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.

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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.

Isolated fructose causes renal injury in animals,[65-67] and fructose consumption from soft drinks (ie, HFCS) is associated with kidney disease in humans.[68] Chronic isolated fructose feeding in rodents is associated with diffuse glomerulosclerosis,[69] whereas sibling rodents fed starch do not develop this renal abnormality or diabetic microangiopathy as fructose-fed rodents do. Sucrose feeding in rodents causes intercapillary glomerulosclerosis,[70] and fructose alone promotes other diabetes-related microvascular complications, such as impaired motor nerve conduction velocity (ie, neuropathy).[71] Postprandial fructose levels are associated with retinopathy in patients with type 2 diabetes,[72] and animal data have revealed that fructose is the component of sucrose that leads to retinopathy.[73] Isolated fructose feeding in rats also causes arterial atherogenesis.[74]

Overall, the evidence in the literature suggests that added fructose—from sucrose or HFCS—is associated with a variety of undesirable biological effects in both humans and animals. These effects may include epigenetic regulation of intestinal fructose transporters during early development, making absorption of future ingested fructose more efficient from the gastrointestinal tract and thereby inducing further harm.[14] Nonetheless, many of the adverse biological effects (eg, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension) can be reversed by reducing sources of added fructose in the diet.[41,75,76]

OBSERVATIONAL DATA

Although fructose is found naturally in some whole foods, such as fruits and vegetables, consumption of these foods poses no problem for human health and indeed may be protective against diabetes and broader cardiometabolic dysfunction.[77,78] Moreover, consumption of whole fruits and vegetables is associated with reduced premature mortality.[79] The difference may be a matter of dose and context; fructose in natural foods exists in lower concentrations (eg, the peach example from earlier) and is accompanied by water, fiber, antioxidants, and other whole-food constituents. In this way, whole foods are very much unlike the predominant sources of fructose in the American diet: processed products, with their high amounts of added sugars, high proportions of fructose, and low amounts of natural compounds that might slow absorption or buffer the sugar load.

Processed foods (including beverages), created in industrial manufacturing plants, bear little resemblance to whole foods grown on living botanical plants. The consumption of processed foods and beverages is associated with markedly poor health outcomes.[80,81] A recent meta-analysis of human studies revealed that increasing consumption of fructose from processed foods and beverages is associated with higher fasting blood glucose levels.[82] Sugar-sweetened beverages (which are most often actually HFCS-sweetened) may be of particular concern. These products provide the greatest quantities of added fructose in the diet,[83] and their consumption is notably high in individuals with diabetes, particularly those whose condition is undiagnosed.[84] Observational studies have found that sugar-sweetened beverages are associated with type 2 diabetes, abdominal obesity, and the metabolic syndrome.[85-89] Stronger associations are noted in larger studies of longer duration,[90,91] and systematic reviews and meta-analyses corroborate these adverse effects.[85,92-94]

Even 100% fruit juice (although technically not a sugar-sweetened beverage) provides high concentrations of fructose, removed from its usual biological context (eg, whole fruit). The consumption of fruit juice is associated with both increased body weight and risk of diabetes[95-97]; associations that are also seen with the consumption of artificially sugared beverages[98] but not with the consumption of whole fruits (examples of fructose content per 100 g: peach [1 g], raspberries [2g], strawberries [2 g], blackberries [3 g], cranberries [3 g], apple [6 g], grapes [7 g]).[19,99]

Carbohydrate intake, particularly intake of sucrose (glucose and fructose), has been directly correlated with fasting insulin levels and insulin concentrations 2 hours after a glucose load.[100] But correlations were not as strong when looking solely at starch. The observational study that produced these findings used a 7-day weighed-food assessment, which provides a relatively robust method to estimate nutrient intake, giving more credence and relevance to the findings.

Other observational studies have found that insulin levels directly correlate with dietary sucrose intake,[101] and higher total sugar intake is independently and significantly associated

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with lower β-cell function.[102] In particular, in one study, sugar-sweetened beverage consumption was associated with lower insulin secretion in overweight children, suggesting that consuming these beverages for an extended period can place added stress on β-cells and promote insulin deficiency.[102] The authors of the study concluded that "modest reductions in sugar intake could potentially preserve β-cell function and prevent metabolic disorders."

Additional ecologic data suggest that the availability of sugars is independently associated with an increased prevalence of diabetes, even after adjustment for other covariates.[26,103] Each extra year of exposure to high sugar availability has been associated with an increased prevalence of diabetes.[26] Moreover, the risk of diabetes was 11-fold higher with each 150-kcal per person per day increase in sugar vs 150-kcal per person per day increase in total calorie availability.[26] Because no other food types have yielded significant associations with diabetes prevalence after controlling for obesity, calorie intake, and other confounders, the implication is that sugar—compared with other food types—is particularly harmful for inducing diabetes.

Among the sugars, HFCS availability has independently predicted greater diabetes prevalence, even when adjusting for obesity and total sugar and calorie availability.[10] Because HFCS may have as much as 50% more fructose in it than glucose, the suggestion is that added fructose is particularly detrimental for promoting diabetes.[17]

CLINICAL TRIALS

One human trial investigated the isocaloric exchange of sucrose for starch among individuals with normal glucose tolerance. When sucrose was provided in a "nibbling pattern" (small doses at frequent intervals throughout the day), no statistically significant increase in insulin levels was found,[104] suggesting (as with the difference between processed foods and natural fruit) that dose and context are important. However, even lower doses buffered by other dietary constituents resulted in increased fasting glucose levels in the trial.[104]

Moreover, in another trial—this time among adults who were already likely insulin resistant (having an exaggerated insulin response to a sucrose load)—substitution of sucrose for wheat starch produced more obvious detriment.[40] In the trial, sucrose of 5%, 18%, or 33% of total daily calories replaced an isocaloric amount of wheat starch, but the overall carbohydrate level was held constant in all groups. Men receiving 18% sucrose had significantly higher mean fasting serum insulin levels at 6 weeks vs those receiving 5% sucrose. In women, the 33% sucrose diet caused a significantly higher fasting insulin level vs the 18% sucrose diet. In addition, the 6-week mean glucose levels, the serum insulin response to a sucrose load, and the glucose response to a sucrose load were all higher for men and women when comparing the 18% and 33% sucrose diets vs the 5% sucrose diet.

Similar findings were reported from another trial in which sucrose was substituted for wheat starch in glucose-intolerant individuals. Sucrose, compared with wheat starch, produced increases in fasting serum insulin, insulin to glucose ratio, and insulin response to a given sucrose load.[64]

Taken together, the trials above suggest (1) that replacing glucose-only starch with fructose-containing sucrose results in significant adverse metabolic effects, (2) that adverse effects are broader with increasing baseline insulin resistance, and (3) that adverse metabolic effects are more profound with greater proportions of added fructose in the diet.

One of the trials suggests that consuming a diet low in sucrose (5%) may normalize fasting insulin levels. Indeed, the prevalence of individuals being classified as having diabetes or borderline diabetes was more than 50% lower on the 5% sucrose diet vs the 18% and 33% sucrose diets.[40]

Conversely, a recent meta-analysis of controlled feeding trials in individuals with diabetes indicated that isocaloric exchange of isolated fructose for other carbohydrates actually improved glycemic control.[105] However, most of the included trials had major limitations, including short duration and a study population of patients who already had diabetes and often were using hypoglycemic agents or insulin-sensitizing medications. The conclusions from this meta-analysis may not apply to individuals without insulin resistance or to insulin-resistant individuals who are not using antidiabetic medications. More important, almost all of the included studies in this meta-analysis were funded by the food industry, which raises serious

concerns about financial conflicts of interest and bias. Indeed, another recent meta-analysis found that among trials with financial conflicts to the food industry, 83.3% found insufficient support of a positive association between sugar-sweetened beverage consumption and weight gain, whereas among trials without any reported conflicts, the same percentage (83.3%) found that sugar-sweetened beverage consumption was a potential risk factor for weight gain.[106]

In a trial of men with both normal and elevated insulin levels, replacing starch with moderate amounts of isolated fructose (7.5%-15% of total caloric intake) for just 5 weeks caused elevations in fasting glucose and insulin levels and also led to elevations in insulin and glucose responses to a sucrose load.[107] Replacing starch with sucrose or isolated fructose was found in another trial to increase fasting blood glucose in patients with type 2 diabetes.[108]

Nonetheless, all these dietary-replacement trials likely have low applicability to the real world, where isocaloric exchanges are unlikely and sugar may be consumed in addition to, rather than in place of, starch and other dietary constituents. Overall overconsumption may result because sugar stimulates increased food intake[109,110] and additional intake of other sugary foods in particular[111] or because it fails to induce satiety, particularly if ingested in liquid form.[112] Trials that restrict total calories may miss effects related to postprandial hyperglycemia, hyperinsulinemia, compensatory hypoglycemia, and increased hunger due to sugar intake.[113-115]

Widespread metabolic derangements are seen when sucrose is consumed. A randomized trial that consisted of 14 young men following either a high-sugar diet (260 g of sucrose) or a moderate-sugar diet (115 g of sucrose) found lower high-density lipoprotein cholesterol levels and increases in *N*-acetyl-glucosaminidase—an early indicator of kidney damage—among the high-sugar group.[116] Detriment occurred after just 3 weeks, and markers did not improve after 2 weeks of reverting back to a diet lower (albeit still rather high) in sugar. Another randomized trial tested a diet high in isolated fructose (200 g/d), specifically in 74 adult men, and found increases in fasting insulin level and homeostatic model assessment index (a measure of insulin resistance and β-cell function).[46]

Human trials also suggest that protection from diabetes and its consequences can be achieved by limiting added-fructose consumption. A study randomizing 131 patients to 2 different diets low in added fructose found significant and comparable improvements in serum glucose and insulin resistance vs baseline.[76] Lowering fructose intake from 59 to 12 g/d has been shown to lower fasting insulin levels in patients with chronic kidney disease.[75] A low-fructose diet has also been shown to lower blood pressure and inflammation and improve renal function.[75]

DISCUSSION

From 1776 to 1994, the estimated consumption of added sugar by Americans increased from 4 lb per person per year to 120 lb per person per year.[80] Approximately 75% of all *packaged* foods and beverages in the United States today have sugars added to them,[117] and 13% of the US population consumes at least 25% of their total calories as added sugars.[118] Estimated consumption of sugar-sweetened beverages has increased from 10.8 gallons per person per year in 1950 to 49.3 gallons in 2000.[80] The proportion of total sugar consumed in the form of beverages has also increased, from one-third of the total added sugar intake in the 1960s and 1970s to two-thirds in 2000.[80] The mean daily consumption of fructose is now 83.1 g per person in the United States,[118] which is likely an underestimation[10] because fructose is not required to be disclosed on nutrition labels and amounts that actually occur in processed foods are higher than once thought.[17] More worrisome, up to 20% of the population exceeds 100 g/d of fructose consumption.[66]

At current levels, sugar consumption and fructose consumption in particular—in concentrations and contexts not seen in natural whole foods—are fueling a worsening epidemic of type 2 diabetes.[25,64,107,119] Even without existing data for the duration of diabetes' 20-year incubation period,[4,120] shorter-term basic science evidence, observational data, and clinical trial findings present compelling evidence to suggest that added sugar and especially added fructose (provided from HFCS and sucrose) present a serious and increasing public health problem.

Several dietary guidelines appropriately recommend consuming whole foods rather

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than foods with added sugars. However, the American Diabetes Association and the 2010 Dietary Guidelines for Americans do not recommend restricting fructose-containing added sugars to any specific level. More worrisome, is that the 2010 Dietary Guidelines for Americans allow up to 19% of total caloric intake as added sugars (depending on total caloric intake),[121] and the Institute of Medicine allows up to 25% of calories as added sugars in its recommendation statements (regardless of total calorie intake).[122] Encouragingly, the World Health Organization recommends that added sugars should make up no more than 10% of an entire day's caloric intake, with a proposal to lower this level to 5% or less for optimal health.[123] Such levels would be similarly restrictive to the existing American Heart Association recommendation to consume no more than 6 tsp (24g, providing 100 calories) of sugar per day for women and 9 tsp (36 g, providing 150 calories) of sugar per day for men.[124] Whereas less restrictive guidelines place individuals at risk for development or worsening of diabetes, more restrictive recommendations have the potential to help protect populations from diabetes and its CV and other consequences. Essential points regarding added sugars and fructose promoting type 2 diabetes are summarized in Table 1 and Table 2.[124,125]

TABLE 1. Essential Points Regarding Added Sugars and Fructose

Added sugar and high-fructose corn syrup elevate diabetes risk *independent* of their effect on weight.[10,26]
High-fructose corn syrup elevates diabetes risk even when adjusted for overall sugar availability and caloric intake.[10]
Fructose is the likely moiety of sucrose and high-fructose corn syrup that induces insulin resistance.[25]
In animals and humans, isocaloric replacement of starch (chains of glucose) with sucrose (glucose and fructose) or fructose has been found to do the following: 1. Increase fasting insulin levels[64,119] 2. Reduce insulin sensitivity,[23,56,58] 3. Increase fasting glucose concentrations[104] 4. Increase glucose and insulin responses to a sucrose load[64,119] 5. Reduce cellular insulin binding[23]
Biological response to fructose consumption may have been adaptive for early human ancestors who encountered fructose rarely and in low concentrations in the form of ripened fruit.[11,13] The same biological response is maladaptive when the fructose is encountered frequently and in high concentrations as added sugar in processed foods.
Approximately 75% of all foods and beverages in the United States contain added sugars.[117]
The Institute of Medicine and 2010 Dietary Guidelines for Americans allow for an added sugar intake, which–if consumed at the upper recommended limit—could reasonably induce type 2 diabetes mellitus.
By limiting sugar to 5% to 10% of total caloric intake, the harmful effects of sugar, particularly fructose, on insulin resistance could be minimized.
Reducing fructose consumption may protect against diabetes and its complications,[40,76] including early mortality from cardiovascular causes.[125]

CONCLUSION

There is no biological need for any added sugars in the diet, particularly those containing fructose (eg, sucrose and HFCS). Although biological response to fructose consumption may have been adaptive for early human ancestors, this response evolved from fructose encountered rarely (at least in populations not living in tropical regions) and in low concentrations in nature. The same biological response is maladaptive when the fructose is encountered frequently and in high concentrations in processed foods. Indeed, what once conferred a survival advantage in the context of scarcity may be a decided disadvantage in the context of overabundance. Avoiding processed foods altogether would be ideal, although this end seems unlikely given the current prominence—indeed predominance—of processed foods in the US diet. Dietary guidelines should encourage individuals to replace processed foods with whole foods, such as fruits and vegetables, and should incentivize industry to add less sugar, especially fructose-containing varieties, to food and beverage products. Most existing guidelines fall short of this mark at the potential cost of worsening rates of diabetes and related CV and other consequences. The existing basic science evidence, observational data, and clinic trial findings suggest that reducing consumption of added sugars, particularly added fructose, could translate to reduced diabetes-related morbidity and potentially premature mortality. At an individual level,

TABLE 2. How Sucrose and High-Fructose Corn Syrup Cause Type 2 Diabetes Mellitus

Increased liver fat accumulation and subsequent hepatic insulin resistance[28]
Increased free fatty acid release from very-low density lipoprotein, resulting in intramyocellular lipid accumulation and skeletal muscle insulin resistance[28]
Decreased cellular adenosine triphosphate, leading to reduced cellular binding of insulin and a possible reduction in the number of insulin receptors[23]
Increased inflammation and oxidative stress, leading to β-cell damage and reduced insulin secretion[28]

limiting consumption of foods and beverages that contain added sugars, particularly added fructose, may be one of the most effective strategies for ensuring one's robust future health.

Abbreviations and Acronyms: **CV** = cardiovascular; **HFCS** = high-fructose corn syrup

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