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Multicenter Study Evaluating Intrarenal Oxygenation and Fibrosis Using Magnetic Resonance Imaging in Individuals With Advanced CKD

To the Editor: The chronic hypoxia theory states that hypoxia and interstitial fibrosis are key contributors to progression of chronic kidney disease (CKD).[1] Presence of fibrosis may further enhance the hypoxia by limiting oxygen transport, resulting in a perpetual cycle of hypoxic injury and progressive loss of kidney function. Blood oxygenation level dependent (BOLD)[2] and diffusion[3] magnetic resonance imaging (MRI) can provide information on renal oxygenation and fibrosis, respectively. The methods rely on endogenous contrast mechanisms that do not require exogenous contrast administration and that are widely available on major vendor platforms.

Table 1. Baseline characteristics of study population

Variable	CKD, $n = 127$	Control, $n = 13$
Age, yr	65 ± 12	59 ± 9
Male, *n* (%)	81 (64)	6 (46)
Race, *n* (%)		
White	73 (57)	7 (54)
African American	39 (31)	3 (23)
Other	15 (12)	3 (23)
Diabetes, *n* (%)	64 (50)	0 (0)
eGFR, ml/min per 1.73 m^2	33.4 ± 7.2	90.7 ± 11.9
UACR, mg/g	161 (20–584)	n/a
HGB, g/dl	12.9 ± 1.7	n/a

eGFR, estimated glomerular filtration rate; HGB, serum hemoglobin; n/a, not available; UACR, urine albumin to creatinine ratio shown as median (interquartile range).

We report baseline MRI data in 127 individuals with advanced CKD (mean estimated glomerular filtration rate [eGFR] = 33.4 ± 7.2 ml/min per 1.73m^2) who participated in the COMBINE (CKD Optimal Management with BInders and NicotinamidE) study, a multicenter clinical trial that aimed to test whether

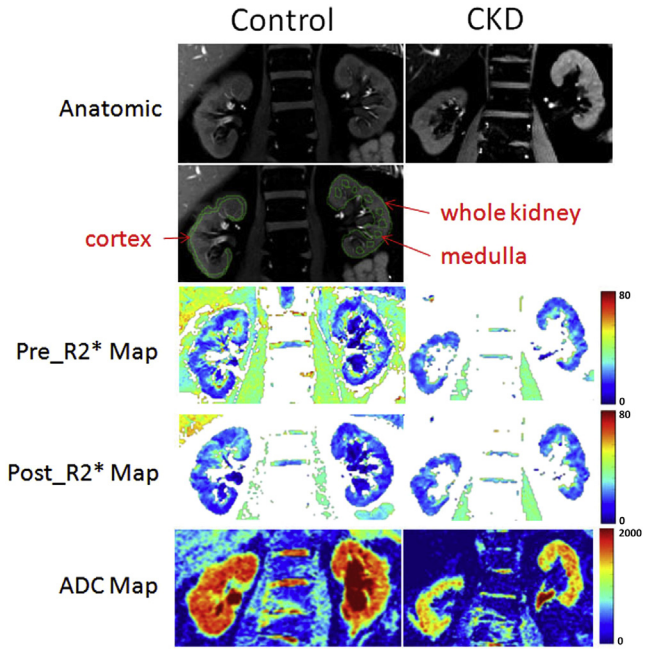

Figure 1. Illustration of typical magnetic resonance imaging data from a representative subject from the control and chronic kidney disease (CKD) groups. Shown are anatomical images, pre- and post-furosemide R2*, and apparent diffusion coefficient (ADC) maps. The maps are scaled similarly using the same color bar for both control and CKD. Note that changes in medullary regions in control, but not in CKD on the post-furosemide R2* map compared with the pre-furosemide R2* map. Also included is an illustration of sample regions of interest (ROIs) defined for the analysis of R2* maps. Cortical ROIs (outlined in green) are defined as thin regions parallel to the outer boundary of the kidney covering the entire length of the kidney. Also shown are whole-kidney ROI and multiple small ROIs in the medulla.

Table 2. Comparison of magnetic resonance imaging parameters between study groups

	CKD/ Control	*n*	Mean	SD	*P*[a]	Mean difference (confidence interval)
Oxygenation						
R2*_Cortex (s^{-1})	Control	13	18.74	2.37	**0.022**	−1.811 (−3.322 to −0.3)
	CKD	123	20.55	3.10		
R2*_Medulla (s^{-1})	Control	13	29.03	3.87	**<0.01**	5.278 (2.890 to 7.665)
	CKD	121	23.75	3.22		
R2*_Kidney (s^{-1})	Control	13	22.15	2.25	0.38	0.611 (−0.810 to 2.032)
	CKD	123	21.54	2.76		
R2*_(Kid-Cor) (s^{-1})	Control	13	3.41	1.89	**<0.01**	2.453 (1.303 to 3.604)
	CKD	123	0.96	0.89		
R2*_MC ratio	Control	13	1.57	0.28	**<0.01**	0.403 (0.230 to 0.577)
	CKD	121	1.17	0.15		
Response to furosemide						
ΔR2*_Cortex (s^{-1})	Control	13	0.42	0.86	0.11	−0.461 (−1.035 to 0.112)
	CKD	54	0.88	1.02		
ΔR2*_Medulla (s^{-1})	Control	13	6.28	3.46	**0.002**	3.747 (1.578 to 5.915)
	CKD	54	2.54	2.47		
ΔR2*_Kidney (s^{-1})	Control	13	2.03	1.13	**0.014**	0.927 (0.217 to 1.638)
	CKD	54	1.11	0.87		
Fibrosis						
ADC	Control	13	1.67	0.08	**< 0.01**	0.219 (0.165 to 0.273)
($\times 10^{-3}$ mm^2/s)	CKD	126	1.45	0.17		

ADC, apparent diffusion coefficient; CKD, chronic kidney disease; R2*_(Kid-Cor) = R2*_Kidney − R2*_Cortex; R2*_MC ratio = R2*_Medulla / R2*_Cortex.
[a]By Student 2-tailed *t* test.

nicotinamide and lanthanum carbonate would safely lower serum phosphate and FGF23 levels compared with placebo. Relaxation rate R2* served as the BOLD MRI index; higher values represent decreased oxygenation.[2] Apparent diffusion coefficient (ADC) was the diffusion MRI index; lower values may be due to increased fibrosis.[4] Similar MRI data obtained in a small group ($n = 13$) of healthy volunteers were used for comparison. Detailed MRI methods are provided as Supplementary Methods and specific MRI parameters are listed in Supplementary Table S1.

RESULTS AND DISCUSSION

Table 1 summarizes the baseline characteristics of the study population.

Figure 1 shows examples of MRI data in both a healthy volunteer and an individual with CKD. Table 2 summarizes the differences in MRI measurements between the trial participants with CKD and the healthy control group. Consistent with current literature on studies from single sites,[5–7] cortical R2* was modestly higher in the group with CKD versus the control group, suggesting decreased cortical oxygenation. R2*_Medulla was lower in participants with CKD compared with healthy volunteers, suggesting increased medullary oxygenation. This seemingly contradictory observation has been reported before in preclinical studies[8] using invasive measurements and in human studies using BOLD MRI.[9,10] In a remnant kidney model, direct oxygen levels measured using microelectrodes at 6 to 8 weeks showed increased tissue oxygen levels.[8] In the

Table 3. Comparison of magnetic resonance imaging measures by diabetes status

	CKD/Control	*n*	Mean	SD	*P*[a]	Mean difference (confidence interval)
Oxygenation						
R2*_Cortex (s^{-1})	Diabetes	61	20.55	3.00	0.99	0.007 (−1.106 to 1.118)
	No diabetes	62	20.54	3.23		
R2*_Medulla (s^{-1})	Diabetes	60	24.13	3.32	0.21	0.745 (−0.412 to 1.901)
	No diabetes	61	23.38	3.10		
R2*_Kidney (s^{-1})	Diabetes	61	21.61	2.62	0.78	0.143 (−0.846 to 1.132)
	No diabetes	62	21.46	2.92		
R2*_MC ratio	Diabetes	60	1.19	0.17	0.11	0.043 (−0.010 to 0.097)
	No diabetes	61	1.15	0.13		
Response to furosemide						
ΔR2*_Cortex (s^{-1})	Diabetes	17	0.78	1.178	0.634	0.156 (−0.510 to 0.822)
	No diabetes	37	0.93	0.958		
ΔR2*_Medulla (s^{-1})	Diabetes	17	1.76	1.47	0.054	1.137 (−0.022 to 2.296)
	No diabetes	37	2.90	2.76		
ΔR2*_Kidney (s^{-1})	Diabetes	17	0.96	0.93	0.439	0.208 (−0.335 to 0.751)
	No diabetes	37	1.17	0.84		
Fibrosis						
ADC	Diabetes	63	1.40[a]	0.15	**< 0.02**	0.097 (0.038 to 0.156)
($\times 10^{-3}$ mm^2/s)	No diabetes	63	1.50	0.19		

ADC, apparent diffusion coefficient; CKD, chronic kidney disease.
[a]$P < 0.05$ by Student 2-tailed *t* test.
Bold values indicate $P < 0.05$.

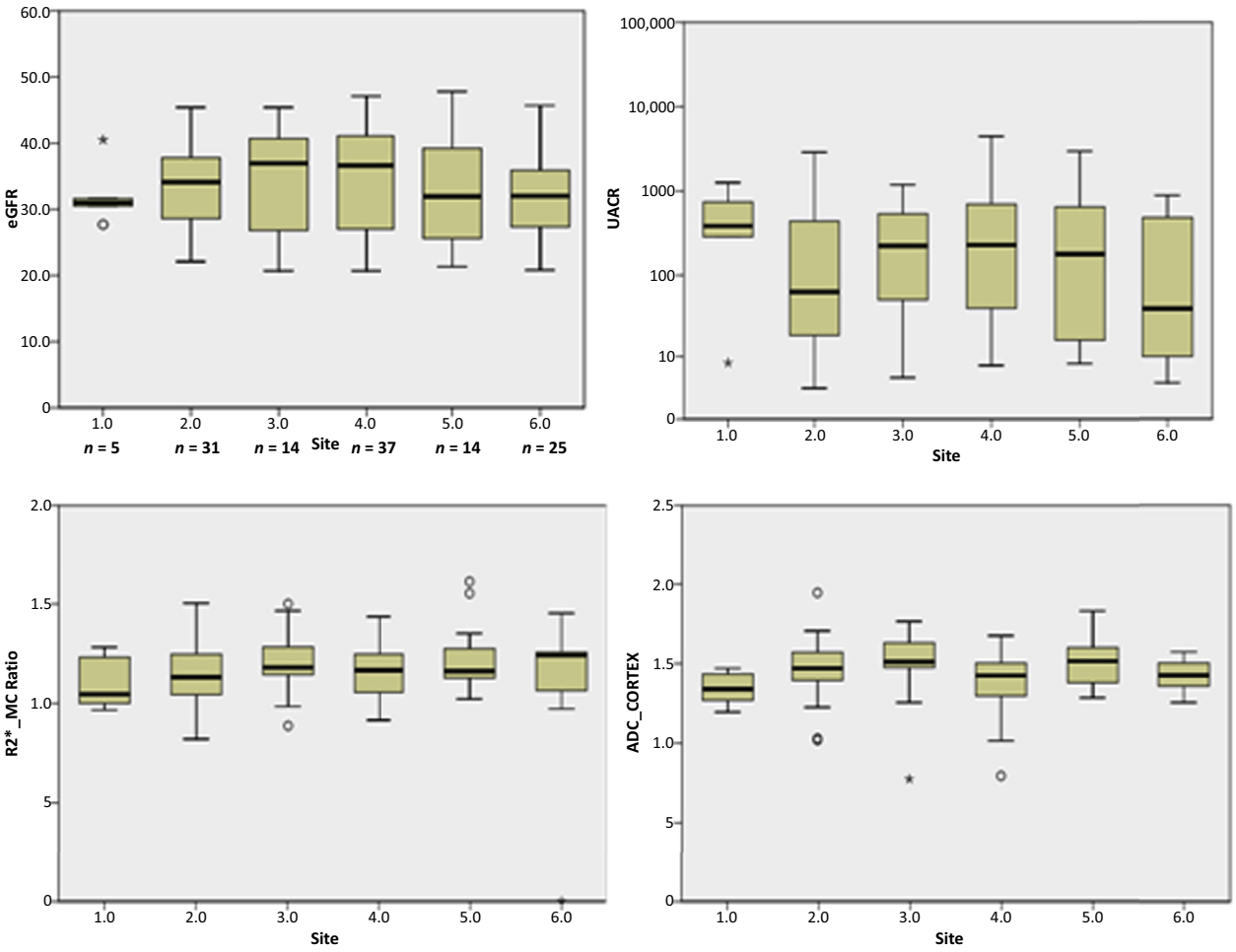

Figure 2. Box plots summarizing the measurements from each of the 6 sites. R2*_MC ratio is an objective measure to compare data from different scanners, because R2* is sensitive to field inhomogeneities and coil position, for example. It was also the parameter that showed the largest difference compared with healthy controls. For reference, we also include estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) values across the sites. Analysis of variance showed no differences in any of the measurements between sites. Circles represent outliers, and asterisks represent extreme outliers, i.e., $> 1.5 \times$ interquartile range. ADC, apparent diffusion coefficient.

same model, at an early phase (4–7 days), tissue hypoxia was observed.[11] These observations suggest the possibility that with advanced kidney disease, the decrease in renal perfusion is surpassed by decreased oxygen consumption that results from reduced delivery of glomerular filtrate and reduced tubular sodium transport.[12]

Because cortico-medullary contrast is reduced in CKD,[13] identification of medulla may be challenging, especially when using small regions of interest (ROIs). This difficulty may result in lower interreader agreement for medullary ROIs, as has been reported previously.[14] We had a high interreader agreement in medullary ROIs (Supplementary Table S2), and we included whole-kidney ROI specifically to mitigate the limitation of small ROIs for evaluating medulla. The difference between kidney and cortex ROIs could be used as an indirect estimate of medullary R2* with a higher degree of objectivity. Consistent with R2*_Medulla, changes in R2*_(Kid-Cor) show a net positive mean difference value when compared with controls (Table 2), whereas R2*_Cortex had a negative mean difference. This supports that the observed increase in R2*_Medulla is not an artifact of using small ROIs. Prior studies have reported increased medullary oxygenation using both small ROIs[10] and more objective concentric ROI method.[9]

The response to furosemide provides an index of active tubular sodium reabsorption in the medulla.[15] Consistent with prior reports, we observed a blunted response to furosemide in participants with CKD compared with controls.[6,16] Notably, for the analysis of response to furosemide, we excluded participants with CKD who were chronically treated with loop diuretics, given a prior study reporting lower response in such individuals.[17]

Lower ADC values are associated with the presence of fibrosis.[3,4] The cortical ADC estimates from this study in the healthy volunteers are comparable with a recent report,[3] and as also previously reported, we observed lower cortical ADC in participants with CKD compared with controls (Table 2). The cortical ADC values in our participants with CKD were lower

Table 4. Spearman correlations between magnetic resonance imaging parameters and renal function in the participants with CKD

		$ADC_{diffusion}$	eGFR	Log(UACR)
Oxygenation:				
	ρ	0.011	−0.027	−0.111
R2*_Cortex	*P*	0.903	0.769	0.225
	n	122	123	122
	ρ	0.184[a]	0.195[a]	−0.311[b]
R2*_Medulla	*P*	**0.044**	**0.032**	**0.001**
	n	120	121	120
	ρ	0.062	0.026	−0.209[a]
R2*_Kidney	*P*	0.500	0.775	**0.021**
	n	122	123	122
	ρ	0.223[a]	0.150	−0.225[a]
R2*_MC ratio	*P*	**0.014**	0.100	**0.013**
	n	120	121	120
Response to furosemide:				
	ρ	−0.009	0.045	−0.080
ΔR2*_Cortex	*P*	0.952	0.748	0.571
	n	53	54	53
	ρ	0.257	−0.018	−0.139
ΔR2*_Medulla	*P*	0.063	0.899	0.321
	n	53	54	53
	ρ	0.053	0.086	−0.239
ΔR2*_Kidney	*P*	0.705	0.539	0.085
	n	53	54	53
Fibrosis:				
	ρ	1.000	−0.053	−0.167
ADC	*P*		0.557	0.063
	n	126	125	125
Conventional parameters:				
	ρ	−0.053	1.000	−0.105
eGFR	*P*	0.557		0.244
	n	125	126	125
	ρ	−0.167	−0.105	1.000
Log(UACR)	*P*	0.063	0.244	
	n	125	125	126

ADC, apparent diffusion coefficient; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.
[a]Correlation is significant at the 0.05 level (2-tailed).
[b]Correlation is significant at the 0.01 level (2-tailed).
Bold values indicate $P < 0.05$.

than previously reported[3] (1.45 ± 0.17 vs. 1.63 ± 0.14 × 10^{-3}mm^2/s), probably due to the lower mean eGFR in our study in comparison with the mean eGFR in the prior study (33.4 vs. 71.2 ml/min per 1.73 m^2). Interestingly, 50% of the group with CKD had diabetes, and participants with CKD with diabetes had significantly lower ADC compared with those without diabetes (Table 3).

Table 5. Linear regression of MRI indices with UACR and eGFR

Dependent variable	Predictors	β	SE	*P*	Adjusted[a] β	Adjusted[a] SE	Adjusted[a] *P*
R2*_Medulla	UACR[b]	−1.125	0.342	**0.001**	−0.798	0.364	**0.021**
	eGFR	0.081	0.040	**0.048**	0.080	0.039	**0.044**
R2*_MC ratio	UACR[b]	−0.039	0.016	**0.017**	−0.035	0.017	**0.048**
	eGFR	0.004	0.002	**0.049**	0.004	0.002	**0.038**
R2*_Kidney	UACR[b]	−0.569	0.300	0.061	−0.353	0.316	0.267
	eGFR	0.016	0.035	0.649	0.013	0.034	0.703

eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; UACR, urine albumin to creatinine ratio.
[a]Adjusted for age, race, gender, and diabetes status.
[b]Log transformed.
Bold values indicate $P < 0.05$.

Table 6. Linear regression of ADC with R2* indices

Dependent variable	Predictors	β	SE	*P*	Adjusted[a] β	Adjusted[a] SE	Adjusted[a] *P*
ADC	R2*_Medulla	0.010	0.005	**0.036**	0.011	0.005	**0.043**
	R2*_MC ratio	0.157	0.107	0.144	0.156	0.112	0.165

ADC, apparent diffusion coefficient.
[a]Adjusted for estimated glomerular filtration rate and log-transformed urine albumin to creatinine ratio.
Bold values indicate $P < 0.05$.

To characterize MRI measurements across all clinical sites, we examined box-whisker plots for R2*_MC Ratio, ADC_Cortex, eGFR, and urine albumin to creatinine ratio (UACR) by individual sites (Figure 2). Analysis of variance showed no significant differences in any of these parameters between sites.

Finally, we explored associations of MRI measurements with clinical parameters in participants with CKD (Table 4). R2*_Medulla and R2*_MC Ratio showed significant association with eGFR and UACR (Table 5). These relationships remained significant after adjusting for age, race, gender, and diabetes status. The association of medullary R2* with UACR may be interesting because higher UACR is considered to be a predictor of fast progression.[18] R2*_Medulla was associated with ADC and remained significant even after adjusting for eGFR and UACR (Table 6). ADC was also associated with diabetes status, and remained significant even after adjusting for eGFR and UACR (Table 7). Further studies are necessary to confirm these findings. Race and gender did not show differences in any of the MRI parameters (data not shown).

Limitations

Our study was performed in patients with a 20 < GFR < 45 ml/min, so conclusions based on these results cannot be generalized to patients with all stages of CKD. Sodium intake was not controlled, which has been shown to affect renal medullary oxygenation.[19] Use of hand-drawn

Table 7. Linear regression of ADC with diabetes status (0 = no; 1 = yes)

Dependent variable	Predictors	β	SE	*P*	Adjusted[a] β	Adjusted[a] SE	Adjusted[a] *P*
ADC	Diabetes status	−0.097	0.030	**0.002**	−0.096	0.031	**0.003**

ADC, apparent diffusion coefficient.
[a]Adjusted for estimated glomerular filtration rate and log-transformed urine albumin to creatinine ratio.
Bold values indicate $P < 0.05$.

ROIs for the medulla may not be objective.[14] Ideally, future studies should use fully automated segmentation of the kidneys performed on high-contrast anatomic images that are coregistered to the BOLD MRIs.[20] It is not clear whether stopping angiotensin-converting enzyme inhibitors/angiotensin receptor blockers for 1 day before MRI and oral loop diuretics only on the day of the MRI is sufficient in this group of participants with advanced CKD. Use of the same dose of furosemide in individuals with lower renal function may not be optimal. Participants in this study did not undergo kidney biopsy, so we cannot directly determine correlations of the MRI findings with biopsy-proven fibrosis measures. The 6 centers enrolled participants from varying clinic settings. The control group had a limited number ($n = 13$) and were all from a single center. All participating sites used MRI scanners from a single vendor.

In conclusion, our data support the feasibility of using renal BOLD and diffusion MRI in multicenter trials and the data are consistent with prior reports based on single-site studies. These data combined with other results from a recent report[21] support planned international initiatives, such as BEAt-DKD,[22] that involve longitudinal multicenter trials using multiparametric MRI. Overall, our observations in advanced CKD further confirm the reduced renal cortical oxygenation and presence of renal fibrosis consistent with the chronic hypoxia hypothesis. The medullary oxygenation was significantly increased compared with controls and is also consistent with prior reports. The significantly lower ADC in participants with diabetes is novel and may have clinical relevance. Future studies to monitor progressive changes in eGFR are needed to verify if and which of these MRI parameters are specific to progressive CKD. In participants with advanced CKD, evaluating response to furosemide may be limited by the low baseline medullary R2* and their potential chronic use of loop diuretics.

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DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Methods.

Table S1. MRI acquisition parameters.

Table S2. Intra- and interreader agreement.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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