OBESITY-RELATED VARIATIONS IN T2* AND FAT CONTENT OF MURINE BROWN AND WHITE ADIPOSE TISSUES BY CHEMICAL-SHIFT MRI

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- INTRODUCTION: In rodents, brown adipose tissue (BAT) is a significant contributor to thermal regulation and energy expenditure, particularly non-shivering thermogenesis **[1]**. In contrast to white adipose tissue (WAT), which functions to store energy in the form of lipids, BAT metabolizes fat to generate heat and maintain core body temperature. BAT is also involved in the dissipation of excess energy from food intake through heat production via diet-induced thermogenesis. In contrast to WAT, BAT is characterized by smaller adipocytes replete with mitochondria **[2]**. Furthermore, BAT is densely vascularized as blood perfusion is needed to supply nutrients during thermogenesis, as well as to transport the produced heat **[3]**. Several recent works have demonstrated signal contrasts between BAT and WAT in mice with non-invasive MRI, using either spectroscopy **[4, 5]** or chemical shift water-fat decomposition techniques **[6]**. The purpose of this work was to investigate whether differences in mitochondrial and vascular supply, and consequently the presence of iron between BAT and WAT, can be exploited for detection of BAT using quantitative MRI. We hypothesize that this would lead to detectable differences in T_2* relaxation rates and fat content in vivo. Since blood flow is increase during BAT activation **[7]**, we further hypothesize that in mice with greater thermogenic demand, T_2* of stimulated and metabolically active BAT will be lower than in animals with lesser BAT activity.

- METHODS: ***Animals.*** Three groups of male mice were prepared in this study, consisting of wild-type C57BL6 lean controls (n=6), a group of ob/ob mice that were fed for four weeks (n=6), and another group of ob/ob mice that were fed for eight weeks (n=8). These three groups will be subsequently referred to as lean, obese-4, and obese-8, respectively. We chose the ob/ob mouse as a model for impaired thermogenesis. With a thick layer of subcutaneous WAT insulation, these animals have reduced thermogenic demands compared to leaner wild-types. All animals were fed ad libitum standard rodent chow. They were housed two to three animals per cage at an ambient temperature of 23°C, on 12-hour light/dark cycles. For MRI, all mice were sedated with sodium pentobarbital (40 mg/kg). No inhaled anesthetics were used. During imaging (~10 min, 11 sec), the animals were not placed on a heating pad and cardiac and respiratory rates were not monitored. ***MRI.*** We utilized an investigational version of the IDEAL pulse sequence in this work **[8, 9]**. IDEAL is a generalized water-fat decomposition technique that produces registered water and fat image series and quantitative T_2* and PDFF (proton-density fat fraction) maps. The IDEAL algorithm accounts for signal-confounding factors such as the complex multi-peak spectrum of fat, T_1 and noise bias, and correction for T_2*, as well as system imperfections such as magnetic field inhomogeneity and eddy currents. All animal experiments were performed on a 3T system (MR750, GE Healthcare), using an eight-channel wrist coil. Mice were scanned individually. The pulse sequence was a 3D coronal SPGR acquisition, with TR=41.4ms, first TE=2.6ms, echo spacing=1.4 ms, echo train length=6, one signal average, flip angle=5° to minimize T_1 bias, bandwidth=±100 kHz, and native 0.47x0.28x0.8mm^3 resolution. Scan time for each animal was ~10 min. For image analysis, the largest and most easily identifiable BAT depot in mice --- the dorsal interscapular depot --- was measured, along with the gonadal WAT fat pads. Four to six ROIs were drawn across the T_2* and PDFF maps in each BAT and WAT depot of each animal.

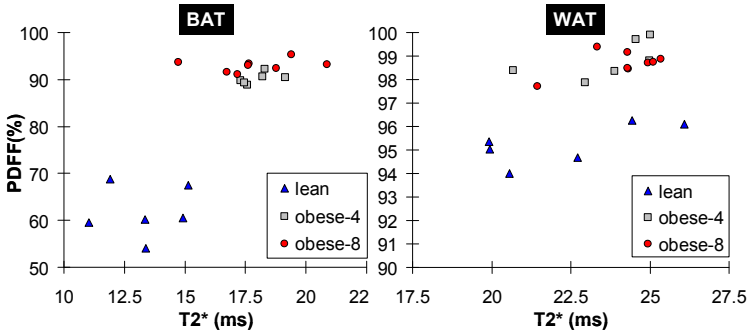

FIG. 1: Scatter plots of T_2* and PDFF for BAT (top left) and gonadal WAT (top right) for the lean (triangle), obese-4 (square), and obese-8 (circle) mice groups. Note the condensed PDFF (%) scale for WAT from 90-100%. Group distributions are shown in Table 1.

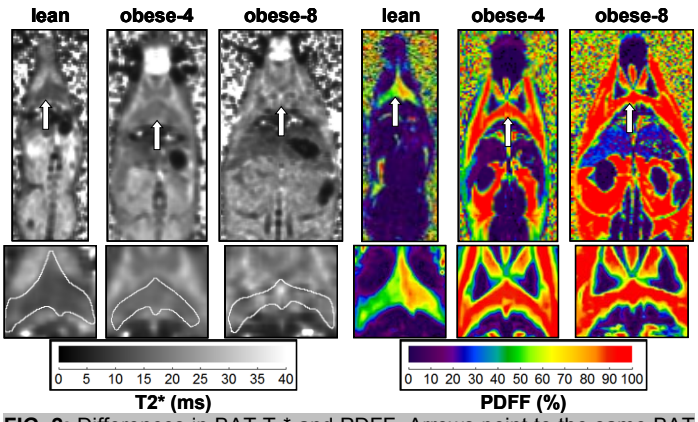

FIG. 2: Differences in BAT T_2* and PDFF. Arrows point to the same BAT location. Note that the triangular BAT depot is clearly visible in the PDFF maps. However, based on the signal contrast in the T_2* maps, the depot is only visible in the lean and obese-4 examples. It is indistinguishable from surrounding WAT in the obese-8 example. Enlargements show white outlines drawn about the BAT depot perimeter on the T_2* maps.

- RESULTS: **FIG. 1** and **TABLE 1** summarize measurements from the three mice groups. There were significant differences in both metrics between groups. Comparing vertically along the table (across groups), it is evident that BAT T_2* and PDFF in the lean group were significantly lower than those of the obese-4 and obese-8 groups ($p<0.001$). However in WAT, the nominal values of T_2* and PDFF appear similar across groups, especially between the ob/ob mice. BAT PDFF was the only significant comparison between obese-4 and obese-8 groups ($p<0.01$), whilst all other properties (BAT T_2*, WAT PDFF, WAT T_2*) were not significant. In other words, BAT T_2* and PDFF values in the obese-4 and obese-8 groups appear very WAT-like. Alternatively by comparing horizontally along the table (within each group), it is evident that BAT T_2* and PDFF measures in the lean control group were significantly different (and lower) than their counterpart WAT values from the same animals. For the obese-4 and obese-8 groups, BAT values were nominally closer to those of WAT, but nonetheless remain consistently lower. **FIG. 2** illustrates representative T_2* and PDFF single slice images of the interscapular BAT depot from each mice group. The visual difference between the control lean and the two ob/ob examples are evident. Note the small body shape and near absence of WAT in the lean example. Additionally, note that in the T_2* map of the lean and obese-4 mice, the outline of the triangular interscapular BAT depot is noticeable. Such T_2* tissue contrast is not present and visually absent in the obese-8 example.

TABLE 1.	BAT		WAT	
	PDFF (%)	T_2* (ms)	PDFF (%)	T_2* (ms)
lean	61.8 (±5.5)	13.3 (±1.6)	95.2 (±0.9)	22.3 (±2.6)
obese-4	90.2 (±1.2)	18.0 (±0.7)	98.8 (±0.8)	23.7 (±1.7)
obese-8	93.0 (±1.3)	17.9 (±1.8)	98.7 (±0.5)	24.1 (±1.2)

- CONCLUSION: In conclusion, the present work has demonstrated the feasibility of a chemical-shift-based quantitative MRI technique for simultaneous measurement of T_2* and PDFF as unique in vivo functional biomarkers of BAT. Given that the diets between the lean, obese-4, and obese-8 groups were the same, the measured variations in BAT were predominantly due to metabolic and thermogenic differences between the animals.

- REFERENCES: **[1]** Himms-Hagen J, NEJM 1984;311:1549-1558. **[2]** Menschik Z, The Anat Record;1953:1164:439-455. **[3]** Cannon B, Physiol Rev 2004;84:277-359. **[4]** Hamilton G, JMRI 2011;34:468-473. **[5]** Branca R, MRM 2011;65:313-319. **[6]** Hu H, JMRI 2010;31:1195-1202. **[7]** Foster D, Can J Physiol Pharmacol 1979;57:257-270. **[8]** Reeder S, MRM 2004;51:35-45. **[9]** Vasanawala S, MRM 2011; doi:10.1002/mrm.22986.