

How safe is fructose for persons with or without diabetes?¹⁻³

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In this issue of the journal, Livesey and Taylor (1) present a meta-analysis of clinical trials evaluating the effects of fructose intake. They concluded that fructose is safe at doses of <90 g/d and that it may have the added benefit of lowering concentrations of glycated hemoglobin (HbA_{1c}). This meta-analysis is difficult to interpret, because it involves randomized and nonrandomized studies of differing designs, mixed populations (diabetic and nondiabetic, lean and obese), different control diets (including some sucrose-based diets that contained fructose), different study durations, and limited endpoints; it also represents an analysis by an industry-sponsored group of a highly selected list of studies (42 of 3331). Nevertheless, it is important to discuss the conclusions of Livesey and Taylor in light of current knowledge of fructose and its metabolic effects.

Fructose is a simple sugar found in honey, fruit, table sugar (sucrose), and high-fructose corn syrup (HFCS). Because of the worldwide increase in the consumption of these sweeteners, fructose intake has quadrupled since the early 1900s (2). The past 30 y have witnessed an even greater acceleration in consumption, in part because of the introduction of HFCS; this phenomenon parallels the rise in obesity, diabetes, hypertension, and kidney disease (2, 3). Whereas associations do not prove cause-and-effect, experimental studies in animals have shown that fructose can induce most features of the metabolic syndrome, including insulin resistance, elevated triglycerides, abdominal obesity, elevated blood pressure, inflammation, oxidative stress, endothelial dysfunction, microvascular disease, hyperuricemia, glomerular hypertension and renal injury, and fatty liver. These effects are not seen in animals pair-fed glucose or starch, which suggests that the mechanism is not mediated by excessive caloric intake (4). The consumption of large amounts of dietary fructose also can rapidly induce insulin resistance, postprandial hypertriglyceridemia, and blood pressure in humans more than starch (or glucose) does in controls (3, 5, 6). Moreover, it is a potential risk factor for fatty liver disease (7).

Fructose causes metabolic syndrome because of its unique metabolism that results in intracellular ATP depletion, uric acid generation, endothelial dysfunction, oxidative stress, and lipogenesis (3, 8). An understanding of the mechanisms clarifies the variability of responses reported in the literature. Rodent studies are often criticized, because they typically use large supraphysiological doses (60%). However, rodents are resistant to fructose because they synthesize vitamin C, have low uric acid concentrations, and have good endothelial function (3). If uric acid concentrations are raised (9) or if low doses are prolonged (10),

then insulin resistance is readily induced. The variability in human studies can also be explained by a clarification of fructose metabolism (3). For example, fructose uniquely up-regulates its own transporter (Glut5) and metabolism (fructokinase) (7), and, thereby, the more fructose one eats, the more sensitive one becomes to its effects. This is a potential explanation for the fact that obese persons appear to be more sensitive to the lipogenic effects of acute fructose ingestion than are nonobese persons (6).

Fructose consumption is associated with weight gain, but, as Livesey and Taylor discuss, that association has not been consistently shown in short-term clinical trials. Nevertheless, fructose does not appear to trigger the endocrine signals involved in the long-term control of energy balance to the same extent as does glucose (8). Ingestion of glucose stimulates insulin secretion, which also results in the release of leptin by adipocytes and the inhibition of ghrelin secretion from the gastrointestinal tract, and these alterations stimulate centers in the brain that regulate satiety and energy homeostasis. However, fructose does not acutely stimulate insulin, which would lead to attenuated leptin and ghrelin responses (11). In one study, subjects fed fructose reported a greater appetite the following day than did glucose-fed controls (11). Chronic administration of fructose also may result in leptin resistance. In one study, rats fed fructose for 4 mo developed leptin resistance and, when switched to high-fat high-energy diets, showed greater energy intake and weight gain than did starch-fed controls (12).

Fructose does not acutely raise blood glucose. As such, fructose has a lower glycemic index than do starch-based foods, and it has been used as an energy source in diabetes patients because it may aid glycemic control. The conclusion by Livesey and Taylor that, in a small number of studies, HbA_{1c} was lowered in subjects receiving fructose is consistent with this finding. Whereas low (catalytic) doses of fructose may improve glucose control in diabetes patients, the effects of fructose in inducing features of metabolic syndrome, stimulating the production of

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advanced glycation endproducts, and causing cataracts in diabetic animals make fructose a poor choice for a diabetes patient, a conclusion also held by the American Diabetes Association (13). Indeed, we have proposed that it is the fructose content of sweeteners (sucrose and HFCS, which have a relatively high glycemic index due to the presence of glucose) that is largely responsible for correlation of the glycemic index with cardiovascular disease in persons without diabetes and that a better index for cardiovascular risk may be a fructose index based on the percentage and amount of fructose in various foods (3).

One of the central issues raised in the article by Livesey and Taylor is whether high doses of fructose (>50 g/d) are safe. They concluded that fructose intake up to 90 g/d may actually be beneficial because of its effects of lowering HbA_{1c} concentrations, despite the potential countering effects of increases in plasma triglycerides. However, it is probably misleading to conclude that this amount of fructose consumption is safe by examining only the effects of fructose on plasma triglycerides, weight, and HbA_{1c}. Indeed, there is increasing evidence that high fructose intake can also raise blood pressure, decrease insulin sensitivity, lower glucose tolerance, increase apolipoprotein-B concentrations, and cause microvascular disease, glomerular hypertension, renal injury, fatty liver, systemic inflammation, endothelial dysfunction, oxidative stress, and activation of the renin angiotensin system (5, 14, 15). Whereas some of these effects have been reported only in animals, these findings raise important questions about the safety of high doses of fructose in humans.

In conclusion, obesity and diabetes rates were low when total fructose intake was in the range of 25–40 g/d. Conclusions as to the safe and prudent amounts of fructose consumption will require carefully controlled dose-responses studies in different populations, including subjects with metabolic syndrome who are at greater risk of diabetes and cardiovascular disease, rather than depending on meta-analyses of existing studies of mixed design and duration. Clinical trials with low-fructose diet interventions also will be useful in determining the effects of lowering fructose consumption on metabolic outcomes.

RJJ and MS are listed as inventors on pending patent applications related to blocking the effects of fructose on the metabolic syndrome and renal disease. RJJ also is the author of the book *The Sugar Fix*, published by Rodale, Inc. LSG-L and MPL had no personal or financial conflict of interest.

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