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Accelerated Five-Dimensional Echo-Planar Correlated Spectroscopic Imaging to assess Lipids and Metabolite differences between Type-2 Diabetic and Healthy Calf Muscle

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Synopsis

Obesity-related diseases such as Type 2 Diabetes have become increasingly widespread. This condition can be characterized in part by changes in the fat composition of muscle, specifically in the relative concentrations of extra-myocellular (EMCL) and intra-myocellular (IMCL) lipids. Although 1D MRS techniques have been applied to assess skeletal muscle metabolite composition, they are hindered by lipid contamination from EMCL and spectral overlap which can complicate quantitation and differentiation from IMCL. 2D MRS improves spectral dispersion, allowing clear separation of both EMCL and IMCL and determination of the unsaturation index of muscle lipids. In this study, we apply a 5D (3D spatial + 2 spectral) echo-planar correlated spectroscopic imaging (EP-COSI) technique to assess the lipid and metabolic differences within the calf muscle among three groups of subjects – diabetic, age-matched healthy, and young healthy controls.

Introduction

Obesity-related diseases such as Type 2 Diabetes have become increasingly widespread¹⁻². This condition can be characterized in part by changes in the fat composition of muscle, specifically in the relative concentrations of extra-myocellular (EMCL) and intra-myocellular (IMCL) lipids³⁻⁴. Previous findings from 1D MRS, for example, have shown a negative correlation of IMCL with insulin sensitivity⁵⁻⁶. There are also differences in the amount of type I and type II muscle fibers between diabetic and non-diabetic populations, which can be reflected in the metabolic properties measurable with MRS⁷. Although 1D MRS techniques have been applied to assess skeletal muscle metabolite composition, they are hindered by lipid contamination from EMCL and spectral overlap which can complicate quantitation and differentiation from IMCL. 2D MRS improves spectral dispersion, allowing clear separation of both EMCL and IMCL and determination of the unsaturation index of muscle lipids. In this study, we validate a 5D (3D spatial + 2 spectral) echo-planar correlated spectroscopic imaging (EP-COSI) technique⁸ to assess the lipid and metabolic differences within the calf muscle among three groups of subjects – diabetic, age-matched healthy, and young healthy controls.

Methods

In an IRB-approved study, 12 diabetic patients, 10 healthy age-matched and 9 young healthy controls were recruited to record 5D EP-COSI data in calf, using a 3T scanner with the following parameters: TR = 1.5 s, TE = 35 ms, voxel size = 1.5 × 1.5 × 1.5 cm³, matrix size = 16 × 16 × 8, spectral width SW2 = 1190 Hz, SW1 = 1250 Hz, 512 t₂ points, 64 t₁ increments. Both a water and non-water-suppressed scan were acquired for eddy current and phase corrections. The data was non-uniformly undersampled in the k_y-k_z space and t₁ dimension for an acceleration factor of 8, resulting in a total scan time of 28.8 minutes, and the 5D EP-COSI data was reconstructed using a Group Sparsity-based compressed sensing algorithm. The ratios with respect to Cre3.0 (creatine at 3 ppm) were quantified using peak integral values for the following metabolites: FAT (lipids at 1.4 ppm), Cre3.0, Cho (3.2 ppm), Cre3.9, UFD (olefinic fat at 5.4 ppm), carnosine (8 ppm), EMCL1 & EMCL2, IMCL1 & IMCL2. The EMCL and IMCL unsaturation indices (UI) were defined as EMCL1/EMCL2 and IMCL1/IMCL2, respectively. The respective changes in the EMCL and IMCL UI's among the three groups were determined.

Results

The 5D EP-COSI technique measures 2D MRS data within multiple slices, allowing for broad coverage of the calf muscle (Figure 1). Spectral characteristics can be differentiated among the various muscle compartments in the calf - soleus (SOL), tibialis anterior (TA) and gastrocnemius (GAS) (Figure 2). Differences among these regions can be seen in Figure 3 in which the diagonal peak of carnosine (8 ppm) is present in all soleus muscles, the diagonal creatine peak at 3.9 is split into a doublet all tibialis anterior muscles but remains a single peak in the soleus. The doublet is due to residual dipolar coupling in the type 2 muscle fibers. The EMCL UI shows significant decrease in the TA, SOL and GAS, whereas the IMCL UI shows decreases only in the SOL and TA among all groups (Figure 4). There is no significant changes of IMCL1 and IMCL2 in the diabetic group within the TA.

Discussion

Compared to 1D MRS findings, 2D COSY spectra in different muscle regions show feasibility of separating the unsaturated lipids from the saturated portions and detection of choline, creatine, myo-inositol, taurine and carnosine at a resolution of 3.4ml. Even though there were significant differences between the diabetics and young healthy volunteers, less or no significance in age-matched healthy subjects compared to diabetics. Another drawback was due to minimal detection of resonances on the aromatic region due to chemical shift displacement error (CSDE) that can be minimized by using adiabatic RF pulses for the VOI localization. Quantitative results can be further improved by using optimal methods such as prior-knowledge fitting (ProFit).

Conclusion

Our pilot validation of the 5D EP-COSI sequence shows changes in unsaturated and saturated lipids as well as metabolites in type 2 diabetes compared to healthy subjects. Further validation is essential to demonstrate the reliability of the findings in vivo.

Acknowledgements

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Figures

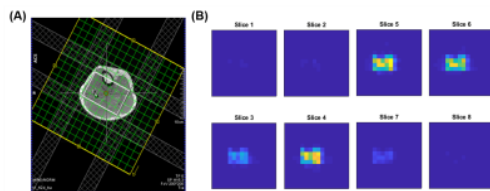


Figure1: (A) Axial localization of the volume of interest (VOI) in the calf muscle. (B) The hypo-intense region in the multi-slice chemical shift images of creatine (at 3.9 ppm) reflects the location of the tibial marrow, which lipid-dominant. Four main central slices contain the highest signal-to-noise ratio (SNR).

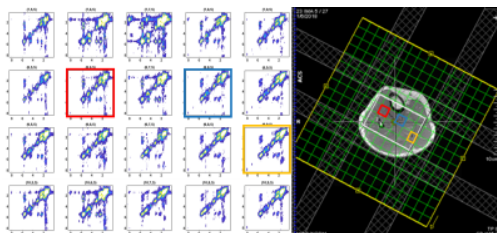


Figure 2: (Left) Multi-voxel COSY spectra in a 4 x 5 region covering the tibialis anterior (red), soleus (blue), and gastrocnemius (yellow) muscles in the calf (right) of a 55 year-old type-2 diabetic patient.

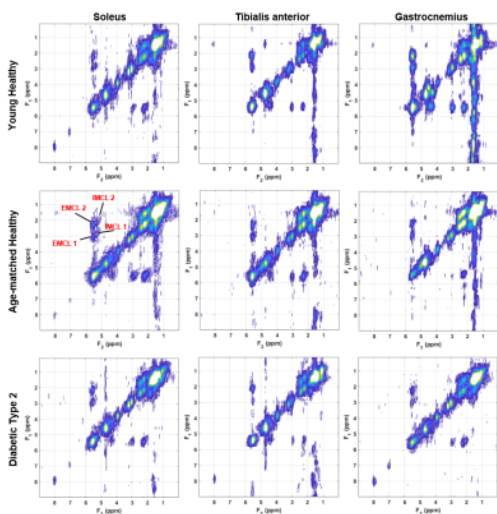


Figure 3: Extracted spectra within the soleus, tiabialis anterior, and gastrocnemius calf muscles in one young and one age-matched healthy volunteer and a type-2 diabetic patient. Note the diagonal peak of carnosine (8 ppm) present in the soleus muscles from all three individuals. The diagonal creatine peak at 3.9 is split into a doublet all tibialis anterior muscles, whereas it remains a single peak in the soleus. IMCL and EMCL are indicated in red text.



Figure 4: Mean EMCL1 & EMCL2 ratios with respect to creatine at 3.0 (Cr3.0) and mean EMCL and IMCL unsaturation indices (UI) for all three groups - type-2 diabetic (T2DM) patients, age-matched healthy (AMH) and young healthy (YH) controls - in (A) the tibialis anterior, (B) soleus, and (C) gastrocnemius calf muscles.(D) IMCL1 and IMCL2 ratios within all muscle regions.