responsible for obesity. Obesity is a multifactorial disease—a disease of energy imbalance appearing in individuals with genetic susceptibility in an environment rich in HFCS and other caloric sweeteners mixed with high-fat foods. As we have argued (5), it is HFCS in beverages that has the strongest relation with the growing epidemic of obesity. A review of calorically sweetened beverages by Vartanian et al (6) showed that beverage intake was significantly related to calorie intake in 10 of 12 cross-sectional studies and in all 5 longitudinal studies. Because beverages are not the sole sources of energy in the diet, it is not surprising that fewer studies showed the relation with weight gain than with energy intake. It is noteworthy that none of the studies showed the reverse effect, ie, a protective effect of soft drinks against weight gain. HFCS and sugar, which is half fructose, particularly when combined with fat, are thus contributors to the epidemic of obesity and the metabolic syndrome and provide a good marker for highly processed foods, the kinds I try to avoid when shopping. These high-HFCS-containing, highly refined-carbohydrate diets are the ones that Taubes (7) calls the ‘‘bad calories’’ in his recent book titled Good Calories, Bad Calories.

White also tries to minimize the importance of the small changes in LDL particle size in Swiss children reported by Aeberli et al (2). In contrast with his perception, small, significant changes in cardiovascular disease risk factors in children of this age related to differences in fructose cannot be lightly brushed aside, because corporate profits cannot be used as a basis for running any risk of decreasing the health of our children. The Bogalusa Heart Study has shown the importance of small changes in body weight at the upper end of the age group in children at risk of developing cardiovascular disease risk factors (8). Thus, we need to do all we can to protect the younger generation from potentially risky foods.

Fructose may also be detrimental to adults (3). A recent paper by Dhingra et al (9) showed that consumption of soft drinks, a major source of fructose, is related to the development of cardiovascular disease risk factors in participants in the Framingham Heart Study. Johnson et al (3) note the relation between the rise in sugar consumption and cardiovascular disease and point out that uric acid, a predictor of cardiometabolic risk, is one of the byproducts of fructose metabolism. The litany of potentially ill effects associated with fructose thus continues to mount and has been a major factor responsible for my change in position from the time of the FASEB review for FDA in 1986.

White also points out that the percentage of calories from added sugars has decreased, but fails to note that total fructose intake has increased because total added sugars have increased (4). The effects of fructose on LDL particle size, the effects of fructose on uric acid production (a predictor of heart disease), and the prediction of weight gain in several prospective clinical trials give me serious concerns about the future of products with high levels of fructose from whatever source, particularly when mixed with fat.

In her letter, Hine notes that the polyol pathway in diabetics is an added source of fructose, and I thank her for this addition to the list of endogenous sources of fructose. She also notes that Glut-5, the fructose transporter, is somewhat more abundantly distributed than I had indicated. It is interesting that these are abundant in many cancers. The biological meaning of this is unclear to me. This being said, the important message is that most fructose is metabolized in the liver with utilization of ATP. The decrease in available ATP during the metabolism of fructose can be graphically seen with magnetic resonance image spectroscopy. The outcome of this metabolism, as noted in the report by Johnson et al (3), is an increase in uric acid. My concerns about the health implications of fructose in our diets—from whatever source—are as strong as when I wrote the editorial.

No conflicts of interest were reported.

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Reply to JS White

Dear Sir:

The correlation between fructose and LDL particle size, after adjustment for confounders, including protein intake, was not ‘‘slight,’’ but highly significant (P = 0.024) (1). As clearly stated in our article, the data show no effect of fructose on total and LDL cholesterol. This finding is consistent with previous data reporting correlations of LDL particle size with plasma triacylglycerols and plasma HDL, but not with LDL cholesterol (2). As we stated in our article, because a decrease in LDL particle size is one of the first detectable changes in the development of dyslipidemia (3), modulation of LDL particle size—possibly a reflection of early insulin resistance—may be an early, unfavorable metabolic effect of fructose. The low free fructose intakes in our sample are typical of what European diets provide and suggest a potent effect of even low intakes of fructose on LDL particle size.

No conflicts of interest were reported.

Michael B Zimmermann
The interaction between intestinal fatty acid-binding protein 2 polymorphism and delta-6 desaturase activity in obese children

Dear Sir:

In a study recently reported in the Journal, Morcillo et al (1) examined the interaction between intestinal fatty acid–binding protein 2 (FABP2) polymorphism and the intake of dietary fats; they determined that the FABP2 Thr54 polymorphism was associated with insulin resistance in subjects with a high intake of sunflower oil. Weiss et al (2) confirmed that, among sedentary nondiabetic persons following a low-fat diet, FABP2 Thr54 carriers have lower glucose tolerance, lower insulin action, and higher lipid oxidation rates than do Ala54Ala carriers. These results were very interesting to our group, which had studied the effect of FABP2 polymorphism on delta-6 desaturase (D6D) activity in obese children (3).

In our study of 32 obese children with a mean (± SD) age of 12.0 ± 3.0 y, the allele frequencies were 0.66 and 0.34 for the FABP2 Ala54 and Thr54 polymorphisms, respectively. Among the FABP2 genotypes, no significant difference in age, body mass index, fasting glucose, insulin, or serum lipoproteins was observed. The content of arachidonic acid (AA) in fasting plasma was significantly lower in Thr54Thr carriers (x ± SD: 4.15 ± 0.94% wt/wt) than in Ala54Thr (5.24 ± 0.87%) or Ala54Ala (5.24 ± 0.86%) carriers (P = 0.0342, Kruskal-Wallis test). The index of D6D activity, estimated by the (18:3 + 20:3)/18:2 ratio, was significantly (P = 0.0091) lower in Thr54Thr carriers (0.05 ± 0.02) than in Thr54Ala (0.07 ± 0.02) or Ala54Ala (0.08 ± 0.02) carriers.

Recently, the linkage between D6D activity and obesity was investigated by Warensson et al (4). This study found that the risk of being overweight was increased by ∼60% for each 1-SD increase in D6D activity, which was estimated by the fatty acid profile of serum cholesteryl esters. Our group also studied D6D activity in children and found that the D6D was activated in obesity (5). The hypothetical mechanism proposed in rodent animal models is that the increased oxidation of AA must be met by compensatory activation of D6D (6). However, the activities of D6D and delta-5 desaturase are not modified in insulin-resistant animals, even though insulin is a strong activator of these enzymes (7, 8).

In an earlier study (5), our group found that ∼25% of obese children had low plasma AA content (> 1 SD below the mean) and a low ratio of AA to linoleic acid, probably because of an impaired compensatory production of AA. In addition, the obese children with low AA content had higher insulin concentrations, although their percentage body fat, waist circumference, and leptin concentrations were similar to those in obese children with normal AA content. AA itself affects the insulin sensitivity of adipocytes because AA can act as a ligand for peroxisome proliferator–activated receptor-γ (9). Our results are compatible with the suggestion by Das (10) that impaired D6D activity is associated with insulin resistance, and they may partly explain the metabolic heterogeneity of obesity. Furthermore, our recent study of FABP polymorphism suggests that Thr54Thr may be a predisposing factor for the impaired D6D activation in obesity. We speculate that the modulation of the absorbed fatty acid composition by FABP2 genotype may affect D6D activity and AA content and, thereby, insulin sensitivity.

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