**Impact of isocaloric fructose and glucose diets on lipid metabolism studied in vivo by multinuclear MR spectroscopy**

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**Target audience:** General audience and those dealing with metabolism and MR spectroscopy.

**Purpose:** The excessive intake of processed fat and soft drinks rich in fructose contribute to increased numbers of obesity worldwide. Consumption of fructose sweetened drinks among patients with non-alcoholic fatty liver is 2-3 times higher compared to patients without steatosis [1]. Fructose is associated with increased plasma triglycerides (TG), visceral adipose tissue accumulation, hypersecretion of apolipoprotein (Apo)B48 and impairment of insulin responses particularly in postprandial state [2]. However, these effects of fructose are not clearly disassociated from an excessive caloric intake. Thus, we aimed to investigate in vivo the impact of isocaloric diets of fructose and glucose in their ability to induce lipid deposition in hepatic, muscle and adipose tissues using 1H MRS, MRI, and test whether the intake of these sugars promotes changes in hepatic energy (13P MRS). Furthermore, we resolved the sources of hepatic triglycerides (HTG) into dietary and hepatic synthesis with 1H13C MRS and 1H NMR.

**Methods:** Adult C57Bl6 mice were fed over 8 weeks with 60% glucose or 60% fructose diets. Whole-body glycemic control was assessed throughout the diets with glucose tolerance test and insulin measurements. MR was performed on mice under anaesthesia (isoflurane 1-2% in gas mixture with 50%O2/50%N2O). Abdominal adipose tissue volume was assessed by MRI at 11.7T ( Biospec, Bruker Biospin) at 0, 4 and 8 weeks of diets. Mice were placed in a 1H quad. volume coil and 25 continuous axial slices from the abdominal region were acquired using a spin-echo sequence: matrix 256x256, TR/TE of 1500/16ms and 1024 av. 1H weighted images were processed with Image3 (NIH, USA). Hepatic and intramyocellular lipids were assessed at the same diet times with 1H MRS at 11.7T and 7T (Clinscan, Bruker Biospin). HTG were assessed with a 31P MRS. Furthermore, we resolved the sources of hepatic triglycerides (HTG) into dietary and hepatic synthesis with 1H13C MRS and 1H NMR.

**Results:** Glucose and fructose mice had similar body-weight gain over 8 weeks and similar caloric intake. Glucose tolerance was impaired in both groups at 8 weeks, although insulin levels were higher in fasted fructose mice (0.5±0.19 vs 0.28±0.08ng/ml, p<0.05). After 8 weeks of diet, abdominal adipose tissue was mildly increased, 21±18% vs. 24±15% in fructose and glucose mice. IMCL content was maintained throughout the diet, as shown by the IMCL/Tcr ratio at baseline and 8 weeks, of fructose (1.4±1.7 vs. 1.9±0.7) and glucose (1.5±0.6 vs. 2.0±0.3) mice. Levels of HTG increased within 4 weeks in both groups, however more significantly in fructose than in glucose mice (8.4±4.6% vs. 5.5±2.4%, p<0.05). During the last 4 weeks, HTG content in fructose and glucose mice was similar to that of week 4 (7.9±2.4% vs. 4.8±2.5%, Fig.1). Hepatic energy levels were found similar between fructose and glucose mice: ATP (1.9±1.1mM vs. 1.6±1.2mM), Pi (2.9±1.0mM vs. 3.3±1.0mM), NADPH (1.6±1.1mM vs. 2.2±1.3mM) and PME/ATP (2.5±1.1 vs. 2.7±2.1). To determine if fructose promoted absorption of dietary lipids, for instance through the hypersecretion of ApoB48, we investigate in vivo whether an oral load of [U-13C]algal lipids (5g/kg) was given to trace 13C enrichment in the HTG pool. Using 1H13C MRS we determined that, 5h after the bolus, HTG pool of fructose and glucose mice had a 13C enrichment of 3.2±1.6% vs. 4.3±2.3%, which corresponds to a “dietary” absorption of 2.6±1.7% vs. 3.9±2.3% (p=0.15). De novo lipogenesis, investigated by 1H NMR, was found significantly increased in fructose fed mice compared to those fed with glucose (5.3±3.0 μmol/g vs. 2.4±1.1 μmol/g, p=0.01, Fig.2).

**Discussion:** Our data demonstrate that isocaloric fructose and glucose feeding over 8 weeks causes similar changes in abdominal adipose tissue and intramyocellular lipid content. Both diets promote HTG accumulation, however in fructose fed mice this ectopic lipid accumulation is significantly higher. This seems to be solely a result of increased hepatic de novo lipogenesis, and not increased dietary fat uptake. Unlike acute doses of fructose, a continuous dietary supply of this sugar does not modify hepatic energy levels.

**Conclusion:** Fructose consumption represents a risk factor for the development of steatosis and whole-body insulin resistance.


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