In vivo assessment of fatty diabetic kidney by diffusion weighted and BOLD MRI in rats

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Target audience: Researchers and clinicians interested in imaging-function correlates in the kidney.

Purpose: Type II diabetes leads to microvascular complications including nephropathy [1]. The Zucker diabetic fatty (ZDF) rat is a model of type II diabetes and metabolic syndrome that exhibits progressive renal fibrosis. There is increasing interest in using diffusion-weighted MR imaging (DW-MRI) to assess fibrosis in the kidney. Our previous studies in murine models of unilateral ureteral obstruction and dietary phosphate overload have shown excellent correlation between MRI and kidney histopathology, where the apparent diffusion constant (ADC) determined by DW-MRI inversely correlates with the severity of fibrosis [2,3]. It has also been shown that blood oxygen level dependent (BOLD) MRI measures renal hypoxia where hypoxic tissue shows lower T2* [4]. The purpose of this study was to test our hypothesis that a combination of DW- and BOLD-MRI would reflect histopathological and functional changes *in vivo* in the kidney.

Materials and Methods: We used 8-month old male ZDF *fa/fa* and matched lean (+/+) control animals (N=4). MRI studies were conducted in a 3 Tesla (T) whole-body human scanner (Achieva™, Philips Medical Systems, Best, Netherlands) with a small solenoid coil (I.D. 63 mm). Under anesthesia with 1.5-2% isoflurane mixed in 100% oxygen, the animals were placed supine with the abdomen centered with respect to the center of a RF coil. Low-resolution localizer imaging was first performed on the abdominal region to confirm the location and orientation of the kidneys. T2 weighted multi-slice coronal images (T2WI) encompassing both kidneys were obtained with a fast spin echo sequence (TR/TE = 2000/80 ms, 80 mm FOV, 200×180 matrix, 2 mm slice thickness, gapless, 4 NEX). On single 2 mm coronal slab delineating both kidneys, multi-echo gradient echo sequence was conducted to measure T2* where ten echoes at different TEs from 6.8 ms to 68 ms were collected. Other parameters were: TR = 200 ms, 80 mm FOV, 100×100 matrix, flip angle = 18º, NEX = 8, affording a total scan time of 2.6 min. Subsequently, diffusion weighted imaging (DWI) was conducted in the same imaging slab with multi-shot EPI sequence with four b-values of 0, 350, 600, and 1000 s/mm^2. Other parameters were: TR/TE = 1000/77 ms, 80 mm FOV, 100×84 matrix, EPI factor = 21, NEX = 1, affording a total scan time of 2.5 min. The T2* and ADC maps were generated pixel by pixel using an image analyze software (ImageJ) by fitting to the function, $S_1=S_2 \times \exp(-TE \times T2^{*-1})$ for T2*, and $S_1=S_2 \times \exp(-b \times ADC)$ for ADC, where S_1 and S_2 are signal intensities at different TEs (6.8~68 ms) or b-values (350~1000 s/mm^2), respectively. T2* and ADC were measured in the renal cortex on three regions-of-interests (ROIs, size = 2 mm^2) in each kidney avoiding the area affected by susceptibility artifacts, and an average value of six T2*s and ADCs was defined as the representative of the animal. Values are expressed as mean ± standard deviation (SD).

Results and Discussion: Blood glucose levels were 145.3±15.4 and 438.0±230.5 (P<.05) in the +/+ and *fa/fa* groups. Figure 1 shows representative T2WI, T2* and ADC maps of the +/+ and *fa/fa* rats. In all *fa/fa* rats, marked dilatation of the renal pelvis and heterogeneous signal intensity in the renal parenchyma were observed on T2WI. The T2* values (ms) of renal cortex in the *fa/fa* group (10.08 ± 0.94) were lower than in the +/+ group (40.77 ± 2.58, P <.0001, Fig.2A), indicative of a more hypoxic renal cortex in *fa/fa* rats. This is compatible with previous studies showing normal glomerular filtration and tubular Na reabsorption (surrogate O_2 consumption) in the face of reduced renal plasma flow (surrogate O_2 supply) in ZDF rats [5]. The mean renal ADCs (× 10^{-3} mm^2/s) was also ~35% lower in the *fa/fa* group (1.69 ± 0.47 vs. 2.65 ± 0.40, P <.05, Fig.2B), compatible with the marked histologic renal fibrosis. These results would correspond to hydronephropathy, tubular atrophy and interstitial fibrosis, which have been shown predispose to increased risk of loss of renal function [6]. The study suggests that a combination of DW- and BOLD-MRI has the potential to provide biomarkers for *in vivo* to characterize and predict histopathological and functional changes in diabetic kidney abnormalities.

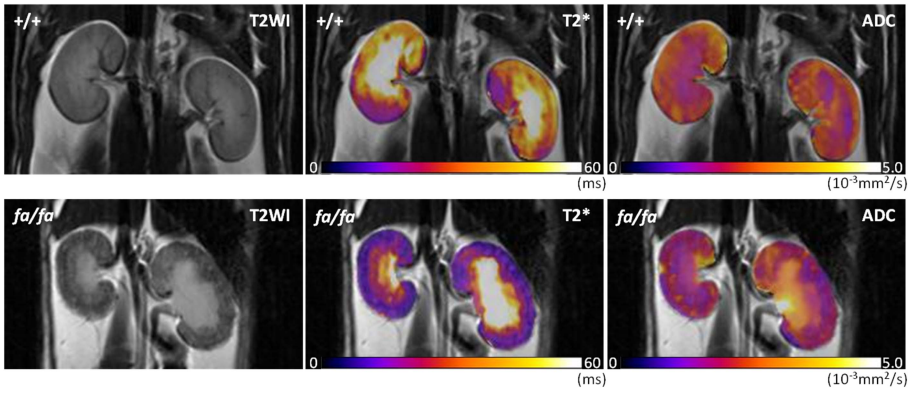

Fig 1. Typical T2WI (left), T2* map (middle) and ADC map (right) of the lean group (upper) and the fatty group (bottom). Dilatation of renal pelvis and heterogeneous signal change are observed in the fatty rat on T2WI. Both T2* and ADC values decreased obviously in the renal cortex of the fatty group.

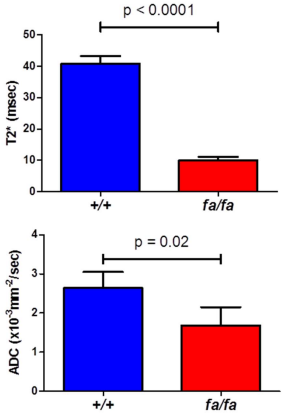

Fig 2. Comparison of T2* (upper) and ADC (bottom) between two groups. P value, by student's t-test.

References: 1. Baynes et al. Oxidative Medicine and Cellular Longevity 2;328 (2009). 2. Togao, et al. Radiology 255;772 (2010). 3. Doi, et al. JBC 11:8655-65 (2011). 4. Inoue et al. J Am Soc Nephrol 22;1429 (2011). 5. Alavi et al. Clin Nephrol 43;318 (1995). 6. Chander et al. J Am Soc Nephrol 15;2391 (2004)