Evaluation of high fat diet induced obesity in rats by longitudinal MRI and MRS in abdomen, liver and skeletal muscle

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Introduction: Obesity is a medical condition in which excess body fat accumulates in areas such as abdomen, liver and skeletal muscle to the extent that it may contribute to several health problems such as type 2 diabetes. In this study, experimental rodent models of obesity were used to investigate fat accumulation in metabolic disorders by performing longitudinal in vivo measurements of adipose fat in abdomen, liver and skeletal muscle of male Fischer rats (F344). All our measurements are correlated with body weight, food intake and blood chemistry.

Methods: Group I rats (n=4) were fed with high fat diet (Research Diets, D12079B) and group II received control diet (Clea Japan, CE2) from 4 to 17 weeks of age. MRI and MRS measurements were performed on a 7 Tesla Bruker ClinScan using volume transmit and surface receive coils in abdomen, liver and skeletal muscle at 5th, 9th, 13th and 17th week of age. Fat estimation in the abdomen was based on axial image segmentation. Abdomen imaging was performed by T_2 weighted spin echo sequence with a FOV of 55 x 55 mm and matrix size of 256 x 256. Abdomen images in the coronal plane were used as reference and water suppressed transverse images from L1 to L5 of the spine were acquired. Segmentation of visceral and subcutaneous fat was performed using graph theoretical method [1] (Figure 1) by a custom-developed MATLAB program. Localized PRESS experiments were performed on liver and skeletal muscle with a voxel size of 4 mm^3 and 3 mm^3, respectively with TR=4.0 sec, TE=13 msec (Figure 2). Liver fat estimation was based on spectral analysis by LCModel. The % liver fat was calculated using concentrations of lipid methyl, methylene, and the water signal [2]. The unsuppressed water signal was employed for eddy current correction. LCModel fitting of skeletal muscle spectrum was used to estimate levels of intra- and extra-myocellular lipids.

Figure 1. (a) Transverse image of rat abdomen (b) segmented subcutaneous fat image (c) segmented visceral fat image.

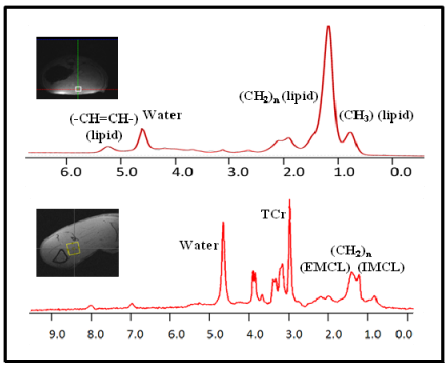

Figure 2. Localized 1D PRESS spectrum of liver and skeletal muscle.

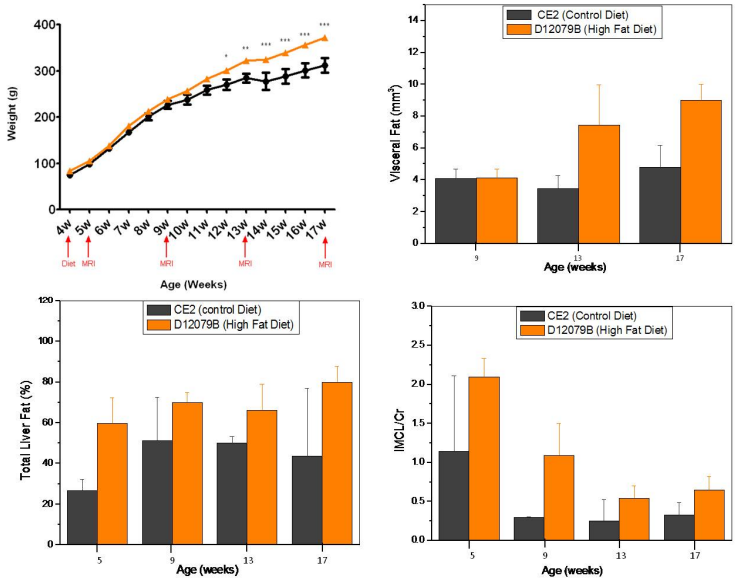

Figure 3. Variation of (a) Body weight (b) Visceral fat (c) Total % fat in liver (d) Intra-myocellular lipid (IMCL/Cr) in skeletal muscle through the age of 4-17 weeks.

Results and Discussion: Results are shown in Figure 3. The orange and gray bars represent the group I (high fat diet) and the group II (control diet) rats, respectively. Increase in the body weight was similar in both groups until about 9 weeks of age. 12th week onwards, the growth in body weight was statistically higher in group I (Figure 3a, $p \leq 0.05$). The visceral fat estimates were performed from the age of 9-17 weeks. At the age of 13th week, a significant increase in the visceral fat was observed in group I whereas, in group II it remained steady. Total liver fat was significantly higher in group I ($p \leq 0.05$) over the period of 5-17 weeks (Figure 3c). The intra-myocellular lipid concentration (IMCL/Cr) in skeletal muscle showed a remarkable decrease between 5th week and the subsequent time points. However, it was always significantly higher ($p \leq 0.05$) in group I (Figure 3d). The comparatively high level of IMCL in young rats has been previously reported [3] and was suggested to be due to their increased metabolic rate, energy expenditure and growth. Cholesterol, triglyceride and leptin were at all time points higher in group I compared to group II. Statistical analysis shows significant difference ($p \leq 0.05$) between these two groups for triglyceride (throughout), cholesterol (at 13th and 17th week), and leptin (at 17th week). Glucose and Insulin level does not show any significant difference between the two groups (data not shown). Correlation analysis shows a close agreement between the blood chemistry and MRS/MRI estimates of fat content at the age of 17th week. A high correlation ($R > 0.78$) with all three parameters, i.e. IMCL/Cr, visceral and liver fat, was observed for Insulin. Cholesterol, triglyceride and leptin give good correlation with visceral fat ($R > 0.80$) and IMCL/Cr ($R > 0.70$), whereas glucose shows moderate correlation with Liver fat ($R = 0.69$) and IMCL/Cr ($R = 0.58$).

Conclusion: The results demonstrate that MRI/MRS can be utilized to follow the adiposity deposit in organs including abdomen, liver, and skeletal muscle and the approach can be used to evaluate the therapeutic potential of novel drugs in rodent models of obesity and diabetes.

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