Adverse Effects of Dietary Fructose

Alan R. Gaby, MD

Abstract

The consumption of fructose, primarily from high-fructose corn syrup (HFCS), has increased considerably in the United States during the past several decades. Intake of HFCS may now exceed that of the other major caloric sweetener, sucrose. Some nutritionists believe fructose is a safer form of sugar than sucrose, particularly for people with diabetes mellitus, because it does not adversely affect blood-glucose regulation, at least in the short-term. However, fructose has potentially harmful effects on other aspects of metabolism. In particular, fructose is a potent reducing sugar that promotes the formation of toxic advanced glycation end-products, which appear to play a role in the aging process; in the pathogenesis of the vascular, renal, and ocular complications of diabetes; and in the development of atherosclerosis. Fructose has also been implicated as the main cause of symptoms in some patients with chronic diarrhea or other functional bowel disturbances. In addition, excessive fructose consumption may be responsible in part for the increasing prevalence of obesity, diabetes mellitus, and non-alcoholic fatty liver disease. Although the long-term effects of fructose consumption have not been adequately studied in humans, the available evidence suggests it may be more harmful than is generally recognized. The extent to which a person might be adversely affected by dietary fructose depends both on the amount consumed and on individual tolerance. With a few exceptions, the relatively small amounts of fructose that occur naturally in fruits and vegetables are unlikely to have deleterious effects, and this review is not meant to discourage the consumption of these healthful foods. ***(Alternative Medicine Review* 2005;10(4):294-306)**

Introduction

The consumption of fructose, primarily from high-fructose corn syrup (HFCS), has increased considerably in the United States during the past several decades. The increase in HFCS consumption far exceeds the increases in intake of any other food or food group. HFCS is now used extensively in carbonated beverages and other sweetened drinks, baked goods, candies, canned fruits, jams, jellies, and dairy products. Processed-food manufacturers often prefer HFCS to sucrose because it is inexpensive to produce and mixes well in many foods. From 1970 to 1997, annual per capita intake of this sweetener increased from 0.5 pounds to 62.4 pounds, while sucrose consumption decreased from 102 pounds to 67 pounds.[1] During that same time period, fructose consumption (as estimated by disappearance data) from the combined intake of sucrose and HFCS increased by 26 percent, from 64 g/day in 1970 to 81 g/day in 1997. Perusal of the labels on many processed foods suggests that HFCS intake now exceeds that of sucrose, although published data after 1997 are not available. In contrast, intake of naturally occurring fructose from fruits and vegetables is only about 15 g/day.

Sucrose is a disaccharide, consisting of one molecule of glucose and one molecule of fructose. HFCS, on the other hand, contains fructose (55% by weight; 56.7% of total calories) and glucose (42% by weight; 43.3% of total calories) in their monosaccharide forms. If only the monosaccharide form of fructose is considered, per capita fructose consumption (excluding that which occurs naturally in fruits

Alan R. Gaby, MD – Private practice 17 years, specializing in nutritional medicine; past-president, American Holistic Medical Association; contributing editor, *Alternative Medicine Review*; author, *Preventing and Reversing Osteoporosis* (Prima, 1994) and *The Doctor's Guide to Vitamin B6* (Rodale Press, 1984); co-author, *The Patient's Book of Natural Healing* (Prima, 1999); published numerous scientific papers in the field of nutritional medicine; contributing medical editor, *The Townsend Letter for Doctors and Patients* since 1985.
Correspondence address: 301 Dorwood Drive, Carlisle, PA 17013

and vegetables) increased from less than 0.5 g/day in 1970 to more than 40 g/day in 1997 (more than an 80-fold increase). Distinguishing free fructose from the fructose contained in sucrose is more than a mere academic exercise, because there may be significant differences in the way these two forms of fructose are absorbed and metabolized.

It is generally agreed that excessive consumption of refined sugar of any type is undesirable. Because it consists primarily of "empty calories," replacing more nutritious foods with sugar decreases one's intake of vitamins, minerals, amino acids, essential fatty acids, and other beneficial nutrients. In addition, refined sugars are energy-dense (i.e., they provide a large number of calories in a small volume) and contain no fiber. Because it takes a relatively large number of calories from energy-dense foods to produce a feeling of fullness, excessive intake of sweets can lead to overeating and obesity. Sucrose consumption is widely recognized as a major cause of dental caries. Sucrose is also considered by some investigators to be a contributing factor in ischemic heart disease, diabetes mellitus, insulin resistance, attention deficit-hyperactivity disorder, reactive hypoglycemia (and its associated symptoms), and other conditions, although the research is conflicting and the medical community is divided on these issues.

In contrast to sucrose and glucose, some nutritionists regard fructose as a relatively safe form of sugar. Because it does not require insulin for uptake into cells, moderate fructose intake does not adversely affect blood-glucose levels, at least in the short term.[2] In addition, when compared with sucrose, short-term fructose consumption appears less likely to cause symptoms of reactive hypoglycemia, or to trigger hypoglycemia-related overeating. For these reasons, fructose is often recommended for people with diabetes and is included in many weight-loss products and "energy bars."

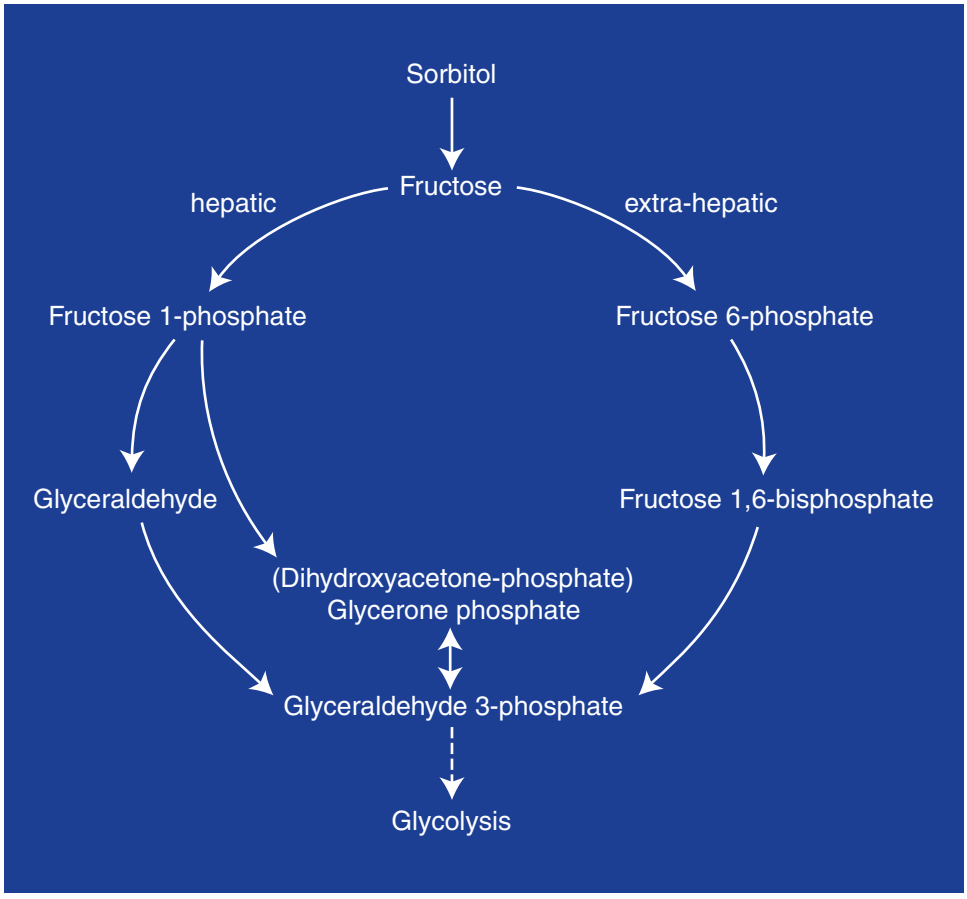
However, while fructose consumption has not adversely affected glycemic control in most studies, fructose has deleterious effects on other aspects of metabolism (Table 1). As a reducing sugar, fructose reacts with protein molecules to form toxic advanced glycation end-products (AGEs), which appear to accelerate the aging process and to play a role in the pathogenesis of diabetes complications and cardiovascular disease. Fructose is a highly reactive reducing sugar, and promotes the formation of AGEs to a considerably greater extent than other reducing sugars (e.g., glucose and lactose). Fructose consumption has been shown to cause hypertriglyceridemia and hyperuricemia and, in individuals consuming a hypercaloric diet, to induce insulin resistance. Fructose has also been implicated as the main cause of symptoms in some patients with chronic diarrhea or other functional bowel disturbances. Finally, there is evidence that excessive fructose consumption is responsible in part for the increasing prevalence of obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease. Although the long-term effects of fructose consumption have not been adequately studied in humans, the available evidence suggests it may be more harmful than is generally recognized.

The extent to which a person might be adversely affected by dietary fructose depends both on the amount consumed and on individual tolerance. Even some of the healthiest people might experience negative effects from the massive amounts of fructose present in some modern Western diets. For those who have a genetic or acquired weakness in their capacity to metabolize this sugar, relatively modest increases in fructose intake might also cause problems.

Table 1. Potential Adverse Health Effects of Dietary Fructose

Obesity
Accelerated aging
Insulin resistance
Diabetes mellitus
Complications of diabetes (nephropathy, retinopathy, neuropathy)
Non-alcoholic fatty liver disease
Hypertriglyceridemia
Hyperuricemia
Chronic diarrhea
Irritable bowel syndrome
Urticaria

Figure 1. Fructose Metabolism



Absorption, Metabolism, and Serum Levels

Fructose is absorbed in the small intestine by a process of facilitated diffusion.[3] As much as 80-90 percent of ingested fructose is absorbed intact,[4] although wide variations in the capacity to absorb fructose have been demonstrated in healthy volunteers.[5] A small proportion of orally administered fructose may be converted to glucose and lactate during transport through the intestinal wall, but evidence for such a conversion is conflicting.[6] Absorbed fructose is transported via the portal vein to the liver, where it is metabolized by fructokinase to fructose-1-phosphate (Figure 1). This molecule is cleaved by aldolase B to form dihydroxyacetone phosphate and glyceraldehyde, both of which can be further metabolized in the glycolytic pathway.[7]

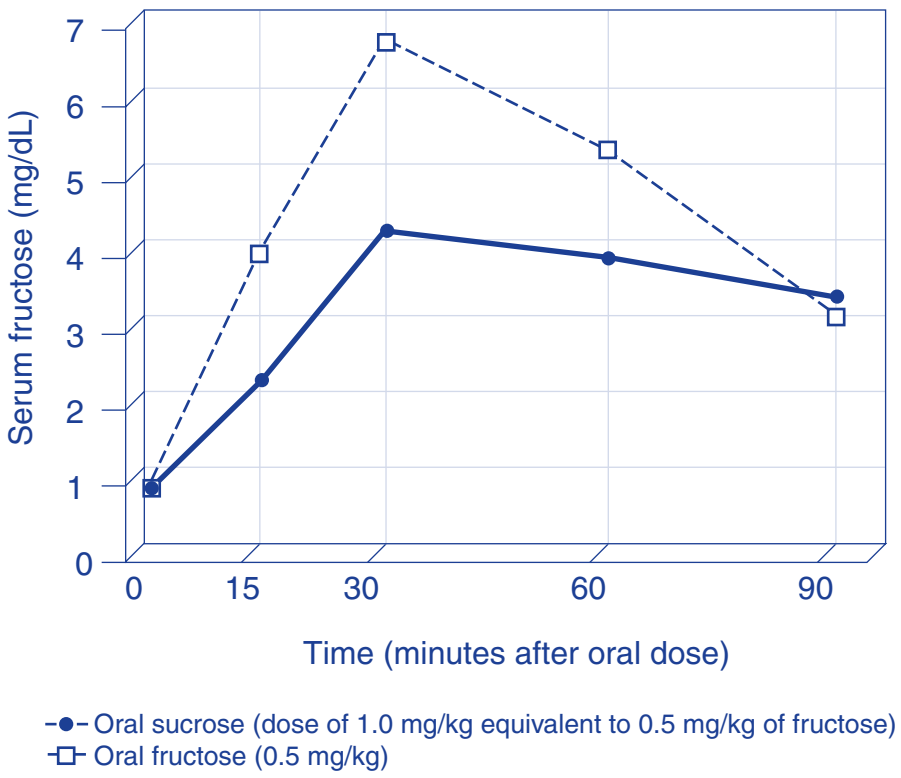
The concentration of fructose in fasting blood of healthy humans is typically 1 mg/dL or less.[4,6,8] After oral administration of a fructose load in doses ranging from approximately 18 g (0.25 g/kg of body weight)[8] to 100 g,[9] the mean plasma or serum fructose concentration increased in a dose-dependent manner, to values ranging from 4.5-13.0 mg/dL. Peak fructose concentrations were seen 30-60 minutes after fructose ingestion. At 90 minutes, the mean serum fructose concentrations with progressively increasing fructose doses (0.25, 0.5, 0.75, and 1.0 g/kg of body weight) were 2.0, 5.0, 7.7, and 13.6 times as high as the respective fasting concentrations. A 20-ounce soft drink, which contains 32.6 g of fructose, would therefore be expected to increase the fasting serum fructose concentration by approximately four-fold.

Serum fructose concentrations also increased after ingestion of a sucrose load. However, the mean peak serum fructose concentrations were 36-41 percent lower after consumption of 0.5 and 1.0 g/kg of sucrose than after equivalent amounts of fructose (0.25 and 0.5 g/kg, respectively). Figure 2 illustrates the effect of sucrose (1.0 g/kg) compared with fructose (0.5 g/kg) on serum fructose levels. The blunted rise in serum fructose concentration after sucrose (compared with fructose) ingestion is probably related to the fact that the fructose portion of sucrose is not available for absorption until sucrose is hydrolyzed by intestinal brush-border enzymes. The fructose portion of sucrose is, therefore, presumably absorbed more slowly than fructose ingested as the monosaccharide.

The increase in serum fructose concentrations after ingestion of fruit or a mixed meal of whole

foods has not been investigated. It is likely that such increases would be negligible, because of the relatively small amount of fructose present in natural foods and because the fructose in fruits and vegetables would presumably be absorbed relatively slowly. It might reasonably be expected that the small amounts of slowly absorbed fructose present in natural foods would be completely or almost completely metabolized by intestinal and hepatic enzymes, and that little or no fructose would escape from the liver into the systemic circulation. In contrast, the rise in serum fructose concentration that occurs after ingestion of a bolus of fructose or sucrose is probably due to an inability of the intestinal and hepatic enzymes to metabolize the load completely. Thus, there appears to be no evolutionary precedent for the substantial increase in plasma fructose concentrations that results from eating high-fructose (and, to a lesser extent, high-sucrose) diets.

Figure 2. Serum Fructose Levels after Oral Ingestion of Sucrose versus Fructose

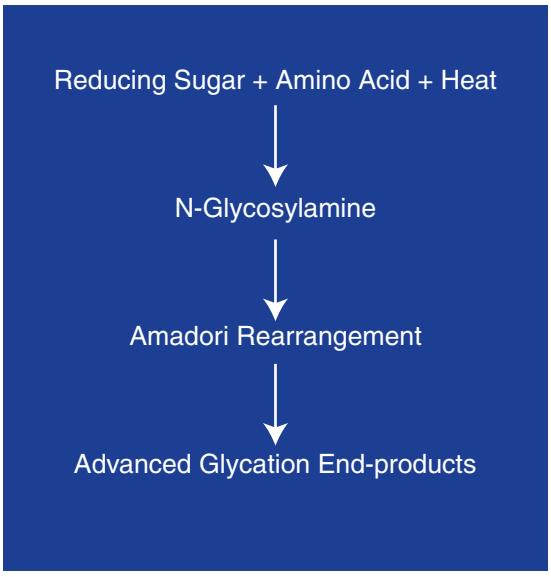


Fructose, Advanced Glycation End-Products, and Aging

Reducing sugars, such as fructose and glucose, react with proteins and amino acids to form substituted amino sugars. This reaction, known as the Maillard reaction (also called glycosylation or glycation), usually occurs at the site of a lysine side-chain, but reducing sugars can also react with tryptophan, arginine, and possibly other amino acids. The initial products of the Maillard reaction undergo further reactions and rearrangements to form AGEs, which accumulate indefinitely on long-lived molecules such as collagen and DNA (Figure 3). There is evidence that AGEs play a role in the aging process;[10] in the pathogenesis of the vascular, renal, and ocular complications of diabetes;[11-13] and in the development of atherosclerosis.[14,15]

The rate at which the Maillard reaction occurs depends on both the concentration of the reducing sugar involved and its degree of reactivity. While the circulating concentration of fructose is substantially lower than that of glucose, fructose is much more reactive than glucose with respect to participation in glycosylation reactions. *In vitro*, the rate of non-enzymatic glycosylation of hemoglobin was 7.5 times greater,[16] and the rate of protein cross-linking (a manifestation of aging) was 10 times greater,[17] in the presence of fructose than in the presence of glucose. Thus, the large percentage increases in serum fructose concentrations that occur after ingestion of fructose or sucrose may have clinical consequences, even though absolute fructose concentrations remain

Figure 3. The Mailard Reaction – Formation of Advanced Glycation End-Products



low in comparison with glucose concentrations.

Rats were fed a commercial diet for one year and had free access to water or to solutions containing 250 g/L of fructose, glucose, or sucrose.[18] None of the sugar solutions had any effect on plasma glucose concentrations. However, glycosylated hemoglobin levels and concentrations of lipid peroxidation products (measured in urine) were significantly higher in fructose-fed rats than in those given sucrose, glucose, or water. In addition, three measures of aging – the solubility, cross-linking, and fluorescence of collagen – were each significantly greater in the fructose group than in the other groups. These findings suggest that long-term fructose consumption may accelerate the aging process.

The use of fructose in cooking also has the potential to cause adverse effects. AGEs form during the heating of common foods and, in contrast to *in vivo* AGE formation, they can develop during cooking much more rapidly and in far greater concentrations.[19] Approximately 10 percent of ingested AGEs are absorbed, of which two-thirds are retained in tissues in reactive forms.[19] Dietary AGEs have been shown to accelerate the progression of nephropathy and to shorten survival times in an animal model of diabetes.[20] In humans with diabetes, the mean concentration of C-reactive protein (a marker of inflammation and an independent risk factor for cardiovascular disease) was 135-percent higher when the diet was high in AGEs than when cooking methods were altered to reduce the dietary AGE content.[19]

The rate of AGE formation during cooking would presumably be far greater in the presence of fructose than in the presence of a non-reducing sugar such as sucrose. While most of the AGE content of a typical Western diet is derived from the heating of high-protein or high-fat foods, such as meats, butter, and cheese,[21] the use of HFCS in the baking of breads, pastries, pies, and other foods would be expected to increase dietary AGE levels further.

Diabetes Mellitus

In short-term studies in humans, fructose ingestion did not have a deleterious effect on glucose metabolism, except when it was fed in very large amounts. On the contrary, it generally improved glycemic control, presumably because only a small proportion of ingested fructose is converted to glucose. In one study, nine healthy individuals, 10 with impaired glucose tolerance, and 17 with type 2 diabetes were given a 50-g load of glucose, sucrose, or fructose. In all three groups, ingestion of fructose, compared with glucose or sucrose, when given either alone or with a meal, resulted in significantly lower insulin responses, serum glucose levels, and glycosuria.[22] In another study, ingestion of fructose-sweetened cakes and ice creams resulted in lower serum glucose and insulin responses than did sucrose-sweetened cakes and ice creams.[23] In diabetic patients on insulin, consumption of a test meal containing 30 g of fructose resulted in less fluctuation in insulin requirements over the ensuing 24 hours than a meal containing 30 g of sucrose.[24] In studies lasting 3-8 days, substitution of sucrose or starch with fructose improved glycemic control in patients with type 1 or type 2 diabetes.[2,25]

Similarly, no adverse effects of fructose feeding on glycemic control were seen in studies lasting 1-3 months. In a series of patients with diet-controlled type 2 diabetes, substitution of sucrose by fructose (13% of calories) for three months had no significant effect on fasting plasma glucose levels or postprandial plasma glucose and insulin responses.[26]

In another study, 10 type 2 diabetics were randomly assigned to consume for four weeks a diet containing 10-percent fructose and 40-percent complex carbohydrate, or a control diet containing 50-percent complex carbohydrate and little or no fructose. After a one-month washout period, each person consumed the alternate diet for an additional four weeks. Compared with the control diet, the fructose-containing diet resulted in improved glycemic control and greater insulin sensitivity.[27] In other studies of healthy volunteers[28] and patients with type 1 or type 2 diabetes,[29] a diet containing 20 percent of energy from fructose did not adversely affect fasting plasma glucose levels, although it did result in significant increases in serum total- and LDL-cholesterol levels.

On the other hand, supplementing the diet of healthy male volunteers with 3 g fructose per kg of body weight per day, which increased total caloric intake by 25 percent, resulted in insulin resistance after as little as six days.[30] In another study, ingestion of a very large amount of fructose (1,000 kcal per day) induced insulin resistance in healthy volunteers after one week.[31] Thus, if fructose intake is very high, or if it leads to excessive energy consumption, it does have an adverse effect on glucose regulation.

When considering only its effects on glucose levels, fructose seems to be a safe or even desirable sweetener for people with diabetes, as long as it is used in moderation. However, the adverse effects of fructose on other aspects of metabolism might more than counterbalance its benign influence on glycemic control. Fructose unfavorably affects each of the three major factors that are thought to contribute to the pathogenesis of diabetic end-organ damage: glycosylation of tissue proteins, intracellular accumulation of sorbitol, and oxidative stress.

With regard to glycosylation, fructose is a potent inducer of the Maillard reaction, as mentioned previously. Fructose feeding (62% of the diet) of male (but not female) rats also significantly increased sorbitol concentrations in the liver and, in the context of marginal copper deficiency, increased sorbitol concentrations in the kidney as well.[32] In addition, rats fed fructose (250 g/L in drinking water) had a significant increase in lipid peroxidation, compared with rats fed the same amount of glucose or sucrose and those given pure water.[18]

The combined effect of these actions of fructose might be to accelerate the development of diabetic complications (such as retinopathy, neuropathy, nephropathy, and cardiovascular disease), even in the absence of an adverse effect on glycemic control. That possibility is supported by a study in which nondiabetic rats were fed a diet containing 68-percent carbohydrate, provided as either fructose, sucrose, or glucose.[33] Almost all retinas from the rats fed fructose or sucrose showed pathologic changes that were histologically indistinguishable from diabetic retinopathy, even though blood glucose levels remained normal. In contrast, rats fed glucose had essentially normal retinal vascular systems.

In a cross-sectional study of 38 patients with type 2 diabetes, those with the highest postprandial plasma fructose concentrations had a 75-percent prevalence of proliferative diabetic retinopathy, which was significantly higher ($p < 0.03$) than the prevalence in patients with intermediate (23.1%) or low (38.5%) postprandial plasma fructose levels. Nephropathy prevalence was also non-significantly higher (66.7%) in the group with high postprandial fructose concentrations than in the other two groups (38.5% and 30.8%, respectively).[34] No significant differences in glycemic indicators or mean duration of diabetes were seen among the groups with high, intermediate, and low fructose levels. In addition, there was no significant correlation between postprandial fructose and glucose concentrations.

These results indicate that high postprandial fructose concentrations are associated with retinopathy and possibly nephropathy in patients with type 2 diabetes. Of note, even among patients with the highest levels, the mean postprandial fructose concentration was less than 1 mg/dL. Thus, if the association between fructose concentrations and diabetic complications is causal, then even small increases in plasma fructose levels (as might result from drinking a beverage sweetened with HFCS or sucrose) would be undesirable.

Moreover, long-term fructose consumption may promote the development of diabetes, even though fructose usually has no adverse effects on glucose tolerance in the short- and intermediate term. In rats, long-term feeding of moderate amounts of fructose (15% of the diet by weight) resulted in impaired

glucose tolerance[35] and a high-fructose diet (72% by weight) resulted in the development of diabetes mellitus and diffuse glomerulosclerosis.[36]

The association between consumption of sugar-sweetened beverages and risk of type 2 diabetes was assessed in an eight-year prospective study of 51,603 women participating in the Nurses' Health Study II.[37] After adjustment for potential confounders, women consuming one or more sugar-sweetened soft drinks daily had a relative risk (RR) of type 2 diabetes of 1.83 (p for trend < 0.001) compared with those who consumed less than one of these beverages per month. The results were attenuated after further adjustment for body mass index and caloric intake, but remained statistically significant (RR = 1.32; p for trend = 0.04). Consumption of fruit punch was associated with a similar increase in diabetes risk. When this study was begun in 1991, HFCS had already largely replaced sucrose as a sweetener for beverages. Thus, the results of this study demonstrate that increasing consumption of HFCS is associated with an increased risk of developing type 2 diabetes.

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a common condition, affecting 10-24 percent of the general population in various countries, and 57.5-74 percent of obese individuals.[38] NAFLD includes hepatic steatosis (fatty liver) and steatohepatitis (fatty liver with hepatitis), and is diagnosed in patients whose liver disease cannot be explained by excessive alcohol intake. This condition may progress to cirrhosis and liver failure. Risk factors for NAFLD include obesity, type 2 diabetes (with or without obesity), insulin resistance, and hypertriglyceridemia. Of note, each of these risk factors can occur as a result of excessive fructose consumption.

High-fructose diets have induced fatty liver in rats[39] and ducks;[40] such diets have also caused increases in hepatic lipid peroxidation[41] and activation of inflammatory pathways in the liver of rats.[42] That fructose consumption can cause progressive liver disease in humans is demonstrated by the inborn error of metabolism known as hereditary fructose intolerance (HFI). This rare condition, which is inherited in an autosomal recessive manner, results from a deficiency of the fructose-metabolizing enzyme aldolase B, which occurs in the liver, kidney, and intestine. Persons with HFI develop abdominal pain, vomiting, and hypoglycemia after ingesting fructose, sucrose, or sorbitol (sorbitol is metabolized to fructose). Continued ingestion of these sugars causes liver and kidney damage, which can progress to cirrhosis, liver failure, and death. Strict avoidance of fructose, sucrose, and sorbitol results in rapid improvement, if liver and kidney damage have not already progressed too far.

Although the prevalence of HFI has been estimated to be only 1 in 26,000 in Central Europe, approximately 1.25 percent of the population is heterozygous for the disorder.[43] At least 35 different mutations have been identified in the aldolase B gene of patients with HFI,[44] and one patient has been described in whom the mutant aldolase B enzyme retained partial activity.[45] That raises the possibility that other polymorphisms of the aldolase B gene also exist, some of which are perhaps relatively common and may reduce the activity of the enzyme to varying degrees. Heterozygotes for one of these purported mutations, or for one of the known HFI mutations, would have a reduced capacity to metabolize fructose. While these mutations would not have been expected historically to cause any major health problems, they could presumably cause liver disease or other disorders in people consuming large amounts of fructose or sucrose.

The extent to which excessive fructose and sucrose consumption might be contributing to the high prevalence of liver disease in Western societies has not been systematically investigated. However, one clue can be found in a study of healthy non-obese males who consumed a diet containing 20-35 percent of calories as sucrose for 30 days. During the study, three of 11 participants (27%) developed markedly increased levels of alanine aminotransferase (4.33-9.22 times the upper limit of normal) and moderate increases in aspartate aminotransferase (1.04-3.64 times the upper limit of normal), changes suggestive of liver injury.[46] The results of a follow-up study indicated that both surplus calories and excess sucrose consumption played a role in the rise in enzyme levels.[47] As glucose has not been implicated as a cause of liver disease, it is likely that the fructose moiety of sucrose was the culprit. HFCS from oversized soft drinks may also have contributed to the pronounced

elevations in liver enzymes that occurred after Morgan Spurlock (of "Super Size Me" fame) subjected himself to a "McDonald's-only diet" for 30 days.[48]

Additional evidence that fructose can cause liver damage is that intravenous administration of fructose (250 mg/kg of body weight over five minutes) to healthy volunteers resulted in a 75-percent reduction in the hepatic concentration of adenosine triphosphate (ATP) – the body's main storage form of energy – within 10 minutes. Sixty minutes after fructose administration, the ATP concentration was still reduced by about 40 percent compared with baseline.[49] Patients with obesity-related non-alcoholic steatohepatitis recovered significantly more slowly from fructose-induced hepatic ATP depletion than did healthy age- and sex-matched controls.[50] A significant decrease in hepatic ATP concentration has also been observed after intravenous administration of as little as 62.5 mg fructose per kg of body weight,[51] which is equivalent to 4.4 g for a 70-kg person.

The effect of oral fructose on hepatic ATP levels has not been examined. However, the findings from the intravenous studies are consistent with the hypothesis that ingestion of large amounts of fructose could overwhelm the capacity of the liver to metabolize it, resulting in transient hepatic dysfunction. Repeated episodes of fructose-induced hepatic stress could lead to progressive hepatic injury. Moreover, fructose appears to be more toxic to a diseased liver than to a healthy one.

Functional Bowel Disturbances

Unlike glucose, which is completely absorbed in the intestine, the capacity to absorb fructose is limited. When healthy volunteers were challenged with varying doses of a 10-percent fructose solution, absorption capacity ranged from 5 g to more than 50 g of fructose.[5] Unabsorbed fructose may serve as an osmotic load that draws fluid into the intestinal lumen, resulting in symptoms such as diarrhea, abdominal pain, bloating, flatus, belching, and discomfort. Symptoms may also result from the action of colonic bacteria on unabsorbed fructose.[52] Approximately 50 percent of fructose malabsorbers experience gastrointestinal symptoms after ingesting fructose.[53]

Twenty-five patients (ages 31-77 years; median, 52 years) with functional bowel disturbances were challenged with 25 g of fructose in a 10-percent solution. Thirteen patients (52%) had fructose malabsorption (defined as an increase of breath hydrogen of at least 10 parts per million); of those, 12 experienced gastrointestinal symptoms, which were often marked. In seven of these patients, the calculated absorption capacity was less than 15 g.[54] In a study of 183 patients with unexplained gastrointestinal symptoms who were challenged with 50 g of fructose, 73 percent showed evidence of fructose malabsorption.[3] In patients with gastrointestinal symptoms and fructose malabsorption, a diet free of, or low in, fructose often relieved symptoms.[53,55,56]

Glucose enhances the absorption of fructose, and malabsorption of fructose typically occurs only if more fructose than glucose is present.[57] Thus, a person who malabsorbs fructose would usually show normal absorption of the same amount of fructose when administered as sucrose (which is 50% glucose) or as a mixture of equal parts glucose and fructose.[5] In contrast, sorbitol inhibits the absorption of fructose. Simultaneous ingestion of these two sugars in amounts, which by themselves are well tolerated, may elicit symptoms in some people.[58]

Pears and apples contain more fructose than glucose, and substantial amounts of sorbitol are present in pears, apples, cherries, and plums. In contrast, oranges and white grapes contain equal amounts of fructose and glucose. The high concentration of fructose and the presence of sorbitol may explain why apple juice and pear nectar have been found to be a common cause of chronic non-specific diarrhea in children.[57,59,60] White grape juice, on the other hand, is generally well tolerated by children who experience symptoms from apple juice.[61]

HFCS, which contains more fructose than glucose, may be an important cause of symptoms in some patients with irritable bowel syndrome or other functional bowel disturbances. In these patients a short-term trial of a diet free of fructose and sorbitol would be worthwhile.

Obesity

The increase in HFCS consumption over the past several decades has mirrored the increase in obesity during that time. Observational studies are consistent with the possibility that increased fructose consumption is one of the causal factors in the current obesity epidemic. In a prospective study of 51,603 women participating in the Nurses' Health Study II, during a mean follow-up period of approximately eight years, higher consumption of sugar-sweetened beverages was associated with greater weight gain, after adjustment for lifestyle and dietary factors.[37] In a 19-month prospective study of 548 schoolchildren (mean age, 11.7 years) from public schools in Massachusetts, an increase over baseline in the intake of sugar-sweetened drinks during the study period was associated with an increased incidence of obesity, even after adjusting for total energy intake. For each additional daily serving, there was an increase in mean body mass index of 0.24 kg/m^2 ($p = 0.03$) and a 60-percent increase in the frequency of obesity ($p = 0.02$).[62] Virtually all of the sweetened drinks consumed by participants in these studies were made with HFCS.

The results of the latter study suggest that the association between HFCS consumption and obesity is due in part to metabolic changes induced by fructose or HFCS, rather than merely to an increase in total energy intake. In studies in baboons, consumption of sucrose, compared with glucose, promoted the development of abdominal obesity, suggesting that the fructose moiety of sucrose was responsible for the increase in abdominal fat.[63] In addition, some strains of mice showed an increase in visceral fat accumulation when fed a high-fructose diet.[64]

In a field trial, 644 British schoolchildren (ages 7-11 years) were randomly assigned to a control group or to an education program designed to reduce their consumption of carbonated drinks (both sweetened and unsweetened). The mean consumption of carbonated drinks decreased by 50 mL/day in the intervention group and increased by 16.7 mL/day in the control group. After 12 months, the approximate percentage of overweight and obese children had increased in the control group from 20 percent to 27.5 percent, compared with a decrease in the intervention group from 20 percent to 19.8 percent.[65]

In contrast to the apparent obesity-promoting effect of fructose and HFCS, fructose has been used successfully as a component of various weight-loss programs. On one popular diet, 36-42 g of fructose is consumed in small increments throughout the day in combination with a recommended list of salads and high-protein foods.[66] In 21 obese patients who followed this diet program, the mean weight loss was 14.5 pounds after four weeks. Twenty of the 21 patients expressed no feeling of hunger and were unanimous in satisfaction with the diet. Fructose appears to aid in weight loss by suppressing appetite for a few hours after it is eaten.[67] Unfortunately, most people who consume fructose do not do so in conjunction with a strict, low-calorie, weight-loss diet. For those who do, additional studies are needed to determine whether the beneficial effects of short-term weight loss outweigh the adverse biochemical effects of fructose consumption.

Fructose and Triglycerides

Both human and animal[68] studies have shown that fructose consumption can increase triglyceride levels. In one study, 24 healthy adults received two isoenergetic diets in random order for six weeks each.[69] One diet provided 17 percent of energy as fructose. The other diet was sweetened with glucose (14% of energy) and contained only three-percent fructose. Both diets were composed of common foods and contained nearly identical amounts of carbohydrate, protein, fat, fiber, cholesterol, and saturated, monounsaturated, and polyunsaturated fatty acids. In men, the fructose diet produced significantly higher fasting, postprandial, and daylong plasma triglyceride concentrations than did the glucose diet. The daylong plasma triglyceride concentration was 32-percent greater with the fructose diet than with the glucose diet ($p < 0.001$). The fructose diet had no significant effect on triglyceride concentrations in women.

The triglyceride response to fructose ingestion appears to depend on whether or not a person is carbohydrate sensitive or insulin resistant. Twelve men (mean age, 40 years), who were considered carbohydrate sensitive on the basis of an abnormally high insulin response to a sucrose load, were fed diets containing 0-, 7.5-, and 15-percent fructose for five weeks each, in a crossover design.[70] The fructose

was added to the diet in the form of wafers that contained varying proportions of fructose and starch; the diets were identical except for the wafers. The mean plasma triglyceride concentrations on the diets containing 0-, 7.5-, and 15-percent fructose were 101.6, 131.9, and 163.4 mg/dL, respectively ($p < 0.05$ for each value relative to the previous value).

In contrast, fructose had no effect on triglyceride levels in another group of 12 men who were not considered carbohydrate sensitive. Thus, consumption of moderate amounts of fructose significantly and dose-dependently increased plasma triglyceride levels only in carbohydrate-sensitive men. In another study, a diet containing 20 percent of energy as fructose significantly increased plasma triglyceride levels in male volunteers after five weeks, compared with a similar diet containing 20 percent of calories as cornstarch. The effect of the diet on triglyceride levels was more pronounced in hyperinsulinemic men (+66.7%) than in non-hyperinsulinemic men (+12.5%).[71]

Fructose and Uric Acid

Fructose consumption has been shown in some studies to increase serum uric acid levels. In a study of 21 male volunteers (ages 23-64 years), a diet containing 20 percent of energy as fructose (consumed for five weeks) significantly increased the mean serum uric acid concentration, compared with a similar diet containing 20 percent of energy as starch.[71] In a study of three men who were healthy except for stable neurological disease, consumption of a large amount of fructose (250-290 g/day) for 12 days significantly increased serum and urinary uric acid levels.[72] In another study of 11 healthy volunteers, diets containing 24 percent of carbohydrate as fructose did not alter serum uric acid levels when compared with a diet containing 24 percent of carbohydrate as sucrose.[73] However, as sucrose consists of 50-percent fructose, and as it has itself been shown to increase serum uric acid levels,[74] it is not an ideal control for evaluating the short-term metabolic effects of fructose. In addition to being a risk factor for gout, elevated uric acid levels are associated with an increased risk of cardiovascular disease.[75]

Other Effects of Fructose

In animal studies, diets high in fructose aggravated the pathological effects of dietary copper deficiency, including anemia, cardiomegaly, and hypertriglyceridemia.[76,77] The findings from these studies might have clinical relevance, since many Western diets are marginally low in copper.[78]

Another potential problem with HFCS is that a byproduct called D-psicose is formed during the production of the syrup. Psicose is also produced when sugar is heated. There is one case report of urticaria due to D-psicose.[79]

Conclusion

The available evidence suggests that the consumption of excessive amounts of sucrose, fructose, or HFCS can lead to a wide range of health problems. In some respects, fructose and HFCS are probably even more dangerous than sucrose. Although there are still many gaps in our knowledge, a prudent approach would be to keep the intake of these sweeteners to a minimum. This author typically advises patients not to switch to any of the various sugar substitutes, but, rather, to de-condition their desire for sweets by temporarily avoiding them altogether. After a few weeks, most patients report that natural foods taste sweeter than before.

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