Assessment of Intrahepatic Lipid Composition during Calorie Restriction and Exercise Intervention in Diet Induced Obese Rats by MRS

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Target Audience: Authors interested in changes of liver lipid composition during calorie restriction and exercise intervention

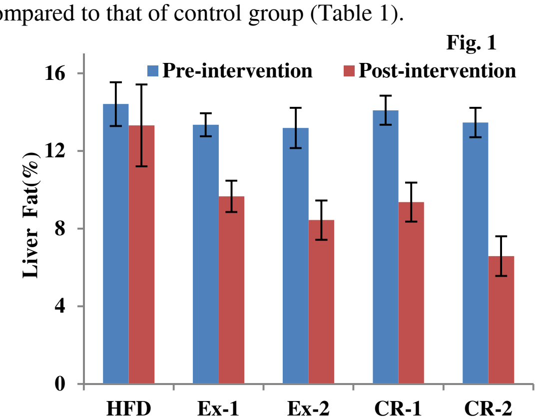
Introduction: Hepatic fat plays a major role in metabolic diseases including obesity, diabetes, and non-alcoholic fatty liver disease[1]. Liver fat is an important target for drug discovery in metabolic diseases and especially saturated fatty acid plays important role in obesity and insulin resistance[2]. *In vivo* magnetic resonance spectroscopy (MRS) permits non-invasive longitudinal assessment of fat fraction, saturated and unsaturated lipids[3-4]. Interventions including exercise and calorie restriction play a major role in anti-obesity and also for recovery from NAFLD. In this study we have estimated the changes in intrahepatic lipid content including, fat fraction, total unsaturated lipids (TUL), fraction of unsaturated lipid (fUL) and unsaturation index (UI) in five groups of high fat diet (HFD) induced obese rat model with exercise and calorie restriction interventions.

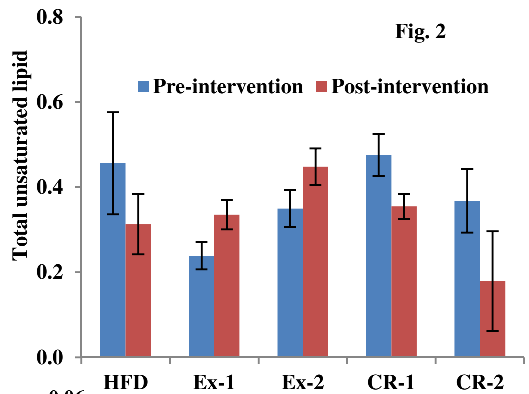
Animal model and Methods: All in-vivo measurements are in compliance and approved by local Biological Resources Center (BRC). Rats (male Fischer 344, Clea Japan) were fed with high fat diet (Research Diet, D12079B) from 5 to 18 weeks of age. After 18 weeks of high fat diet feeding, rats were divided into 5 groups and subjected to exercise and calorie restriction interventions for 4 weeks. Exercise interventions were performed once a day for 30 min (20m/min) Ex-1, and twice a day for 30 min (20m/min) Ex 2 using animal treadmill (Columbus-1055SRM-E54 Exer-3/6-Dual). Calorie restriction was performed with (with 15% calorie reduction compared to control group) CR-1 and calorie restriction (with -30% calorie restriction) CR- 2 interventions. The fifth group did not undergo any intervention and served as control group. In vivo measurements were performed with motion compensated respiratory gating on 7T Bruker ClinScan MR System equipped with 72 mm body coil (transmit) and 20 mm receive only coil. Localized PRESS based MR spectroscopy were performed on liver with a voxel size of 4x4x4 mm^3 and TR = 4.0 sec, TE = 14 msec. LC model was utilized to quantify liver fat by fitting the signals from methyl, methylene resonances normalized to unsuppressed water signal[5]. The intrahepatic lipid composition including TUL (3Lip53/2Lip09) UI (Lip53/ (Lip53+Lip13+Lip21+Lip09) and fUL (3Lip21/4Lip09) were estimated[6].

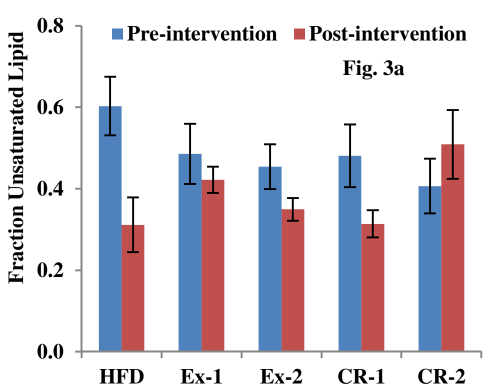
Results: Figure 1 shows the liver fat (%) from all the five groups of rats. The exercise and calorie restricted groups showed significant reduction in liver fat (%) compared to the control group. Calorie restricted (CR2) group showed significant reduction in liver fat compared to other groups. The exercise groups showed significant increase of unsaturated lipids ($P < 0.05$), whereas calorie restriction group showed significant ($P < 0.05$) reduction (Figure 2). Exercise interventions increased the unsaturated lipids probably due to the mobilization of the lipids[7]. The FUL content significantly decreased ($P < 0.05$) in HFD, Ex2 and CR1 groups. Calorie restriction tends to alter the lipids composition by attenuating levels of polyunsaturated lipids[8]. The decrease in fUL is due to increased fraction of saturated lipids (Figure 3a). The UI significantly decreased ($P < 0.05$) in HFD group and CR1 group due to increased proportion of saturated lipid content. The UI of Ex-2 group was significantly ($P < 0.05$) higher compared to other interventions indicating effective rearrangement of lipid composition (Figure 3b). The plasma insulin of both Ex and CR groups were significantly ($P < 0.05$) decreased compared to that of control group (Table 1).

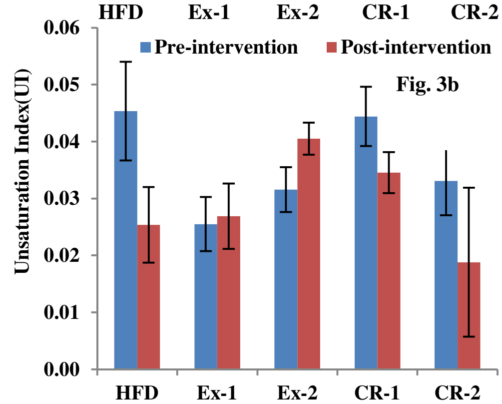
Group	Plasma TG (mg/dL)	
	Pre	Post
HFD	434±100	473±56
Ex1	454±80	498±142
Ex2	501±175	563±249
CR1	463±118	459±76
CR2	507±144	425±70
	Plasma Insulin (ng/mL)	
HFD	4.6±0.9	3.9±0.7
Ex1	4.6±0.6	2.9±0.6$^{\#,*}$
Ex2	4.9±1.3	2.7±1.3$^{\#,*}$
CR1	5.7±2.0	3.6±1.4$^{\#}$
CR2	4.3±1.2	3.3±0.8

Table 1









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Conclusion: Exercise and calorie restriction significantly reduced the intrahepatic lipid content. Our preliminary study shows that the hepatic lipid content can be modulated with optimal interventions in treating metabolic syndrome.