Assessment of Diabetic Nephropathy in Mouse Models: GlucoCEST

Feng Wang[1,2], David Kopylov[3], Zhongliang Zu[1,2], Keiko Takahashi[4,5], John C. Gore[1,2], Raymond C. Harris[4,5], Takamune Takahashi[4,5], and C. Chad Quarles[1,2]

[1]*Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States,* [2]*Institute of Imaging Sciences, Vanderbilt University, TN, United States,* [3]*Drexel University, PA, United States,* [4]*Vanderbilt O'Brien Mouse Kidney Physiology and Disease Center, Vanderbilt University, TN, United States,* [5]*Division of Nephrology and Hypertension, Vanderbilt University, TN, United States*

Target audience: Investigators who are interested in diabetic kidney disease or CEST.

Purpose: Diabetic nephropathy (DN) is the leading cause of renal failure. DN is associated with changes in tissue metabolites (e.g. glucose, glycogen, glycosaminoglycan) that exhibit significant chemical exchange saturation transfer (CEST) effects in MRI. Here we evaluated the utility of CEST imaging to differentiate moderate and advanced diabetic kidney disease and its sensitivity to assess the progression of DN.

Methods: Mice were anesthetized (isoflurane 1.5-2%) and scanned on an Agilent 7T MRI system using a Doty 38 volume coil. CEST images were acquired using a continuous wave (CW) irradiation pulse (5.0 s, 1.0 μT) followed by a 2-shot SE-EPI readout with TR of 7.5 s, TE of 17.6 ms, resolution at 0.5x0.5x1 mm^3, RF offsets from -1500 Hz to 1500 Hz with an interval of 50 Hz. Fat saturation was applied at RF offset -1042 Hz using a sinc-shaped pulse. A control scan was performed with an RF offset of 100 kHz. MTR_{asym} maps were obtained using conventional asymmetric analysis after WASSR (water saturation shift referencing) correction. A peak fitting algorithm was used to decompose overlapped amide (IV), amine (III), hydroxyl (II), direct saturation on free water (DS), and aliphatic (I) peaks around 3.5, 2.2, 1.2, 0 and -3.3 ppm RF offsets, respectively (Fig. 1A). The averaged regional z-spectrum was fit as the sum of 5 peaks of Lorentzian bands. Sensitivity of CEST imaging was evaluated across regular db/m, moderate type II diabetic (db/db), and advanced diabetic db/db eNOS-/- models at the age of week 16, and longitudinally in db/db mice at ages 8, 12, 16, 20 and 24 weeks.

Results: Amide (IV), amine (III) and hydroxyl (II) CEST signals from metabolites, nuclear Overhauser enhancements (NOE) from mobile aliphatic macromolecules (I), and magnetization transfer (MT) effects from immobile macromolecules such as proteins were detected in kidney using z-spectra (Fig. 1). In general, the region of inner medulla and papilla (IM+P) showed higher hydroxyl signal, lower solid MT effects and NOE than outer medulla (OM) and cortex in mouse kidney. This could be due to partial volume effects from urine. CEST contrast at ~1.2 ppm RF offset (peak II) and NOE around -3.3 ppm RF offset (peak I) showed significant regional differences in kidneys of diabetic and regular models. The variation in the hydroxyl peak at RF offset ~1.2 ppm is mainly associated to glucose/glycogen levels. Compared with non-diabetic db/m mice (Fig. 1B-D), the glucose/glycogen signals were increased by 70.1% in outer medulla (OM) in db/db kidneys ($p<0.05$) at 16 wks, with much greater increases in OM (by 181%) and cortex (by 109%) in db/db eNOS-/- kidneys ($p<0.05$). Glucose/glycogen signals in IM+P were increased comparably in db/db and db/db eNOS-/- kidneys ($p<0.05$). Longitudinally, db/db mice exhibited moderate increases ($p=0.351$) in glucose/glycogen levels in IM+P at 8 wks, with significant and progressive increases in IM+P, OM, and cortex at 12, 16 and 24 wks respectively (Fig. 2).

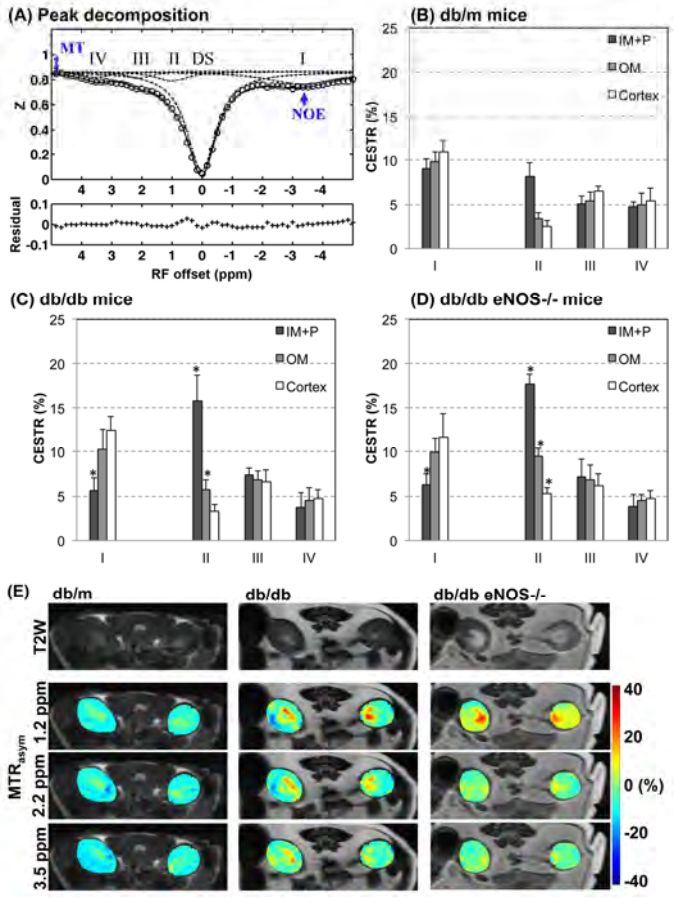

Figure 1. (A) Lorentzian band fitting of the averaged CEST spectra of regular db/m mouse kidney. (B-C) Comparison of the averaged peak amplitude (CESTR) across disease model (n=12 for db/m and n=6 for db/db and db/db eNOS-/- at the age of 16 weeks). *p < 0.05 vs. corresponding peak in the regular mice. (E) MTR_{asym} maps.

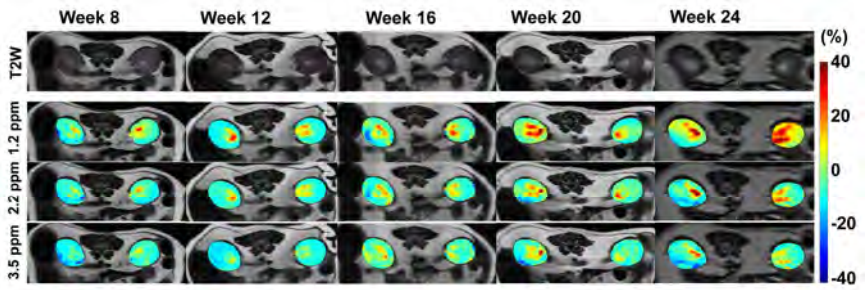

Figure 2. Longitudinal comparison of MTR_{asym} in db/db mice.

Conclusions: The characteristic CEST features observed herein could enable the non-invasive detection of DN and differentiation between moderate (db/db) and advanced (db/db eNOS-/-) DN, and assist the effects of interventions.