MAYO CLINIC

# Added Fructose: A Principal Driver of Type 2 Diabetes Mellitus and Its Consequences

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## Abstract

Data from animal experiments and human studies implicate added sugars (eg, sucrose and high-fructose corn syrup) in the development of diabetes mellitus and related metabolic derangements that raise cardiovascular (CV) risk. Added fructose in particular (eg, as a constituent of added sucrose or as the main component of high-fructose sweeteners) may pose the greatest problem for incident diabetes, diabetes-related metabolic abnormalities, and CV risk. Conversely, whole foods that contain fructose (eg, fruits and vegetables) pose no problem for health and are likely protective against diabetes and adverse CV outcomes. Several dietary guidelines appropriately recommend consuming whole foods over foods with added sugars, but some (eg, recommendations from the American Diabetes Association) do not recommend restricting fructose-containing added sugars to any specific level. Other guidelines (such as from the Institute of Medicine) allow up to 25% of calories as fructose-containing added sugars. Intake of added fructose at such high levels would undoubtedly worsen rates of diabetes and its complications. There is no need for added fructose or any added sugars in the diet; reducing intake to 5% of total calories (the level now suggested by the World Health Organization) has been shown to improve glucose tolerance in humans and decrease the prevalence of diabetes and the metabolic derangements that often precede and accompany it. Reducing the intake of added sugars could translate to reduced diabetes-related morbidity and premature mortality for populations.

Worldwide, approximately 1 in 10 adults has type 2 diabetes mellitus, with the number of individuals diagnosed as having the disease more than doubling from 153 million in 1980 to 347 million in 2008.[1] In the United States, 29 million adults (1 in 11) have type 2 diabetes and another 86 million (more than 1 in 3) have prediabetes.[2] In other terms, approximately 40% of US adults already have some degree of insulin resistance, with projections that nearly the same percentage will eventually develop frank diabetes.[3]

Insulin resistance is associated with hyperinsulinemia, a condition that may promote abdominal-fat storage, increased triglyceride levels, and other metabolic disturbances[4]—all part of a broader metabolic syndrome[5] that is sometimes referred to as insulin-resistance syndrome. Markers of insulin resistance predict future cardiovascular (CV) risk,[6,7] with hyperinsulinemia being an independent risk factor for coronary heart disease.[8,9] Individuals with insulin-resistant (ie, type 2) diabetes have a life

expectancy 5 to 10 years shorter than those unaffected by the disease, with much of the difference due to CV causes.[4]

Given substantial risks in terms of morbidity and mortality, there is great interest in diabetes prevention and treatment. Key to both of these issues is dietary intake, specifically the consumption of added sugars—one of the most fundamental determinants of glucose metabolism. Of the added sugars, fructose appears to be particularly pernicious with regard to glucose metabolism.[10-12] There is a considerable body of basic science evidence, observational data, and clinical trial findings to suggest added fructose—even relative to other sugars—is a primary driver of diabetes development and consequences.

## BASIC SCIENCE DATA

From an evolutionary standpoint, the body's response to fructose may have conferred a survival advantage.[13] Fructose stimulates epigenetic changes[14] and metabolic alterations that

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shunt calories into storage depots in abdominal fat cells.[4] Such effects were desirable for early humans who may have needed to endure long periods of food scarcity. Whereas fructose in Paleolithic times was likely encountered only rarely and seasonally (at least in populations living in nontropical climates) in low concentrations as ripened fruit, fructose today is ubiquitous in all seasons and encountered in high concentrations in processed foods.[11]

At a molecular level, fructose is a monosaccharide that when combined with the monosaccharide glucose forms the disaccharide sucrose, otherwise known as table sugar or simply "sugar". Sucrose is commonly used in processed foods and beverages; however, its predominance in processed items has gradually been surpassed by another sweetener—high-fructose corn syrup (HFCS).[15] Whereas sucrose contains 50% fructose (and 50% glucose), HFCS (particularly as found in soft drinks) commonly contains up to 65% fructose.[10,16,17] The fructose in HFCS represents nearly 50% of the sweetener's weight.[18] By comparison, the fructose in a fresh peach represents only about 1% of the sweet fruit's weight.[19]

In both human[20] and animal studies,[21,22] concentrated fructose loads have been found to decrease adenosine triphosphate content in the liver. This effect may contribute to decreased cellular binding of insulin, possible reduction in the number of insulin receptors, and subsequent insulin resistance.[23,24] Fructose also increases hepatic de novo lipogenesis and reduces hepatic fatty acid oxidation, both of which can lead to increased accumulation of fat in the liver, which subsequently triggers inflammation and hepatic insulin resistance.[25,26] Increased hepatic insulin resistance promotes increased insulin secretion from pancreatic β-cells, which can result in progressive β-cell dysfunction.[27] Over time, deterioration in β-cell function can lead to inadequate insulin secretion, compounding fructose-induced inflammation and oxidative stress, and making hepatic insulin resistance worse.[28-32]

Fructose may also induce peripheral (skeletal muscle) insulin resistance by prompting excessive hepatic free fatty acid production, increased free fatty acid release from very-low density lipoproteins, and intramyocellular lipid accumulation.[28,33] In addition, fructose can increase hepatic gluconeogenesis, raising serum glucose levels and placing further stress on the pancreatic β-cells.[28]

The net result of excess consumption of added fructose is derangement of both hepatic and systemic metabolism and global insulin resistance. Other dietary sugars not containing fructose have been found to be less detrimental in these respects. For example, in a 6-month randomized trial in overweight individuals, compared with isocaloric milk, diet soda, and water, sucrose-sweetened sodas alone increased ectopic fat accumulation and lipids.[34] This finding suggests that sucrose is more harmful compared to lactose and sugar-substitutes.

Sucrose—the combination of fructose with glucose—has also been found to induce insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension when consumed in large quantities, just as fructose does alone.[25,35-52] However, comparing the effects of isolated glucose vs isolated fructose, the negative effect of fructose administration on insulin sensitivity is more pronounced. In fact, decreased insulin binding to monocytes and a 25% reduction in insulin sensitivity have been found in healthy volunteers fed isolated fructose vs glucose.[23] Isolated fructose also induces greater detrimental effects on glucose, insulin, and triglyceride concentrations compared with glucose, and isolated fructose has been found to promote greater food intake, body weight, and liver weight in rodents.[53]

Replacing starch (an all-glucose polymer) with sucrose (glucose and fructose) increases fasting insulin, reduces insulin sensitivity, and leads to increased glucose concentrations.[54-60] The change also leads to a variety of other undesirable metabolic effects, including increased cholesterol, apolipoprotein B, triglycerides, adipose storage, and blood pressure.[54-60] Trials looking at isolated fructose (vs starch or glucose) reveal the same derangements, supporting the notion that fructose is the likely component of sucrose that causes the adverse metabolic effects.[42,52,61-63] Animal data are corroborated by experimental trials in humans, indicating that isolated fructose promotes impaired glucose tolerance vs other types of carbohydrates even when matched for total caloric intake.[23,25,64]

Fructose consumption—as from sucrose or HFCS—has been linked not only to diabetes-related metabolic abnormalities but also to end-organ damage and diabetic complications.