Mapping Murine Diabetic Nephropathy: QMT, CEST and Fat Imaging

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Target audience: Investigators who are interested in quantitative MRI or diabetic nephropathy (DN).

Purpose: Mouse models of diabetes (e.g. regular db/m, moderate type II diabetic db/db and advanced diabetic db/db eNOS-/-) provide especially valuable opportunities for evaluating the role of quantitative MRI as biomarkers of renal nephropathy. The objectives of this study were three fold. The first was to validate and evaluate the reproducibility of quantitative magnetization transfer (qMT), chemical exchange saturation transfer (CEST) and fat imaging for assessing diabetic kidney disease. The second was to determine the potential of these quantitative MRI approaches to distinguish moderate and advanced DN. An ultimate goal is to understand the progression of fibrosis, and lipid and glucose deposition in accelerated diabetic kidney disease.

Methods: Mice were scanned on an Agilent 7T MRI system using a Doty 38 volume coil (anesthetized with isoflurane 1.5-2%). For qMT data acquisition, two data sets were collected with 12 different frequency offsets (TR 24 ms, flip angle =7°, 48 acquisitions), using Gaussian-shaped saturation pulses (flip angles = 220° and 820°, pulse width = 12 ms). Frequency offsets ranged between 800 Hz and 80 kHz with a constant logrithmic interval. The qMT parameters including pool size ratio (PSR) were calculated using a 2-pool Ramani model [1]. The qMT protocol was applied along with 3-point Dixon fat imaging and CEST imaging (61 RF offsets from -5 to 5 ppm). WASSR (Water Saturation Shift Referencing) correction and conventional asymmetric analyses were applied to calculate MTR_{asym} map, and FattyRiot approach [2] was applied to reconstruct water and fat images.

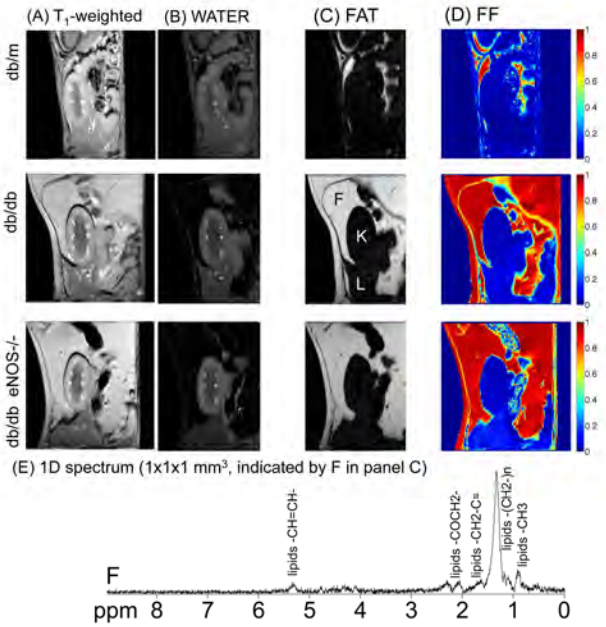

Figure 1. (A) T_1-weighted image, (B-C) water and fat images from reconstruction, (D) fat fraction (FF) map, and (E) characteristic 1D spectrum in fat predominant region.

Results: The fat fraction (FF) surrounding the kidneys of diabetic mice was substantially higher than that found in controls (**Fig. 1**). This is in agreement with reports of human studies. The averaged FF value in the cortex of kidney increased by 105±13% and 129±12% in db/db and db/db eNOS-/- mice respectively. Images with magnetization transfer contrast (MTC) clearly depicted urine retention associated with diabetic kidney disease (**Fig. 2B**). Compared to regular db/m mice, the pool size ratio increased in the cortex, but decreased in medulla and papilla of diabetic mice (**Fig. 2**). Compared to that of db/m mice, the PSR of cortex in db/db eNOS-/- increased by more than 15% while that in db/db mice increased by ~5%. Very high T_{2a} was observed for the low PSR region around inner medulla and papilla in both diabetic models, which indicates urine retention. Positive MTR_{asym} at ~1.2 ppm RF offsets could be due to high glucose level associated with DN (**Fig. 3**). Both MT and CEST parameters were able to distinguish moderate and advanced diabetic kidney disease. Fat imaging was sensitive to diabetic kidney disease, but it could not detect significant difference in FF between kidneys of moderate and advanced DN.

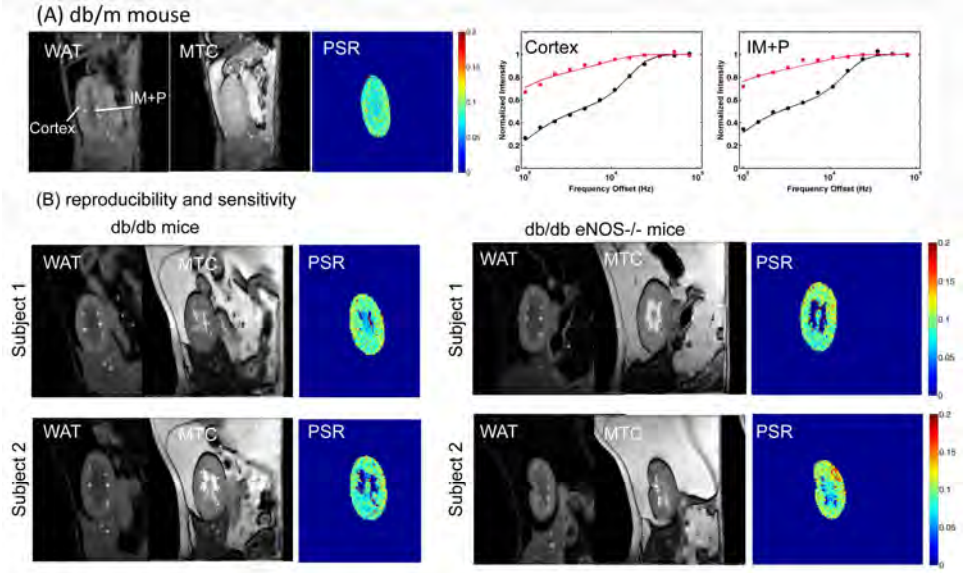

Figure 2. (A) PSR from model fitting of MT spectra. (B) Sensitivity of PSR to DN.

Discussion: Our data demonstrate the potential role of qMT, CEST and fat imaging for determining cellular and molecular changes associated with DN, including fibrosis, glucose level changes and lipid deposition in murine models of diabetic nephropathy. The PSR and glucose levels vary significantly in the cortex of kidneys between moderate and advanced diabetic kidney disease. These findings indicate that qMT, CEST and fat imaging could provide robust and sensitive markers of disease progression in DN.

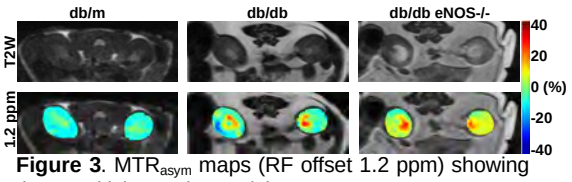

Figure 3. MTR_{asym} maps (RF offset 1.2 ppm) showing the sensitivity to glucose/glycogen.

References:

1. Ramani A, Dalton C, Miller DH, Tofts PS, Barker GJ: **Precise estimate of fundamental in-vivo MT parameters in human brain in clinically feasible times**. *Magn Reson Imaging* 2002, **20**(10):721-731.
2. Berglund J, Kullberg J: **Three-dimensional water/fat separation and T2* estimation based on whole-image optimization--application in breathhold liver imaging at 1.5 T**. *Magn Reson Med* 2012, **67**(6):1684-1693.