Editorial

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Why do sweets fatten our livers?[1–3]

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In recent years, the search for lifestyle changes that will slow the obesity epidemic and its adverse sequelae has turned to dietary sugar. A substantial number of calories come from beverages and desserts made with sucrose or high-fructose corn syrup, which are absorbed as a mixture of glucose and fructose. But apart from weight gain from excess sweet calories, what are the specific metabolic consequences that are harmful to health?

The best-documented adverse effect known for decades is the dyslipidemia that develops with the ingestion of large amounts of sugar, even when substituted calorie for calorie for fat (1). An important mechanism is de novo lipogenesis (DNL), the synthesis of the SFA palmitate, from glucose, fructose, or both. There is a marked increase in DNL after excess carbohydrate calories (2) or the isocaloric substitution of dietary glucose or mixed sugars for starch, complex carbohydrate, or fat (1, 3). Although the absolute quantity of synthesized fat is small, there are large increases in plasma triglyceride concentrations and the ratio of palmitate to the essential fatty acid linoleate (lipogenic index). Triglyceride synthesis and secretion by the liver is increased by the generation of palmitate, glycerol (the backbone of triglyceride), and malonyl coenzyme A (an intermediate that inhibits fatty acid oxidation and channels fatty acids into triglyceride). The fructose component of dietary sugar is particularly lipogenic because of its uniquely high first-pass clearance by the liver. Increased plasma VLDL triglyceride, via cholesterol ester exchange protein, produces the full spectrum of lipid abnormalities (high triglycerides, small dense LDL, and low HDL) that accelerate atherosclerosis. Conversely, DNL and triglyceride synthesis are rapidly suppressed during weight loss (2).

The current study by Sevastianova et al (4) in this issue of the Journal expands the lipogenic effects of dietary sugar beyond dyslipidemia to include fatty liver. The results show for the first time a link between excess dietary sugar and the accumulation of liver fat by DNL, a pathway uniquely stimulated by dietary sugar. A small number of nondiabetic, overweight adults, half of whom had fatty livers, consumed an excess of sugar as candy and beverages for 3 wk. Details of the overall macronutrient composition of the diets were not provided, but the excess sugar intake was close to the 80th percentile of intake in the United States (5). Dietary compliance was judged to be acceptable because the amount of weight gain was that expected for the excess of calories. The results showed that a 2% increase in body weight and similar increases in subcutaneous and visceral adipose tissue were accompanied by a 27% increase in liver fat measured by proton magnetic resonance spectroscopy. Large increases were also observed in fasting plasma VLDL and total triglycerides and DNL, as reflected by the lipogenic index in triglycerides. HDL cholesterol also decreased (LDL size was not measured). These changes were reversed at the end of a 6-mo hypocaloric, low-sugar dietary period. Importantly, for the entire group, the increase in the lipogenic index was positively correlated with the increase in liver and serum triglycerides.

Hepatic steatosis affects a large fraction of US obese adults and children and may progress to nonalcoholic steatohepatitis, cirrhosis, and liver failure. The implication that a persistent excess of calories as dietary sugar can cause or exacerbate fatty liver by DNL, a pathway unique to dietary sugars, lends additional support to public health recommendations to limit dietary sugars. The increased liver fat resulting from increased DNL and the imbalance between triglyceride synthesis and secretion may increase oxidative stress, inflammation, and insulin resistance (6). Indeed, in this study, liver enzymes significantly increased after the high-carbohydrate period, and there was a trend for an increase in fasting serum insulin. Whether triglycerides enriched in SFAs are more damaging to human liver (7) is unknown but deserves further study.

The most tantalizing finding is also the most tentative given the small number of subjects. Unlike subjects with the 148II variant of the gene for a lipase, *PNPLA3*, subjects with the 148MM variant that is associated with fatty liver but low plasma triglycerides did not show an increase in liver fat and plasma triglyceride in proportion to DNL. The authors proposed that this was because of impaired lipolysis of intrahepatic triglycerides and reduced VLDL assembly and secretion. However, given that the increases in liver and plasma triglycerides were similar between groups, this genotype does not appear to affect lipogenic sensitivity to dietary carbohydrate, and other metabolic differences, including response to high-fat diets, must be explored. Alternatively, the relation between the lipogenic index and DNL may have been distorted if the lipase is selective for specific fatty acids. Finally, other genes identified by genome-wide association analysis have been associated with fatty liver, including *ApoC3*, *GCKR*, and *NCAN*, which associate with either high- or low-serum triglycerides (8), but dietary interactions have not been

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evaluated. The small number of subjects sampled precludes testing for other potential confounding variables.

In conclusion, the results provide the impetus for the measurement of liver and plasma triglycerides and DNL after a carbohydrate challenge in a larger number of ethnically diverse subjects tested for genes associated with fatty liver. In this way, the genetic heterogeneity for the lipogenic effects of dietary sugar will be defined. Dietary recommendations to restrict sugars can then have a stronger scientific rationale and target those at greatest risk and the specific mechanism or mechanisms responsible.

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