the prediction of allograft outcome. Our preliminary study identified cortical ADC and T_1 as the parameters with best diagnostic performance for chronic allograft dysfunction, association to histopathology, renal function decline, and graft survival. Our findings agree with a recent study by Friedli et al. in mice and renal transplant patients, in which T_1 , and ADC and their absolute cortico-medullary difference correlated with IF⁷.

Unlike in a previous study⁸, in our study, IVIM PF and D were significantly correlated with Banff scores for vascular and glomerular involvement, but not with IF/TA. The cortical IVIM parameter D^* was a significant predictor of graft outcome, limited however by its poor interobserver and modest test-retest repeatability. In agreement to a previous study in native kidneys, IVIM parameters did not provide improved diagnostic performance of chronic renal dysfunction compared to ADC¹². The positive correlation of cortical DTI FA with the iIFTA inflammation score observed in our study is contrary to observations of reduced anisotropy with IF/TA and cellular infiltration. A strong positive association of FA with fibrosis was also observed in a DTI study of rat models of diabetic nephropathy¹³ with similar b-values and number of diffusion directions as in our study, suggesting that a switch from negative to positive association may occur with severe fibrosis. Unlike previous studies with BOLD, we did not observe significant differences in R_2^* between fibrotic and healthy allografts, or correlations to histopathology¹¹.

The discrepancies in findings between our study and others may be related to differences in pulse sequences (e.g. small field of view diffusion acquisition with different b-values⁷, different range of TEs for R_2^* measurement¹⁴, and Look-Locker sequence for T_1 measurement⁷) and ROI selection methods. The absence of consensus regarding MRI

acquisition protocols and post-processing methods, and of reference values for MRI parameters is a shortcoming of quantitative MRI that can lead to differences between studies⁹.

Our preliminary study was limited by the sample size. Biopsy was performed at a variable time interval (3–12 months) from MRI, during which histological changes may have occurred; only 4 patients in the functional allograft group had verification biopsies. BOLD imaging was only performed at baseline without any physiological challenge, due to inclusion in a lengthy mpMRI protocol; previous studies suggest that changes in BOLD measurements with a physiological challenge¹¹ may be more sensitive to renal allograft dysfunction than baseline measurements alone. Our DTI acquisition had the minimum number of diffusion directions (6); inclusion of more diffusion directions would provide a better quantification of FA. We did not include emerging MRI modalities with utility in renal fibrosis, such as magnetization transfer imaging (MTR) or MR elastography (MRE)¹⁰. MRE data was acquired and detailed analysis will be presented in a separate manuscript.

The results of our preliminary study suggest that future work on diagnosing allograft dysfunction and predicting graft failure should focus on abbreviated mpMRI protocols consisting of anatomical sequences, T₁ mapping and DWI (10 minutes total imaging time). Such abbreviated mpMRI protocols would have greater clinical applicability and adoption. mpMRI parameters should be integrated with clinical variables and novel blood/urine biomarkers for identification of allografts at risk of failure¹⁵.

III. CONCLUSION

mpMRI is promising for the assessment of renal allograft fibrosis, with high repeatability and reproducibility of cortical ADC, D, FA and T₁. The combination of cortical ADC and cortico-medullary difference in T₁ showed promising diagnostic performance for the non-invasive detection of renal allograft dysfunction with fibrosis. Differences in cortical ADC and T₁ values likely reflect fibrosis-associated collagen deposition, tissue edema and inflammation. Future studies on an abbreviated mpMRI approach combining DWI and T₁ mapping may have clinical applicability in the non-invasive detection of renal allograft fibrosis.

IV. METHODS

Patients

This prospective single-center study complied with the Health Insurance Portability and Accountability Act and was approved by the local IRB. Between 2/2016–3/2018, 28 patients with renal transplantation provided written informed consent and underwent mpMRI of the pelvis. Patients with stable allograft function and chronic dysfunction with fibrosis were referred to the study by transplant nephrologists and renal pathologist in consensus. Renal allograft function/dysfunction was defined independently of biopsy, and was based on serum creatinine and eGFR (Supplementary Methods). One stable function allograft patient initially recruited was excluded from analysis due to renal dysfunction indicated by elevated creatinine levels at the time of MRI and a long interval between MRI and biopsy (>2 years).

Image acquisition and analysis

All patients fasted for 4 hours before the MRI. Patients were imaged on the same 1.5T system (Aera, Siemens Healthineers, Erlangen, Germany) equipped with a multichannel spine and body matrix coil and 33 mT/m maximum gradient strength. The 45 minute imaging protocol consisted of axial and coronal T₂-weighted (T2WI) HASTE, axial T₁-weighted imaging, axial dual-echo in- and out-of-phase imaging, coronal oblique IVIM-DWI, DTI, BOLD (R₂^{*}) and T₁ mapping (Table S6), DCE-MRI (in patients with eGFR > 30 ml/min/1.73m²), MR elastography (MRE) and 3D phase-contrast (4D flow) MRI. DCE-MRI, MRE and 4D flow data are presented in separate manuscripts. MRI quantification is described in Supplementary Methods.

Histopathology

Sixteen patients (12/12 chronic dysfunction and 4/15 functional allografts) had percutaneous needle biopsy within a year of MRI (biopsy to MRI delay: 157 ± 87 days). Tissue samples were processed for light microscopy as per standard-of-care at our institution¹⁶ (Supplementary Methods). A threshold-based segmentation method was implemented in MATLAB¹⁷ to quantify the Masson's trichrome stained tissue fraction (Fig. 1).

Statistical analysis

Statistical analysis (Supplementary Methods) was performed using MATLAB and SPSS v. 20 (IBM Inc, Armonk, NY). Two-tailed p-values <0.05 were considered to be statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

mpMRI in a 55 year-old woman with stable functional allograft (eGFR 78.4 ml/min/1.73m²) and a 38 year-old woman with dysfunctional allograft (eGFR 19.9 ml/min/1.73m²) with fibrosis. Representative T₂-weighted images (A, G), diffusion (B–D; H–J), and T₁ (E, K) maps compared between functional allograft (A–F; Banff ci+ct=0+0) and dysfunctional allograft with fibrosis [G–L; moderate IF/TA (Banff ci+ct= 2+2)]. The range and units of quantitative MRI parametric maps are displayed in parentheses, and parameter values in the cortex and medulla of each patient are displayed on the maps. ADC: apparent diffusion coefficient; D: true diffusion coefficient; FA: fractional anisotropy; T₁: longitudinal relaxation time. Masson's trichrome stained pathology slides shown with stained tissue fraction from semi-automated segmentation (F, L), with glomeruli removed (black), and pixels stained for collagen (green). All maps show loss of cortico-medullary differentiation in the fibrotic allograft. In the fibrotic allograft, ADC and D are decreased while T₁ is increased in both cortex and medulla, and FA is decreased in the medulla and increased in the cortex.

Figure 2.

Correlation of MRI parameters with interstitial fibrosis (IF) ci score, tubular atrophy (TA) ct score, and inflammation in area of interstitial fibrosis and tubular atrophy (iFTA) score (in n=16 patients who had biopsies). Cortical longitudinal relaxation time T_1 showed moderate positive association with interstitial fibrosis ci and tubular atrophy ct scores, while cortical fractional anisotropy (FA) showed a moderate positive association to iFTA.

Figure 3.

Correlations of diffusion parameters with histopathological Banff scores of glomerular (g, cg) and vascular dysfunction (cv, ptc) in 16 patients with biopsies. Cortical perfusion fraction (PF) showed moderate negative correlation with glomerulosclerosis (cg), vascular fibrous intimal thickening (cv) and peritubular capillaritis (ptc) scores. Cortical apparent diffusion coefficient (ADC) showed moderate negative correlation with ptc and glomerulitis (g), while true diffusion coefficient D showed moderate negative correlation with g.

Figure 4.

Performance of quantitative MRI parameters and renal volume, as well as mpMRI models (combining T_1 and cortical ADC) for detecting chronic allograft dysfunction with fibrosis, moderate to severe interstitial fibrosis (ci 2–3), moderate to severe tubular atrophy (ct 2–3), a combination of moderate to severe interstitial fibrosis and tubular atrophy (ci+ct 5–6), and eGFR decline of more than 4 ml/min/1.73 m²/year. ROC curves show Sensitivity vs. 1-Specificity for renal volume and the quantitative MRI parameters which correlated to histopathology or eGFR change over time (slope). The line of no discrimination is showed in red (See also Table 2).

Table 1.

Distribution of MRI parameters in the allografts with stable function and those with chronic dysfunction and fibrosis. Values are given as mean $\pm$ standard deviation.

	Renal volume (ml)								
Stable function	274.5 ± 48.3								
Chronic dysfunction	252.1 ± 80.6								
P	0.067								
	Cortex				Medulla				
	D	PF	D*	ADC	D	PF	D*	ADC	ADC (%)
Stable function	1.8±0.2	23.3±5.9	19.6±12.9	2.1±0.1	1.7±0.2	25.2±7.7	21.6±14.5	2.1±0.1	1.2±5.6
Chronic dysfunction	1.6±0.2	20.2±7.8	23.9±16.9	1.9±0.2	1.6±0.2	22.4±5.9	20.8±13.6	1.9±0.1	−0.7±3.3
p	0.037	0.167	0.792	0.007	0.114	0.427	0.867	0.016	>0.99
	FA								FA (%)
Stable function	0.21 ±0.06				0.34±0.09 [¶]				−63.86±31.34
Chronic dysfunction	0.23±0.06				0.33±0.09 ^{¶¶}				−53.55±37.78
p	0.456				>0.990				0.30
	R ₂ *								R ₂ * (%)
Stable function	16.49±3.17				17.82±3.65 [§]				−8.67±14.05
Chronic dysfunction	16.29±2.93				17.36±3.38				−3.98±14.55
p	0.940				0.494				0.899
	T1								T ₁ (%)
Stable function	1149.3±185.1				1557.7±249.4 [□]				−37.0±15.1
Chronic dysfunction	1349.6±215.9				1491.9±244.4 ^{□□}				−11.2±13.8
p	0.017				0.560				<0.001

ADC (10⁻³ mm²/s): apparent diffusion coefficient; D (10⁻³ mm²/s): true diffusion coefficient; D*(10⁻³ mm²/s): pseudo diffusion coefficient; PF (%): perfusion fraction; FA: fractional anisotropy; T₁ (ms): longitudinal relaxation time; R₂* (s⁻¹): transverse relaxation rate

[¶]FA significantly higher in the medulla than in the cortex of functional allografts (p<0.001)

^{¶¶}FA significantly higher in the medulla than in the cortex of allografts with established fibrosis (p<0.001)

[§]R₂* significantly higher in the medulla than in the cortex of functional allografts (p=0.0085)

[□]T₁ significantly higher in the medulla than in the cortex of functional allografts (p<0.001)

^{□□}T₁ significantly higher in the medulla than in the cortex of allografts with established fibrosis (p=0.0068)

Performance of quantitative MRI parameters and renal volume, as well as mpMRI models (combining T₁ and cortical ADC) for detecting chronic allograft dysfunction with fibrosis, moderate to severe interstitial fibrosis (ci 2–3), moderate to severe tubular atrophy (ct 2–3), a combination of moderate to severe interstitial fibrosis and tubular atrophy (ci+ct 5–6), and eGFR decline of more than 4 ml/min/1.73 m²/year. Area under receiver-operating curve (AUC), AUC confidence interval (CI) and p-value are given.

Table 2.

	Stable vs. Dysfunction with Fibrosis		ci 0–1 vs. 2–3		ct 0–1 vs. 2–3		ci+ct 0–4 vs 5–6		Slope eGFR < –4 ml/min/year	
	AUC (CI)	p	AUC (CI)	p	AUC (CI)	p	AUC (CI)	p	AUC (CI)	p
Cortex D	0.74 (0.55–0.93)	0.036	0.79 (0.50–1.00)	0.090	0.68 (0.38–0.96)	0.278	0.65 (0.33–0.97)	0.396	0.69 (0.47–0.91)	0.098
Cortex ADC	0.80 (0.63–0.97)	0.008	0.77 (0.50–1.00)	0.115	0.60 (0.3–0.90)	0.515	0.54 (0.14–0.94)	0.808	0.76 (0.55–0.97)	0.027
Cortex T ₁	0.77 (0.58–0.97)	0.018	0.83 (0.62–1.00)	0.083	0.82 (0.59–1.00)	0.050	0.77 (0.53–1.00)	0.117	0.78 (0.60–0.96)	0.018
T ₁	0.86 (0.74–1.00)	0.001	0.78 (0.55–1.00)	0.149	0.44 (0.08–0.8)	0.713	0.5 (0.17–0.83)	>0.99	0.65 (0.42–0.88)	0.206
Renal volume	0.71 (0.49–0.93)	0.064	0.77 (0.54–1.00)	0.115	0.58 (0.29–0.88)	0.588	<0.5	0.467	0.71 (0.51–0.91)	0.079
mpMRI	T ₁ +ADC		-		-		-		-	
	0.94 (0.85–1.00)	<0.001	-	-	-	-	-	-	-	-

Table 3.

Combination of imaging and clinicopathologic parameters in bivariate Cox proportional hazards models of graft loss/relist eligibility (defined as graft failure, presence on a transplant list, or follow-up eGFR < 20 ml/min/1.73 m²). Imaging and pathology variables with $p \leq 0.1$ on univariate analysis (Supplementary Table S5) were included in bivariate models. Coefficient p-values for the imaging parameters in the bivariate Cox models are given below.

Clinicopathologic Variables	Cortical ADC	Cortical D*	Medullary ADC	Cortical T ₁
Baseline eGFR	0.409	0.530	0.467	0.371
Donor status	0.012	0.064	0.021	0.023
Donor age	0.067	0.043	0.075	0.046
Induction regimen	0.023	0.031	0.021	0.020
Recipient race	0.041	0.117	0.1	0.034
Renal volume	0.061	0.043	0.037	0.036
Time from Transplant	0.028	0.030	0.042	0.027
g	0.1	0.077	0.092	0.108
cg	0.075	0.111	0.048	0.083
ptc	0.16	0.313	0.143	0.134
ci+ct	0.161	0.196	0.164	0.196
i+t	0.067	0.054	0.054	0.059

ADC (10^{-3} mm²/s): apparent diffusion coefficient; D* (10^{-3} mm²/s): pseudo diffusion coefficient; T₁ (ms): longitudinal relaxation time.