

## VIEWPOINT

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## Examining the Health Effects of Fructose

**In the 1990s, excessive** fat consumption was commonly believed to be the main cause of obesity. High sugar consumption was often considered to be innocuous and possibly protective against obesity by displacing dietary fat.<sup>1</sup> A decade later, the American Heart Association linked intake of added sugars to weight gain and recommended substantial decreases in consumption to a daily maximum of 100 kcal for women and 150 kcal for men.<sup>2</sup> Some experts now argue that sugar comprises the single most important cause of the worldwide epidemics of obesity and diabetes, primarily through the effects of fructose at prevailing levels of consumption.<sup>3</sup> This Viewpoint examines the physiological effects of common sugars and argues against a narrow public health focus on fructose.

### Fructose vs Glucose

Fructose, a 6-carbon sugar, is more than twice as sweet as its isomer glucose. Most caloric sweeteners contain approximately equal amounts of these 2 sugars, either linked covalently in sucrose (table sugar) or as monosaccharide mixtures in high-fructose corn syrup and honey. Pure glucose, as found in unmodified corn syrup, has relatively little sweetness, and pure fructose may cause malabsorption in some people, limiting its practical use.

Despite chemical similarities, the metabolism of these 2 sugars differs markedly, and this difference underlies recent health concerns.<sup>3</sup> Following consumption, glucose potently stimulates insulin secretion, promoting glycogen synthesis in the liver and glucose uptake by tissues throughout the body. In contrast, fructose does not directly elicit insulin secretion and is taken up almost exclusively by the liver. Moreover, unlike glucose, the metabolism of fructose is not tightly regulated by liver cell energy state. Consequently, fructose rapidly undergoes glycolysis, fueling *de novo* lipogenesis under some conditions. This newly synthesized lipid may accumulate locally, causing fatty liver and hepatic insulin resistance, or be exported, increasing serum triglycerides, systemic insulin resistance, and fat deposition in adipose tissue. Fructose metabolism may also up-regulate hepatic signal transduction pathways involved in inflammation and drive uric acid production, possibly contributing to hypertension and endothelial dysfunction. Consistent with these mechanisms, feeding studies have demonstrated marked metabolic aberrations—including insulin resistance, dyslipidemia, higher blood pressure, and increased visceral adiposity—among obese individuals consuming fructose compared with glucose.<sup>3</sup>

However, these feeding studies have been criticized for providing unrealistically high amounts of fructose, typically exceeding the 95th percentile of consumption by 50% or more.<sup>4</sup> A recent meta-analysis found no adverse effects of isocaloric substitution of fructose and glucose at average consumption levels for body weight, lip-

ids, blood pressure, uric acid, or insulin levels and found possible benefit for glucose tolerance and glycemic control in diabetes.<sup>5</sup> The monosaccharide feeding studies have also been criticized because humans virtually always consume fructose together with glucose, as in sucrose, high-fructose corn syrup, or honey, not in isolation.<sup>4</sup>

Another argument against fructose having uniquely harmful effects involves the glycemic index, a measure of how food affects blood glucose in the postprandial period. Glucose and most commonly consumed starchy foods (all starches are polymers of glucose) have a high glycemic index, whereas fructose has an exceptionally low value. If the effects of fructose on health predominated, and the various forms of glucose were innocuous, then the glycemic index should have a null or inverse association with disease risk. However, systematic reviews and meta-analyses have linked a high glycemic index diet to the same adverse effects as fructose, including obesity and diabetes.<sup>6,7</sup>

In light of these considerations, a critical scientific question is whether replacement of fructose-containing sweeteners at prevailing consumption levels with glucose (as a monosaccharide or as starch) would provide health benefits. If so, a specific public health focus on fructose may be warranted. If not, then broader measures targeting all highly processed carbohydrate foods would be indicated. However, no modern controlled feeding studies adequately address this question, but research dating back to the 1970s is informative. In 1 study, 9 men and women, aged 37 to 62 years, living in a metabolic ward consumed a high-sugar diet (containing 70% of carbohydrate as sucrose, an average of about 675 kcal/d) or a sucrose-free diet (containing wheat and potato starch), each for 4 weeks. Upon repeated measurements, fasting blood glucose was slightly higher (3 mg/dL) for the sucrose condition but no differences between diets were found in body weight, glucose tolerance, fasting and stimulated insulin, cholesterol, triglycerides, or nonesterified fatty acids.<sup>8</sup>

### Digestion Rate, Not Dose

Fruit is the primary natural source of fructose. Most fruits have about 10 g of fructose, as monosaccharide or sucrose, per 80-kcal serving, comprising at least half the total sugar content. If fructose were toxic at high dosage, then individuals consuming large amounts of fruit might experience adverse effects. However, observational studies report inverse associations between fruit consumption and body weight or risk of obesity-associated diseases, with no evident upper threshold for protection,<sup>9</sup> although some studies do not adequately distinguish between fruits and vegetables. In possibly the only interventional study of its kind, 17 Bantu and white adults in South Africa, aged 20 to 64 years, consuming a Western diet were instructed to eat primarily fruit (20

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servings per day for the typical participant) supplemented with nuts to satisfy basic macronutrient requirements.<sup>10</sup> Despite the extraordinarily high fructose content of this diet, presumably about 200 g/d, the investigators reported no adverse effects (and possible benefit) for body weight, blood pressure, and insulin and lipid levels after 12 to 24 weeks. Nevertheless, findings from this study must be interpreted cautiously because of important design limitations, including lack of an active control group.

The absence of harm from high fruit consumption likely relates to the slow digestion rate of whole fruit compared for example with a sugar-sweetened beverage, producing portal fructose concentrations that do not exceed hepatic metabolic capacity. Although soluble fiber helps to reduce sugar absorption rates from the digestive tract (primarily by increasing luminal viscosity), the physical form and cellular structure of whole fruit probably have a greater effect, by sequestering sugar away from the absorptive surface of the small intestine. In addition, the high micronutrient and antioxidant content of fruit may protect against hepatic inflammation and systemic insulin resistance.

## Conclusions

Few modern studies have compared the long-term effects of glucose, fructose, and starch under physiologically relevant condition, and such research should assume high priority. The available evidence suggests 3 key points. First, fructose in its primary natural form (whole fruit) is not associated with adverse effects up to the limits of human consumption. Second, excessive intake of refined sugar plays a significant role in the epidemics of obesity and related diseases, in part because large amounts of rapidly absorbed fructose can overwhelm hepatic biochemical pathways. Third, rapidly absorbed forms of glucose—present in both sugar and high glycemic index starch—also contribute importantly to these diseases, especially considering their much greater caloric contribution to typical diets than fructose. Therefore, the recommendation to replace fructose with glucose lacks an evidence basis. Rather, public health efforts should focus on reducing intakes of all highly processed carbohydrates, not just refined sugar.

## ARTICLE INFORMATION

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