Quantitative Multi-parametric MRI Evaluation of Kidneys in Subjects with CKD

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INTRODUCTION

Chronic kidney disease (CKD) is considered to be an irreversible and usually progressive reduction in kidney function. Staging of CKD was proposed by National Kidney Foundation in 2002 primarily based on estimations of glomerular filtration rate (GFR) [*Am J Kidney Dis* 2002;39:S1-266] in order to stratify patients at risk under five stages. A key pitfall of this system is not taking age associated changes in GFR into consideration [*J Am Soc Nephrol* 2008;19:844-6]. It is now well accepted that stages 1 and 2 do not really involve kidney disease in subjects without specific risk factors for progressive disease such as diabetes or hypertension. It is very likely that many individuals with early stage 3 disease may also fall into this category. These issues not only unduly overestimate the prevalence of disease but also influence patient management. This has led to interest in development of alternate biomarkers [*Adv Chronic Kidney Dis* 2010;17:469-79] and combination of markers [*JAMA* 2011;305:1593-5] that may identify subjects at risk of progression.

Here, we hypothesize that renal volume, intra-renal oxygenation and apparent diffusion coefficient (ADC) could be used as imaging biomarkers in CKD. Specifically, a cross-sectional study was performed to compare these measurements in healthy subjects, subjects with different stages of CKD and a group of anemic subjects with no renal disease. The staging of CKD was performed based on estimated GFR at recruitment and later using GFR measurements by iothalamate.

METHODS

All procedures were performed with IRB approval and written subject consent. 47 subjects participated to-date: healthy control (n=10), anemic (n=7, Hb levels = 11.1 ± 0.69 g/dl), CKD stage 2 (n=10), 3 (n=10), 4 (n=7), and 5 (n=3) by eGFR. Eleven had diabetes and twelve were talking ACEi / ARBs.

All MRI data was acquired on a 3.0 T whole body scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). **Renal Volume** was measured based on 3D images acquired with a gradient echo sequence (TR/TE/Flip Angle/BW/slice/Matrix = 3.5 ms/1.6 ms/9° /780 Hz/pxl/2-3 mm). **Diffusion weighted imaging** was performed using echo planar imaging (EPI) (TR/TE/Flip Angle/BW/slice/Matrix = 3000 ms/78 ms/90°/1630 Hz/vxl/5 mm/192 x 154 and 36 to 42 cm FOV with 80% phase FOV). Diffusion sensitizing gradients were applied along three different directions for calculating diffusion tensor which is a direction independent measure. Four different b values in the range of 50 - 1000 s/mm^2 were acquired and six acquisitions were averaged for improved signal to noise and to minimize motion artifacts. **BOLD MRI** data was acquired using breath-hold multiple gradient echo sequence with following parameters: FOV = 360 x 245mm, No. of Slice = 5, Slice thickness = 5.0mm, Matrix = 256 x 256, TR = 62ms, No. Echo = 8 equally spaced (3.09–32.3ms), NEX = 1. BOLD MRI measurements were made at baseline and after *iv* administration of 20 mg of furosemide to inhibit *Na* reabsorption along the medullary thick ascending limbs which accounts for about 65% of renal O2 consumption.

Renal volumes were measured by manual tracing of the renal boundary on each slices and then using voxel counting (Image J, NIH). T_2^* or R_2^* maps, and ADC maps were generated on the scanner platform and multiple ROIs were selected in cortex and medulla of both kidneys on each slice.

RESULTS

Summary of Measurements			
	Control (mean ± sd)	CKD (mean ± sd)	p value
Renal Volume (ml)	334.9±21.0	227.9±20.4	< 0.05
R2* Cortex (s^{-1})	21.4±3.6	25.5±5.5	0.006
R2* Medulla (s^{-1})	40.2±7.0	45.7±9.7	0.03
ΔR2* Medulla (s^{-1}) (furosemide)	11.9±4.9	5.1±5.7	0.003
ADC Cortex (x10^{-3} mm^2/s)	2.3±0.35	1.9±0.4	0.003

Table 1 summarizes the different measurements in all subjects with CKD compared controls (healthy + anemic).

Figure 1: (left) Preliminary data obtained in patients with CKD compared to controls. Higher R2* values indicate increased levels of hypoxia in mild to moderate CKD. Note reduced response to furosemide in CKD. This is consistent with the lower GFR in patients with CKD resulting in less sodium load to mTAL. ADC (**middle**) measurements showed a reduction in subjects with CKD with significance reaching in CKD-2. R2* values were correlated with ADC (p<0.05) (**right**).
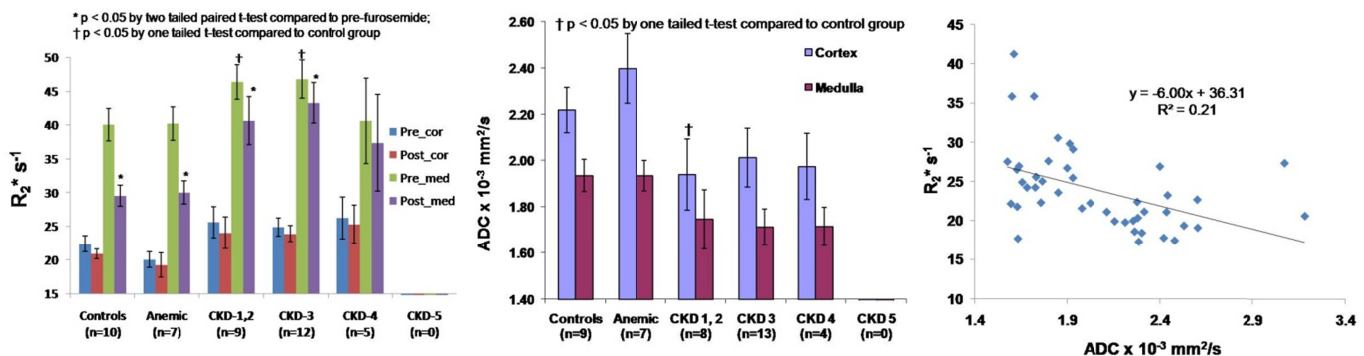
DISCUSSION AND CONCLUSION

- Tissue volume measurements by MRI were found to be significantly correlated with GFR (data not shown).
- While GFR by iothalamate was significantly correlated with estimated GFR (data now shown), the staging changed in 11 of the 27 subjects where GFR measurements were available.
- Cortical ADC measurements were lower in CKD, probably related to fibrosis [*JASN* 22: 1429–1434, 2011]. The b values used in this study may have introduced weighting towards the tubular component. B values above 300 s/mm^2 may be preferable for measuring tissue ADC [*Radiology* 2010;255:772-80].
- BOLD MRI measurements in patients with CKD suggest increasing levels of hypoxia both in cortex and medulla. The increased R2* values reached statistical significance compared to controls in mild to moderate CKD. In addition, a lower response to furosemide in medullary R$_2$* was observed in CKD, suggesting the increase in hypoxia is not related to increased O2 consumption to support *Na* reabsorption which is consistent with decreased GFR.
- The correlation between R2* and ADC measurements suggest higher levels of hypoxia associated with higher level of fibrosis and is consistent with previous report [*JASN* 22: 1429–1434, 2011] .