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Introduction: Chemical Exchange Saturation Transfer (CEST) is a molecular imaging technique that allows indirect detection of protons associated with mobile proteins. Recently a CEST application called glycoCEST has been used to detect glycogen content *in vivo* (Jones CJ, et al PNAS 2008). With glycoCEST, the -OH protons of glycogen are saturated, transfer the saturation to bulk water by way of chemical exchange which reduces the bulk water signal in proportion to the glycogen content. Because the –OH protons resonate 0.75 – 1.25 ppm downfield of water, a plot of the saturation effect vs. the offset frequency of the saturating RF field (the z-spectrum) is asymmetric.

Using glycoCEST to measure glycogen content may provide several advantages to conventional approaches (e.g. ^{13}C MRS or percutaneous biopsy), including improved temporal and spatial resolution; more widespread availability of the necessary equipment; and the ability to measure glycogen in multiple muscles simultaneously. A potential challenge in glycoCEST imaging is the relatively small chemical shift difference between the OH protons and the bulk water resonance. In this case a CEST effect may not be easily determined from the z-spectrum due to direct saturation of the water resonance (Smith SA, et al MRM 2009). However, at ultra-high fields such as 7T, the spectral resolution between the glycogen OH protons and the bulk water protons is larger, which facilitates an easier detction of the glycogen driven CEST effect. The larger chemical shift difference, coupled with the improved signal-to-noise ratio at high field, makes 7T a logical choice for glycoCEST imaging. Therefore the purpose of this study was to determine the feasibility of glycoCEST imaging in human skeletal muscle *in vivo* at 7T. Further, we compared the asymmetry in the CEST spectrum due to glycogen, glycoCEST$_{MTRasym}$, to ^{13}C MRS measures of muscle glycogen, currently the gold standard for determining glycogen content *in vivo*.

Methods: All studies were approved by the institutional review board, and signed, informed consent was obtained prior to study. Five apparently healthy subjects (4 male; age 21-38 years) participated in the study. The subjects had varying physical activity patterns ranging from sedentary (<30 mins. of regular physical activity/week) to very active (>60-90 mins. of physical activity/ day, 6-7 days/week). MR data were acquired using a Philips 7T Achieva whole-body human scanner. Imaging data were acquired using a single-channel T/R extremity coil. Anatomical images (multi-shot, turbo-spin echo (TSE) TSE factor 3, TR/TE 622/13, 16 cm FOV, reconstructed to 512 x 512) were acquired from the leg and used to locate the largest cross section of the calf. Single slice glycoCEST images (TR/TE 75/2.3, 20 cm FOV, B_1 = 3.5 µT, pulse duration 500 ms, at 41 RF offsets between ±2000 Hz plus image an RF offsets of ±80000 Hz) were acquired from the largest cross section of the calf. Regions of interest (ROI) were manually drawn from the medial gastrocnemius (MG) using the high-resolution anatomical images as a guide. The magnitude of the CEST effect was quantified by measuring the asymmetry in the z-spectrum as:

$$GlycoCEST_{MTRasym}(\Delta\omega) = \frac{S(-\Delta\omega) - S(\Delta\omega)}{S_o}$$

where $S(\Delta\omega)$ is the signal S as a function of offset frequency (ω) and S_0 is the mean S in the ±80,000 Hz offset images. glycoCEST$_{MTRasym}$ was characterized as the integral of the z-spectrum within the limits 0.75-1.25 ppm (ref). ^{13}C spectra were acquired from the human calf muscles and a glycogen phantom with a ^{13}C/^{1}H partial volume T/R coil. The glycogen phantom contained 150 mM (glucose units, oyster glycogen, Sigma-Aldrich) and sodium chloride to mimic loading of the coil by the leg. Time domain data were acquired with a pulse-acquire routine using a block RF pulse (TR/TE 425/1.15, flip angle 70°, spectral band-width 16000, 1024 samples, 1600 N_{Ex}). The data were zero-filled to 8192 points, broadened with a 10Hz exponential filter, Fourier transformed, phased, and analyzed using commercially available NMR analysis software (Acorn, Nuts Inc.). The muscle glycogen C-1 resonance was iteratively fit to a Lorentzian line-shape and the area of the peak was expressed relative to the area of the corresponding peak from the phantom. The relationship between the integrated glycoCEST$_{MTRasym}$ was correlated to ^{13}C MRS measures of muscle glycogen using a Spearman's correlation coefficient.

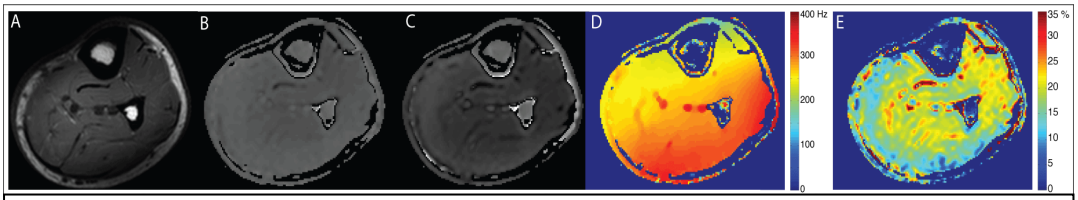

Fig.1: Results from GlycoCEST of skeletal muscle at 7T. A) T1-weighted anatomical image, B) reference image for glycogen resonance (1.0 ppm), C) normalized image for glycogen resonance (-1.0 ppm), D) shift map calculated from polynomial fit with color scale in Hz, and E) asymmetry map for glycogen (1.0 ppm).

Results and Discussion: Figure 1 shows the results from the glycoCEST of skeletal muscle at 7T. Figure 2A shows a sample *in vivo* ^{13}C spectrum. A significant glycoCEST effect is apparent by comparing the reference image at 1 ppm (Fig. 1B) to glycogen –OH sensitive image at -1.0ppm (Fig. 1C). In addition, a glycoCEST effect was apparent in all subjects (Fig. 2B). Linear regression showed a strong (R^2 = 0.64) association between the ^{13}C MRS measurement of muscle glycogen and the glycoCEST$_{MTRasym}$ integral.

Conclusion These data, although preliminary, suggest that glycoCEST imaging at 7T can be used to image muscle glycogen *in vivo*.

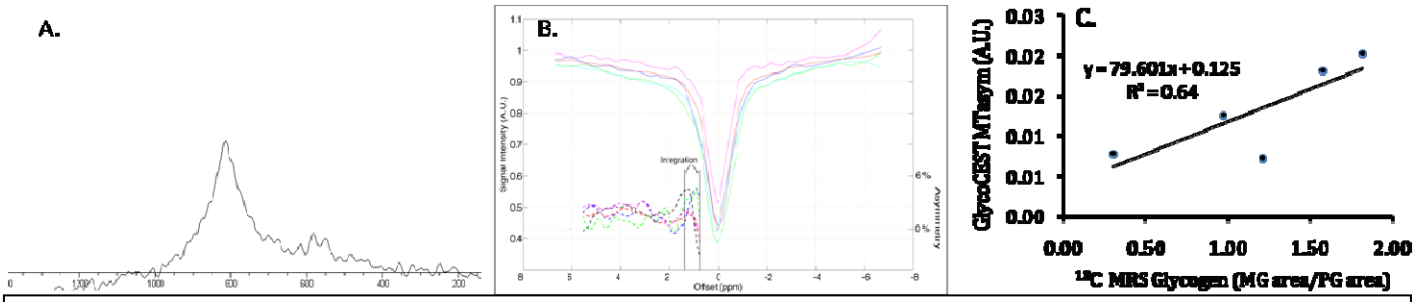

Fig.2 A Sample C-1 glycogen resonance acquired from the leg. B) is the normalized z-spectrum and MTR$_{asym}$ for all 5 subjects. C) shows the relationship between ^{13}C MRS measures of muscle glycogen and the integration of the MTR$_{asym}$ from 0.75 – 1.25 ppm.