MRI detection of glycogen in vivo in diabetic mice at 3 tesla: feasibility and initial experience

M. Kim[1], Q. Chan[1,2], J. Y. Lau[3], S. K. Chung[3], and P-L. Khong[1]
[1]Departement of Diagnostic Radiology, The University of Hong Kong, Hong Kong, Pokfulam, Hong Kong, [2]Philips Healthcare, Hong Kong, [3]Department of Anatomy, The University of Hong Kong

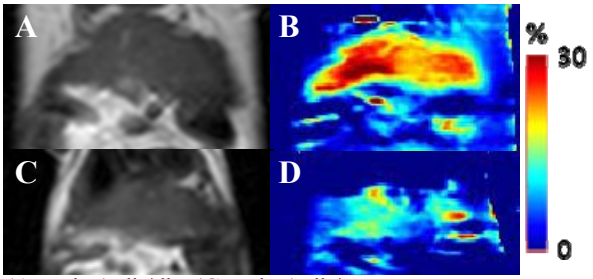
Objective: Diabetes is one of the most common and serious syndromes characterized by disordered metabolism and hyperglycemia and can be a leading cause of other complications [1]. It has been suggested that glycogen content may be abnormal in conditions such as type-2 diabetes (T2D), accounting for about 90% of all cases of diabetes. Thus, methods to quantify glycogen *in vivo* will be a key to understanding the pathophysiology of T2D. Presently, the only non-invasive approach to study glycogen levels and/or glycogen metabolism *in vivo* is magnetic resonance spectroscopy (MRS) using natural abundance 13C-labeled isomers of glycogen in situ. However, requirement of special hardware for 13C MRS limits its wide clinical application. Recently, a water-signal-based glycogen imaging approach called chemical exchange saturation transfer (CEST) was suggested to detect glycogen in *ex vivo* mouse liver [2]. In present study, we tested feasibility of in vivo glycogen detection in diabetic mouse model using CEST imaging.

Materials and Methods: All animal experiments were approved by the local animal research ethics committee. Experiments were conducted in two separate groups of ten C57BL6 mice (male; age range of 8 to 12 weeks): 5 diabetic (db/db) and 5 normal (db/m). Free access to food and water until the time of MRI imaging were allowed. MRI was performed using a Philips 3 tesla Achieva scanner (Philips Healthcare, Best, The Netherlands). RF was transmitted using the body coil and signal was received using a small animal coil with 5 cm-diameters. During imaging, the animal was kept under the optimum dose of anesthesia (approximately 1% isoflurane with air and oxygen mixed at a 3:1 ratio). The imaging volume was centered at the liver. For T_1-weighted (T1w) imaging, 12 multi-slices in coronal were acquired with nominal in-plane resolution of 0.3x0.3 mm^2. Other parameters: repetition time (TR), 400-800 ms; echo time (TE), 10 ms; flip angle (FA), 90 degrees; multi-shot turbo spin echo (TSE) factor, 3; FOV, 40x40 mm^2; NSA, 2; total scan time, 58 sec. For series of consecutive water saturation shift referencing (WASSR) [3] as for field inhomogeneity correction and CEST scans, saturation was accomplished using a block pulse before the TSE acquisition. Single-slice TSE imaging in coronal plane was performed using 36 and 52 offsets for WASSR (range: 1 to -1 ppm) and CEST (range: 4 to -4 ppm), respectively. Imaging parameters: TR, 2000 ms; TE, 9 ms; TSE factor, 34; slice thickness, 2 mm; nominal in-plane resolution, 0.3x0.3 mm^2. RF saturation pulses: 100 ms and 0.1 μT for WASSR, and 400 ms and 0.75 μT for CEST). Total scan time was 2 min. 26 sec. for WASSR and 3 min. 30 sec. for CEST. Five CEST acquisitions were obtained and averaged in order to improve signal-to-noise ratio. For data analysis, a custom-written program in Matlab (Mathworks, Natick, MA, USA) was used. For each voxel, CEST curves were shifted using the frequency shift from the WASSR map. The magnitude of the CEST effect was quantified as $MTR_{asym} = S(\text{-freq})/S_0 - S(\text{freq})/S_0$ where S and S_0 are the saturated and non-saturated intensities. CEST signal was integrated from 0.5 to 1.5 ppm, where hydroxyl groups resonate.

Results: Fig. 1 illustrates representative CEST color maps, comparing the CEST signal intensity of a liver between db/m and db/db mice. The ROI-based mean CEST values with standard deviation (SD) measured from a liver for each mouse show consistent group difference in all mice (Fig. 2). The group averaged CEST values of all mice were 33.14 % (± SD = 4.27 %) and 20.43 % (± SD = 4.27 %) for db/db and db/m, respectively. CEST values were significantly greater in the db/db than db/m (two-tailed paired Student's t-test, $p < 0.005$).

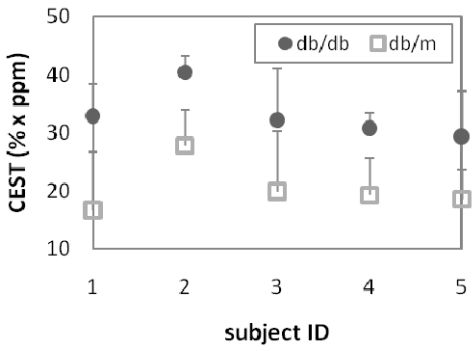
Conclusion: The results of this study suggest that *in vivo* CEST quantification in mouse liver is feasible in a clinical scanner. Its non-invasive detection in situ will help to understand the physiological and metabolic mechanism of glycogen and will further have tremendous utility in the study of T2D in humans.

Fig. 1



(A and B) db/db; (C and D) db/m;
(A and C) T1w; (B and D) CEST map at 1 ppm.

Fig. 2



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