Multiparametric MRI Evaluation of Chronic Kidney Disease – BOLD & Diffusion MRI

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INTRODUCTION

Chronic kidney disease (CKD) is a major healthcare issue with increasing prevalence [JAMA 2007;298:2038-47] and associated cost. CKD is considered to be an irreversible and usually progressive reduction in kidney function. It is classified under five stages based on the level of function. However, the clinical definition of CKD is being questioned because of its inherent lack of specificity [JAMA 2011;305:1593-5]. Additional kidney injury markers are being evaluated along with imaging markers. There is also a growing interest in identifying markers that indicate risk of progression. Preliminary estimates suggest only one-in-three with stage 3 CKD (considered to be moderate) will progress towards stage 5 or End Stage Kidney Disease [Clin J Am Soc Nephrol 2009;4:337-44]. Currently, due to the lack of accepted markers, everyone is managed similarly. Ability to identify those with risk of progression will have an enormous impact on the patient management and hence in the cost to the healthcare system.

Over the last decade, the role of chronic hypoxia in the progression of CKD has gained attention mostly based on pre-clinical data [J Am Soc Nephrol 2006;17:17-25]. Translation to humans has been challenging due to the lack of accepted markers of hypoxia in humans. Blood oxygenation level dependent (BOLD) MRI is the only known non-invasive method currently available to evaluate relative oxygenation status of the kidney. Several reports in the last few years have provided conflicting data regarding the relative oxygenation status of human kidneys with CKD [J Am Soc Nephrol 2011;22:1429-34, PLoS One. 2014 Apr 23;9(4):e95895]. Studies have identified some limitations including subject preparation, use of medications, controlling for confounding factors (e.g. R2* is inherently sensitive to R2), etc. Increased hypoxia is thought to initiate fibrogenesis and fibrosis is considered a hallmark of CKD [Clin Exp Pharmacol Physiol. 2006 Oct;33(10):989-96]. Biopsy remains as the gold standard for evaluating renal fibrosis and it is not applicable to early stages of CKD. However, diffusion MRI has been found useful in assessing renal fibrosis related to CKD [Radiology. 2010 Jun;255(3):772-80].

We are currently performing a study evaluating multiple MRI parameters in a group of stage 3 CKD patients with diabetes. Here, we present preliminary data of ADC and BOLD MRI. We evaluated contribution of differences between CKD and controls in R2 to those in R2*. We also evaluated other confounding factors such as age.

MATERIALS AND METHODS

Subjects: All procedures were performed with approval from the institutional review board and written subject consent prior to enrollment. MRI data were acquired in a group of stage 3 CKD with diabetes (N: 19; age: 68.3 ± 7.4 yr; eGFR: 49.5 ± 9.5 ml/min/1.73 m^2). Subjects were instructed not to take NSAID for 3 days and ACEi/ARB 1 day prior to MRI. For reference, similar data was acquired in a group of healthy subjects (self reported) with normal renal function (N: 12; age: 31.2 ± 13.2 yr; eGFR: 97.9 ± 18.3 ml/min/1.73 m^2). Both groups were instructed to fast after midnight on the day of the MRI and take half the dose of insulin if applicable.

MRI acquisition methods: All experiments were performed on a 3 Tesla whole body scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). The following imaging parameters were used for BOLD: mGRE, TR 62ms, TE 3.09 to 30.53ms, 8 echoes; and Diffusion: SE-EPI, TR/TE= 3000/78 ms, b = 200, 300, 500, 700, and 1000 s/mm^2. R2: SE-EPI. TR/TE= 2000 /54, 75, 100, 125 and 150ms, All acquisitions were made in the coronal orientation with 5 mm slice thickness. While BOLD MRI acquisitions were performed during breath-hold, Diffusion MRI and R2 were performed during free breathing.

MRI analysis methods: Regions of interest (ROI) were manually defined in the cortex using a custom image processing toolbox using Python (Python Software Foundation). ADC maps were analyzed by including the entire parenchyma as ROI, because of limited cortico-medullary differentiation.

Statistical methods: Group wise comparisons were performed using the Student's T-test to assess differences in cortical R2* and perfusion between the control and patient groups. Correlation analysis between R2*, R2, ADC, eGFR, and age was performed using Spearman's correlation coefficient. Linear regression analysis was performed to evaluate ADC and R2* dependence on eGFR. Additionally, multiple linear regression analysis was performed to adjust for age dependence.

RESULTS

Table 1 summarizes the differences in R2*, R2, and ADC values between the two study groups. Table 2 is the summary of pair-wise correlations between R2*, R2, ADC, eGFR and age (Only n=20 (CKD+control) had all R2*, R2, and ADC data available). Figure 1 shows the regression plots for both R2* and ADC as a function of eGFR. However, after adjusting for age, both R2* (slope = -0.08, p=0.12) and ADC (slope = 1.38, p=0.382) did not have a significant relationship with eGFR. Age was found to be a significant confounder.

Table 1: Summary of renal cortical R2*, R2, and ADC values

	CKD	Control	p
R2* (s^{-1})	29.5±9.2 (n=14)	21.5±3.4 (n=11)	**<<0.01**
R2 (s^{-1})	12.2±1.6 (n=14)	12.2±1.0 (n=11)	=0.67
ADC x 10^{-6} mm^2/s	1563.6±151.6 (n=19)	1671.9±73.8 (n=12)	**=0.01**

Table 2: Pair wise correlations

	R2*	R2	ADC	age	eGFR
R2*	1.00				
R2	ρ=0.24 p=0.33	1.00			
ADC	ρ = -0.18 p=0.46	ρ = -0.35 p=0.14	1.00		
age	**ρ =0.51** **p=0.03**	ρ = -0.15 p=0.54	ρ= -0.07 p=0.77	1.00	
eGFR	**ρ = -0.58** **p<0.01**	ρ = -0.01 p=0.98	ρ =0.24 p=0.31	**ρ = -0.62** **p<0.01**	1.00

ρ: Spearman's coefficient

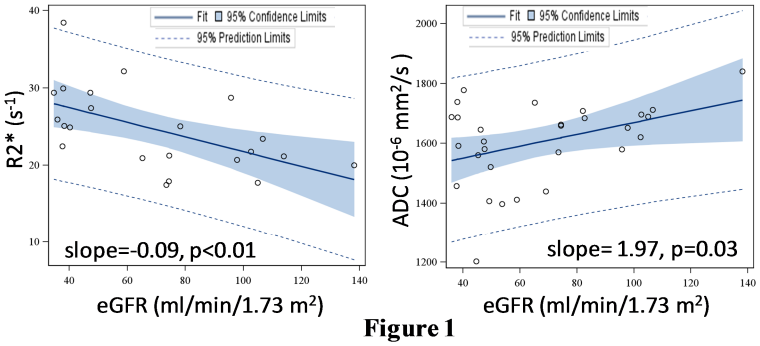

Figure 1

DISCUSSION

The study design minimized the heterogeneity by restricting to diabetics and only stage-3 CKD. Further to normalize the baseline physiology, all subjects were instructed to fast after midnight on the day of MRI. Availability of R2 data confirmed minimal differences between subjects with CKD and controls suggesting that observed differences with R2* are related to oxygenation status.

Both diffusion and oxygenation were reduced in subjects with diabetes and stage-3 CKD compared to controls. These results are consistent with previous reports [J Am Soc Nephrol. 2011 Aug;22(8):1429-34]. R2* was found to be significantly correlated with eGFR and age. A key limitation of the present study design is not including age matched control group. The smaller difference in ADC values in CKD compared to control may be due to the inclusion of only stage-3 CKD in this study and/or the choice of b values compared to a previous report [J Am Soc Nephrol. 2011 Aug;22(8):1429-34].