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Overfeeding of Polyunsaturated Versus Saturated Fatty Acids Reduces Ectopic Fat

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COMMENTARY

Obesity is a worldwide problem that leads to a number of chronic conditions, including diabetes, hypertension, heart disease, chronic kidney disease, and some cancers (1). Obesity results from the slow and steady accumulation of fat as a consequence of eating more carbon-containing compounds in foods than are needed for daily energy expenditure. The effects of obesity are exacerbated in the presence of fat accumulation in the liver, muscle, visceral fat depot, and other organs (2). The mechanisms for ectopic fat accumulation reflect many factors, including genetics, inflammation, dietary fat, fructose, and positive energy balance among others.

The question of whether obesity or ectopic fat accumulation during ingestion of excess calories is influenced differentially by diet has been an intriguing question for more than 100 years (3,4). In this issue, the article by Rosqvist et al. (5) adds another dimension to our understanding of overeating and fat accumulation. The investigators asked whether overeating with a diet with additional polyunsaturated fatty acids (PUFA) would reduce formation of ectopic fat compared with overeating with a diet high in saturated fatty acids (SFA). Their study included 39 normal, but very lean, young men and women, 37 of whom were included in the analyses. For 7 weeks, participants ate muffins enriched with either SFA, as palm oil, or PUFA, as sunflower oil. Diets were adjusted to target a 3% weight gain. This was a well-designed and executed study that included 4-day weighed food records at the beginning and end, use of accelerometers to measure activity, measurement of fatty acid composition of plasma cholesterol esters and adipose tissue triglycerides, and estimation of hepatic stearoyl-CoA desaturase-1 (SCD-1) from the ratio of 16:1n-7/16:0 in cholesterol esters. Fat distribution was measured with magnetic resonance imaging and total fat by a two-compartment model using whole-body plethysmography (Bod Pod; COSMED, Concord, CA). Weight gain was 1.6 kg in both groups. However, the ratio of added lean tissue to added fat during overeating was 1:1 among people on the PUFA-enriched diet and 1:4 among people on the SFA-enriched diet. The groups ate an average of 3.1 muffins/day, which was equivalent to 750 extra kcal/day. Energy expenditure was about 2,684 kcal/day, of which about 1,040 kcal/day were due to activity. Fat in the pancreas decreased similarly in both groups.

The main finding of the new report is that the size and distribution of fat depots varied significantly according to the type of fat that was consumed. The PUFA group gained equal amounts of fat and lean tissue, but those eating the SFA diet gained four times as much fat as lean tissue. In particular, the SFA diet resulted in a significant increase in liver and visceral fat relative to the PUFA diet. Further, the increase in liver fat was positively correlated with increases in SFA as measured by plasma palmitic acid. In contrast, the PUFA diet increased lean tissue significantly more than the SFA diet. But the nature of this "lean tissue" is unclear. Because participants did not change their activity levels during the study, this lean tissue is probably not "active" muscle, although it might represent protein in other tissues.

An increase in dietary fat increases hepatic fat in both normal weight (6–8) and obese (9,10) individuals. As hepatic fat content may be a driver of the metabolic syndrome (11,12), an interesting feature of this trial is that the change in liver fat was strongly related to SFA, but not to similar levels of PUFA. Previously, the same group showed that PUFA decreased liver fat in normal weight individuals (13). In another report from the same group, it was noted that PUFA reduced liver fat compared with SFA (13). The mechanism(s) underlying these differences on hepatic fat content may relate to differential effects on lipogenesis. This is suggested by decreased estimated SCD-1 activity with the PUFA diet and the lack of evidence for differential dietary effects on a marker for

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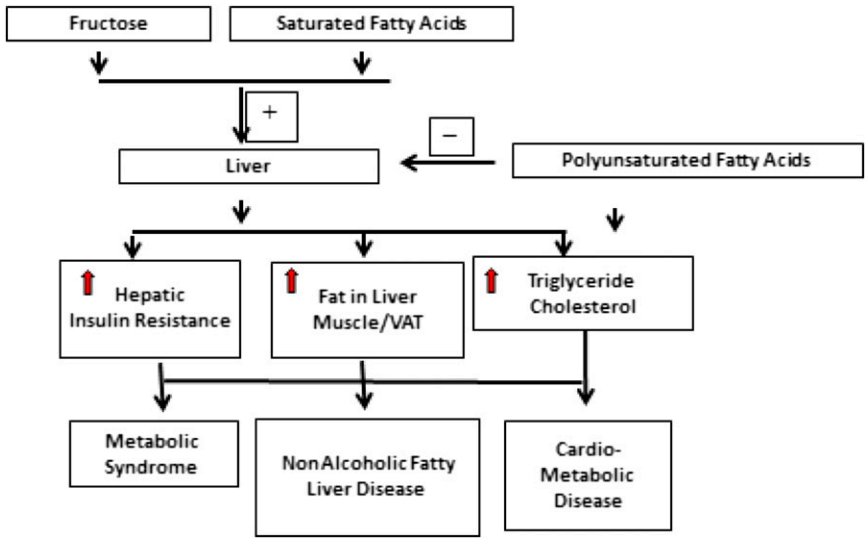

Figure 1—Fructose, fatty acids, and ectopic fat. VAT, visceral adipose tissue.

hepatic fatty acid β-oxidation. Dietary PUFA may suppress hepatic lipogenesis through mechanisms involving transcriptional regulation by SREBP1-c (14) or PPAR-α (15), although the latter effect also would be expected to modulate fatty acid β-oxidation. A role for PUFA-derived eicosanoids in mediating PUFA effects on lipogenesis has also been suggested (16).

Rosqvist et al. (5) note that the observed effects might partly reflect an interaction between fat and fructose because the muffins are a significant source of fructose. In one study, when fat and fructose were overfed individually and in combination, there was an additive effect on liver fat (7). In humans, there is considerable evidence that dietary fructose enhances liver fat and the associated risk of nonalcoholic fatty liver disease (17). As shown in Fig. 1, fructose and SFA may promote hepatic steatosis, whereas PUFA may modulate this interaction.

There are several questions that were not addressed in this study, and these bear consideration for fully assessing the clinical implications of the findings. First, does the dietary SFA-driven hepatic fat increase and/or n-6 fatty acid–driven increase in lean body mass translate into improved plasma lipids and other markers of cardiometabolic risk? This question may be of particular importance in lean, healthy individuals. Second, is SFA intake—as opposed to PUFA—causally related to risk of nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, or might the current findings merely reflect a noncausal association? Finally, the authors raise the question of whether fructose interacts with dietary lipids, but they do not provide us with any clear information on how much fructose there was in the muffins or in the diet as a whole. Finally, although a number of expressed genes were measured in subcutaneous adipose tissue, it was not helpful in explaining the observed effects on hepatic fat metabolism.

Taken as a whole, the findings of the study by Rosqvist et al. (5) provide support for the idea of substituting dietary PUFA for SFA, although the potential clinical benefits stemming from a reduction in hepatic fat and/or increase in lean body mass remain to be demonstrated on a broader scale.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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