Increased Intramyocellular lipids and decreased unsaturation indices and Choline in Diabetes Type 2 and Obesity

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Target Audience: Researchers interested in calf muscle lipids and metabolites of diabetic and young obese patients.

Introduction: Type 2 diabetes (T2D) has progressed into a major cause of preventable death, increasing from approximately 1.5 million diagnosed in the US in 1958 to 21 million in 2010, with an estimated additional 7 million undiagnosed (1). Better understanding of the mechanisms for skeletal muscle insulin resistance (IR) is critical to combating this disease. It is known that striking alterations in skeletal muscle lipid levels are associated with the development of IR and progression to T2D. There has been increasing interest in characterizing the processes resulting in increased intramyocellular lipids (IMCL) using magnetic resonance spectroscopic imaging (MRSI), and investigating body fat distribution using MRI, to determine their relationship to the development of IR and T2D (2-3). Hence, a major goal of this work was to investigate IMCL, extramyocellular lipids (EMCL) and metabolite changes in T2D and obesity using a recently developed multi-echo echo-planar correlated spectroscopic imaging (MEEP-COSI) (4).

Methods: Five diabetic (mean age 55 years), five young obese (mean age 29 years) patients and ten healthy controls (mean age 35 years) were selected for the MRI/MRS study. The entire study was approved by the institutional review board (IRB), and informed consent was obtained from each human subject. A 4D MEEP-COSI sequence was implemented on a Siemens 3T Trio-Tim scanner (Siemens Medical Systems, Germany) running on the VB17A platform and the volume of interest (VOI) was localized using three slice-selective radio-frequency (RF) pulses (90^0-180^0-90^0). Water-suppressed 4D MEEP-COSI data combining 2 spectral and 2 spatial dimensions was recorded and unsuppressed 3D MEEP-COSI data only along k_x, k_y and t_2 dimensions. The following parameters were used for the 4D MEEP-COSI sequence: a) TR/TE 1.5s/30ms, 6x8x2cm^3 voxel for VOI localization, 50Δt_1 increments, 256 bipolar echoes with each echo sampling 16 x-points, 16 y-encoding, FOV= 16x16cm^2 50Δt_1 and NEX=1; b) TR/TE 1.5s/30ms, 6x8x2cm^3 voxel for VOI localization, 256 bipolar echoes with each echo sampling 16 x-points, 16 y-encoding, FOV= 16x16cm^2, Δt_1 =0 and NEX=1 for the water reference MR data from the same voxel as the suppressed MEEP-COSI. A CP extremity transmit/receive knee coil was used. The spectral bandwidths were 1250Hz and 1190Hz along in the F_1 and F_2 dimensions, respectively. The total acquisition time was 10 minutes for the water suppressed 4D MEEP-COSI and approximately 1 minute for the unsuppressed water data. A home-built MATLAB algorithm was used for post-processing the 4D MEEP-COSI data and the unsuppressed water data was used for eddy current correction.

Results: The ratios of IMCL groups and the corresponding unsaturation indices (U.I) (5) calculated from the extracted 2D COSY spectra from the soleus and tibialis anterior locations are presented in Fig.1. Both soleus and tibialis anterior IMCL/Cr ratios were significantly elevated in the diabetics and obese subjects compared to healthy controls ($p<0.05$). Shown in Table 1 is our first time demonstration of regional variation and significantly decreased choline (also known as trimethylamines, TMA) ratios in diabetic and obese subjects compared to healthy controls.

Fig.1.The IMCL/Cr ratios calculated from the extracted soleus (A) and tibialis anterior (C) muscle spectra of healthy (H) volunteers (n=10), young obese (O) subjects (n=5) and diabetic (D) patients (n=5). Respective unsaturation indices for the IMCL group in the soleus and tibialis anterior regions are shown in B and D.

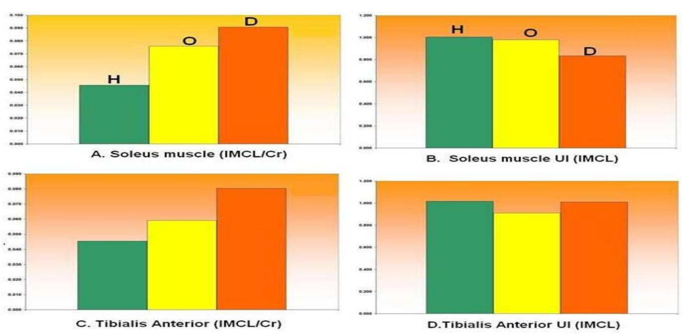

Table 1. Choline ratios (with respect to Cr) in different muscles

Subject Groups	Soleus	Tibialis Anterior
Diabetics	0.678±0.114*	0.534±0.419
Obese	0.924±0.159**	0.692±0.11
Healthy	1.033±0.18	0.671±0.185

* $p<0.05$ between diabetics and healthy;
** $p<0.05$ between obese and healthy subjects

Discussion: The ratios of EMCL groups, and the corresponding U.I values calculated in the soleus and tibialis anterior also showed increased EMCL/Cr ratios and decreased U.I. in T2D and obese groups compared to healthy subjects. Significantly decreased Ch/Cr ratios might reflect changes in membranal composition or phospholipid metabolism in these patients. It has been also shown that the TMA resonance contains carnitine and acetylcarnitine, and both molecules play critical roles in muscle metabolism (6). Extracted 2D spectral information from the 4D MEEP-COSI data is unique in that it separates the contribution of olefinic protons within the IMCL and EMCL pool unlike 1D MRS, thus providing a measure of the degree of the unsaturation of these lipid pools. The ratios and U.I. provide a relative measure of mono- and polyunsaturation in the respective pools.

Conclusion: The 10-minute long 4D MEEP-COSI acquired data enabled quantitation of unsaturated and saturated fatty acids in different calf muscle regions using IMCL ratios and unsaturation indices. The ME-EPCOSI technique has a major potential to be valuable in various clinical studies, such as heart failure or diabetes, where the levels of IMCLs in different muscles can be used as markers for differences in metabolic activity.

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References

1. Zimmet P, Alberti KG, Shaw J. Nature 2001;414:782-787. 2. Petersen KF, Dufour S, Morino K, et al. Proc Natl Acad Sci USA 2012; 109(21):8236-40. Epub 2012 Apr 30. 3. Boesch C, Machann J, Vermathen P and Schick F. NMR Biomed 2006;19(7):968-88. 4. Furuyama J and Thomas MA. Proceedings of the 19th ISMRM; 2011; 1435. 5. Velan SS, Said N, Durst C, et al. Am J Physiol Regul Integr Comp Physiol 2008;295(4):R1060-R1065. 6. Ren J, Lakoski S, Haller RG, et al. Magn Reson Med 2012 Apr 3.