Multi-parametric MRI Evaluation of Chronic Kidney Disease – BOLD & Perfusion MRI

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INTRODUCTION

Chronic kidney disease (CKD) is a major healthcare issue with increasing prevalence and associated cost [1]. CKD leads to 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 [1,2]. Additional kidney injury markers are being evaluated along with imaging markers.

There is a growing interest in identifying markers that indicate the 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 [3]. 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 [4]. 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 [5,6,7]. Studies have identified some limitations including subject preparation, use of medications, controlling for confounding factors (e.g. R2* is inherently sensitive to R2), etc. Chronic hypoxia theory also suggests the cause for the increased hypoxia may be due to reduced blood supply. Arterial spin labeling (ASL) based renal perfusion MRI has shown reduced blood flow in CKD [8].

We present a preliminary analysis of BOLD and ASL perfusion MRI in a group of diabetics with stage 3 CKD

MATERIALS AND METHODS

Subjects: All procedures were performed with approval from the institutional review board and written subject consent prior to enrollment. A group of subjects with stage 3 CKD and diabetes were imaged (N: 16; age: 67.7 ± 7.4 yr; eGFR: 48.1 ± 12.5 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: 13; age: 32.9 ± 13.8 yr; eGFR: 96.5 ± 18.6 ml/min/1.73 m^2). Both groups were instructed to fast after midnight on the day of the MRI and take a half the dose of insulin if applicable.

MRI acquisition methods: All experiments were performed on a 3T whole body scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). Imaging parameters: mGRE, TR 62ms, TE 3.09 to 30.53ms, 8 echoes, slice thickness 5mm; and ASL: FAIR, post labeling delay: 1.5 s (healthy) or 2.0 s (patient), slice thickness 8 mm; with a resolution 1.48 x 1.48 mm. Both acquisitions were made in the coronal orientation. MRI analysis methods: Regions of interest were manually defined in the cortex using a custom image-processing library written in Python.

Statistical methods: Group wise comparisons were performed using the Mann-Whitney-U test to assess differences in cortical R2* and perfusion between the control and patient groups. Cohen's d value (> 0.8 represents Large effect size) is reported in addition to p values for each comparison. Correlation analysis was performed between R2* and ASL measurements using Spearman's correlation coefficient. Linear regression analysis was performed to evaluate ASL and R2* dependence on eGFR. Additionally, multiple linear regression analysis was performed to adjust for age dependence.

RESULTS

Table 1 summarizes the differences in perfusion and R2* values between the two study groups. Table 2 is the summary of pair-wise correlations between R2*, Perfusion, eGFR and age. Figure 1 shows the regression plots for both perfusion and R2* as a function of eGFR.

Table 1: Summary of renal cortical perfusion & R2* values

	CKD	Control	p	d
Perfusion (ml/100g/min)	117±36	203±65	<0.01	1.29
R2* (s^{-1})	28.9±8.5	21.2±3.6	<0.01	-1.1

Table 2: Pair-wise correlations

	R2*	eGFR	Perfusion	Age
R2*	1.00			
eGFR	-0.64	1.00		
Perfusion	-0.45	0.75	1.00	
Age	0.64	-0.70	-0.74	1.00

In all cases p≤0.01

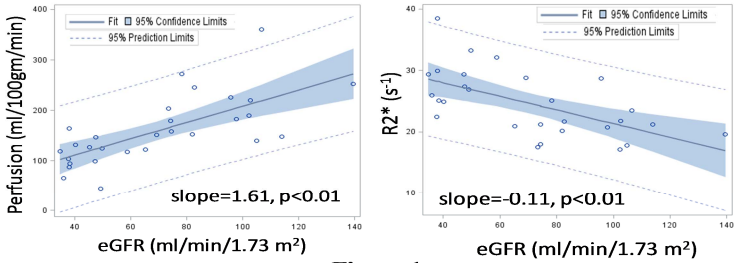

Figure 1

Since R2* and perfusion were found to be significantly correlated with both eGFR and age, additional multiple regression analysis to adjust for age was performed. Perfusion showed a significant relationship even after adjusting for age (slope=1.20, p=0.02). R2* showed only a marginally significant relationship after adjusting for age (slope = -0.07, p=0.09). Age was found to be a significant confounder.

DISCUSSION AND CONCLUSION

The study design minimized the heterogeneity by restricting to diabetics and only stage-3 CKD. To further normalize the baseline physiology, all subjects were instructed to fast after midnight on the day of MRI. Both perfusion and oxygenation were reduced (*i.e.* ↑R2*) in subjects with diabetes and stage-3 CKD compared to controls. These results are consistent with previous reports, which individually evaluated BOLD and ASL perfusion MRI [8,9]. *This is the first study to evaluate both these measurements together*. The significant negative correlation between R2* and perfusion suggests that decreased perfusion may be responsible for increased hypoxia and hence support the chronic hypoxia theory. Both perfusion and R2* were found to be significantly correlated with eGFR and age. A key limitation of the present study design is not including an age and sex matched control group. A previous study reported significant gender based differences in R2* but no age dependence [7]. Another previous study that evaluated age related differences with renal BOLD MRI suggested no significant differences in cortical R2* values between young (25 to 31) and elderly (59 to 79) women [10]. In conclusion, the reductions in renal perfusion and oxygenation in subjects with diabetes and moderate CKD are consistent with chronic hypoxia theory. Note that the reported differences may actually be lower compared to those in progressors because only 1 in 3 with CKD stage 3 progress toward end stage renal disease [3].

REFERENCES: [1] PMID: 21840587, [2] PMID: 20040867, [3] PMID: 19176795, [4] PMID: 16291837, [5] PMID: 22237750, [6], PMID: 22244540, [7] PMID: 24760031, [8] PMID: 22766911, [9] PMID: 21757771, [10] PMID: 9893139