Diffusion-weighted imaging detects early progression of renal fibrosis in a murine model of unilateral ureteral obstruction

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Purpose: In the United States, more than 26 million people suffer from chronic kidney disease (CKD)[1]. Renal fibrosis is the most common cause of CKD[2], and has been investigated with an animal model of unilateral ureteral obstruction (UUO). In this model, the urinary flow is obstructed in one kidney by ligating a ureter, thus increasing hydrostatic pressure of the lumen, and eventually resulting in renal fibrosis within approximately one week after the ligation[3]. The progress of renal fibrosis can be monitored by renal biopsy or non-invasive diffusion-weighted imaging (DWI)[4]. Apparent diffusion coefficient (ADC), a quantitative DWI biomarker, decreases when water movement is more restricted due to increased cell density during the progress of renal fibrosis. The purpose of this study was to evaluate ADC as a reliable imaging biomarker for quantitative assessment of renal fibrosis in an animal model.

Materials and Methods: Two groups of mice (n=5 for group 1; n=4 for group 2) were used. On day 0, group 1 had surgery for UUO, while group 2 was used as a sham group (only incision was applied). T2W MRI and DWI were performed on days 1, 3, and 7 using a 9.4T system (BioSpec, Bruker BioSpin) equipped with a surface coil as receiver. An MR imaging compatible small-animal respiratory gating device (SA instrument, Stony Brook, NY) was used during imaging. All mice were anesthetized with isoflurane (1-2%) during imaging. For kidney volume measurement, axial T2-weighted images were acquired with a T2-weighted fast spin echo sequence (rapid acquisition with relaxation enhancement). The parameters were as follows: TR=3000ms, TE=32ms, rare factor=4, FOV=30×30mm, Matrix size=128×128, 25 slices, slice thickness=1mm, four signals averaged, fat suppression. Diffusion weighted imaging was obtained with a multishot spin echo echo-planar imaging sequence. Three b factors (100, 300, and 700 s/mm^2) were applied in the x direction with the following parameters; TR=3000ms, TE=37ms, diffusion separation time=16ms, diffusion gradient duration=6ms, FOV=30×30mm, Matrix size=144×144, four segments, one 1-mm coronal slice delineating both kidneys. On T2-weighted images, the renal parenchyma (cortex and medulla) and pelvis on both the UUO side and the contralateral side were manually segmented, and measured by ImageJ (version 1.45i; NIH, Bethesda, MD). The ADC value of the renal parenchyma was measured on ADC maps. Statistical difference between groups 1 and 2 was analyzed with unpaired two-tailed Student t test.

Results: The mean volume of renal pelvis and parenchyma was normalized to that on day 1, and then the changes were given in percentage. The volume of renal pelvis on the UUO side increased to 224.5±32.1% (mean±SE) on day 3 and to 509.7±62.0% on day 7, respectively; the volume of renal pelvis on the contralateral side remained the same (figure 1). The volume of renal parenchyma on the UUO side was significantly different from that on the contralateral side on both day 3 and day 7 (p=0.020 and 0.003, respectively). The volume of renal parenchyma on the UUO side increased to 100.7±3.8% on day 3 and decreased to 79.5±5.0% on day 7, respectively; the volume of renal pelvis on the contralateral side increased to 107.5±6.7% on day 3 and 106.1±7.1% on day 7. The volume of renal pelvis on the UUO side was significantly different from that on the contralateral side on day 7 (p=0.020), but not on day 3 (p=0.4). Relative ADC of renal parenchyma was defined as ADC on the ipsilateral side divided by that on the contralateral side. Relative ADC in group 1 was 89.9±1.2% on day 1, 73.7±2.7% on day 3, and 67.8±6.7% on day 7, respectively; Relative ADC in group 2 was 95.8±1.9% on day 1, 103.6±2.4% on day 3, and 98.5±6.2% on day 7, respectively (figure 2). Relative ADC in group1 was significantly different from that in group 2 on days 3 and 7 (p<0.001, and p=0.048, respectively), but not on day 1 (P=0.05).

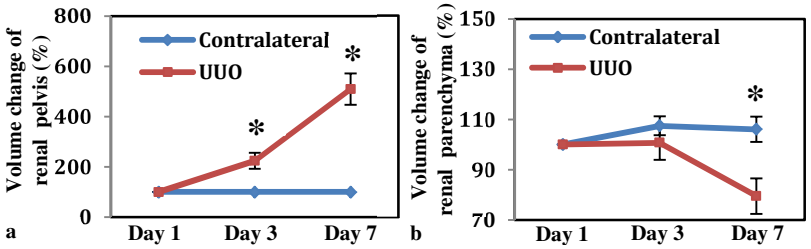

Figure 1: Volume change of renal pelvis (a) and parenchyma (b) normalized to that on day 1. All data are expressed as mean±SE. P<0.05 (*) was considered significant different.

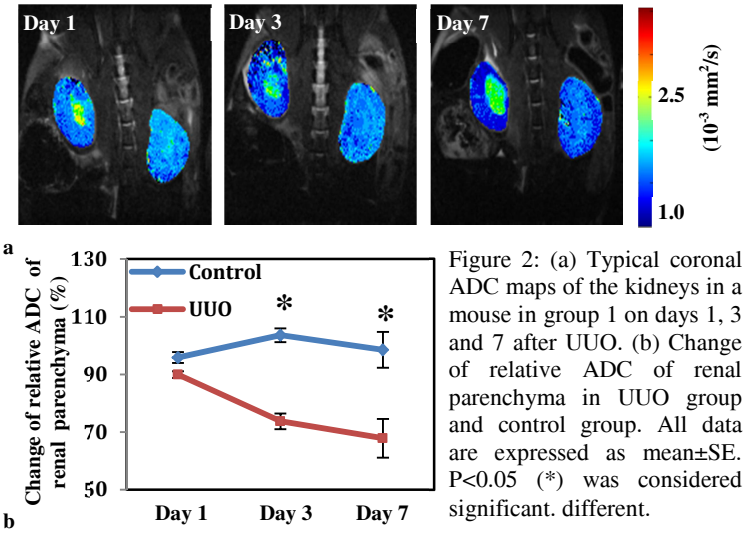

Figure 2: (a) Typical coronal ADC maps of the kidneys in a mouse in group 1 on days 1, 3 and 7 after UUO. (b) Change of relative ADC of renal parenchyma in UUO group and control group. All data are expressed as mean±SE. P<0.05 (*) was considered significant. different.

Conclusion: Relative ADC of renal parenchyma decreased significantly in the UUO group as early as day 3 after surgery when compared with that in the control group. Our results suggest that the ADC change of renal parenchyma could be a reliable imaging biomarker to assess the progression of renal fibrosis in a murine UUO model.

REFs: [1] Coresh, JAMA 2007; 298(17):2038-2047. **[2]** Hewitson, Am J Physiol Renal Physiol 2009; 296(6):F1239-F1244. **[3]** Kawai, Lab Invest 2009; 89(1):47-58. **[4]** Osamu, Radiology 2010; 255(3):772-780.