How bad is fructose?1,2

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This issue of the Journal contains another disturbing article on the biology of fructose (1). Why is fructose of concern? First, it is sweeter than either glucose or sucrose. In fruit, it serves as a marker for foods that are nutritionally rich. However, in soft drinks and other “sweets,” fructose serves to reward sweet taste that provides “calories,” often without much else in the way of nutrition. Second, the intake of soft drinks containing high-fructose corn syrup (HFCS) or sucrose has risen in parallel with the epidemic of obesity, which suggests a relation (2). Third, the article in this issue of the Journal (1) and another article published elsewhere last year (3) implicate dietary fructose as a potential risk factor for cardiovascular disease.

The intake of dietary fructose has increased significantly from 1970 to 2000. There has been a 25% increase in available “added sugars” during this period (4). The Continuing Survey of Food Intake by Individuals from 1994 to 1996 showed that the average person had a daily added sugars intake of 79 g (equivalent to 316 kcal/d or 15% of energy intake), approximately half of which was fructose. More important, persons who are ranked in the top one-third of fructose consumers ingest 137 g added sugars/d, and those in the top 10% consume 178 g/d, with half of that amount being fructose. If there are health concerns with fructose, then this increased intake could aggravate those problems.

Before the European encounter with the New World 500 y ago and the development of the worldwide sugar industry, fructose in the human diet was limited to a few items. For example, honey, dates, raisins, molasses, and figs have a content of fructose. If there are health concerns with fructose, then this increased intake could aggravate those problems.

Fructose is an intermediary in the metabolism of glucose, but there is no biological need for dietary fructose. When ingested by itself, fructose is poorly absorbed from the gastrointestinal tract, and it is almost entirely cleared by the liver—the circulating concentration is $\approx 0.01$ mmol/L in peripheral blood, compared with 5.5 mmol/L for glucose.

Fructose differs in several ways from glucose, the other half of the sucrose (sugar) molecule (4). Fructose is absorbed from the gastrointestinal tract by a different mechanism than that for glucose. Glucose stimulates insulin release from the isolated pancreas, but fructose does not. Most cells have only low amounts of the GLUT-5 transporter, which transports fructose into cells. Fructose cannot enter most cells, because they lack GLUT-5, whereas glucose is transported into cells by GLUT-4, an insulin-dependent transport system. Finally, once inside the liver cell, fructose can enter the pathways that provide glycogen, the backbone for triacylglycerol. The growing dietary amount of fructose that is derived from sucrose or HFCS has raised questions about how children and adults respond to fructose alone or when it is accompanied by glucose. In one study, the consumption of high-fructose meals reduced 24-h plasma insulin and leptin concentrations and increased postprandial fasting triacylglycerols in women, but it did not suppress circulating ghrelin, a major appetite-stimulating hormone (4).

Fructose is metabolized, primarily in the liver, by phosphorylation on the 1-position, a process that bypasses the rate-limiting phosphofructokinase step (4). Hepatic metabolism of fructose thus favors lipogenesis, and it is not surprising that several studies have found changes in circulating lipids when subjects eat high-fructose diets (4). In the study conducted by Aeberli et al (1), dietary factors, especially fructose, were examined in relation to body mass index, waist-to-hip ratio, plasma lipid profile, and LDL particle size in 74 Swiss schoolchildren who were 6–14 y old. In that study, plasma triacylglycerols were higher, HDL-cholesterol concentrations were lower, and lipoprotein (LDL) particle size was smaller in the overweight children than in the normal-weight children. Fatter children had smaller LDL particle size, and, even after control for adiposity, dietary fructose intake was the only marker for foods that are nutritionally rich. However, in soft drinks and other “sweets,” fructose serves to reward sweet taste that provides “calories,” often without much else in the way of nutrition. Second, the intake of soft drinks containing high-fructose corn syrup (HFCS) or sucrose has risen in parallel with the epidemic of obesity, which suggests a relation (2). Third, the article in this issue of the Journal (1) and another article published elsewhere last year (3) implicate dietary fructose as a potential risk factor for cardiovascular disease.

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dietary factor related to LDL particle size. In this study, it was the free fructose, and not sucrose, that was related to the effect of LDL particle size. Studies in rodents, dogs, and nonhuman primates eating diets high in fructose or sucrose consistently show hyperlipidemia (4). The current report by Aeberli et al suggests that the higher intake of fructose by school-age children may have detrimental effects on their future risk of cardiovascular disease by reducing LDL particle size. It is interesting that this study did not find a relation of dietary fructose with triacylglycerols but did find a relation with the more concerning lipid particle, LDL cholesterol. Another recent report has proposed a hypothesis relating fructose intake to the long-known relation between uric acid and heart disease (3). The ADP formed from ATP after phosphorylation of fructose on the 1-position can be further metabolized to uric acid. The metabolism of fructose in the liver drives the production of uric acid, which utilizes nitric oxide, a key modulator of vascular function (3). The studies by Aeberli et al and Nakagawa et al suggest that the relation of fructose to health needs reevaluation.

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REFERENCES