

Health Implications of High-Fructose Intake and Current Research^{1,2}

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ABSTRACT

Although fructose consumption has dramatically increased and is suspected to be causally linked to metabolic abnormalities, the mechanisms involved are still only partially understood. We discuss the available data and investigate the effects of dietary fructose on risk factors associated with metabolic disorders. The evidence suggests that fructose may be a predisposing cause in the development of insulin resistance in association with the induction of hypertriglyceridemia. Experiments in animals have shown this relation when they are fed diets very high in fructose or sucrose, and human studies also show this relation, although with conflicting results due to the heterogeneity of the studies. The link between increased fructose consumption and increases in uric acid also has been confirmed as a potential risk factor for metabolic syndrome, and insulin resistance/hyperinsulinemia may be causally related to the development of hypertension. Collectively, these results suggest a link between high fructose intake and insulin resistance, although future studies must be of reasonable duration, use defined populations, and improve comparisons regarding the effects of relevant doses of nutrients on specific endpoints to fully understand the effect of fructose intake in the absence of potential confounding factors. *Adv Nutr* 2015;6:729–37.

Keywords: antioxidants, fructose, hypertension, oxidative stress, sugar-sweetened beverages

Introduction

It has generally been assumed that a high intake of refined carbohydrates, specifically fructose, may increase the risk of insulin resistance (IR)⁶. This is of particular importance because over the past 3 decades there has been a shift in the amount and source of sweeteners used in developed countries (1). In the past, the intake of fructose has been between 16 and 20 g/d, largely due to the consumption of fresh fruit; however, the consumption of fructose has increased to 60–150 g/d and originates mostly from sucrose (2). In addition, with the advent of isomerization, separation, and crystallization technologies, it became possible to produce crystalline fructose and high-fructose corn syrup (HFCS), a manufactured disaccharide (3). The introduction of HFCS in the 1970s primarily resulted in the accelerated consumption of sweeteners, due to the ease with which HFCS is

solubilized in processed food. Fructose is advantageous because it is at least 1.5 times sweeter than sucrose and inexpensive to produce; consequently, it has been used widely in foods during the preparation of canned fruits, jams, paste candies, cakes, powder for beverages, and soft drinks. This review outlines the effects of dietary fructose on risk factors associated with metabolic abnormalities by using observational data from rodents and humans.

Metabolism of Fructose Compared With Other Dietary Monosaccharides

Fructose is a sugar that exists in foods as a simple sugar and as a component of the disaccharide sucrose, which consists of 1 molecule of glucose and 1 molecule of fructose that are absorbed in the small intestine and transported into the enterocytes via glucose transporter 5 (GLUT5), a specific transporter that is not insulin dependent. Once inside the enterocyte, fructose diffuses into the blood vessels through transport mediated by GLUT2 at the basolateral pole (4), where it is rapidly phosphorylated at the carbon 1 (mediated by fructokinase) or at the carbon 6 (mediated by a hexokinase) positions. Most fructose is phosphorylated at carbon 1 and accumulates rapidly in the liver, where it is hydrolyzed into 2 trioses: dihydroxyacetone and glyceraldehyde-phosphate.

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⁶ Abbreviations used: BP, blood pressure; DNL, de novo lipogenesis; GLUT, glucose transporters; HFCS, high-fructose corn syrup; IR, insulin resistance; IRS-1, insulin receptor substrate 1; MeS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; SREBP-1, sterol regulatory element-binding protein 1.

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These 2 trioses may follow 3 different paths: 1) participate in the glycolytic pathway producing pyruvate, which is converted to lactic acid under anaerobic conditions or enters the citric acid cycle as acetyl CoA under aerobic conditions, thus releasing energy; 2) dihydroxyacetone phosphate may be reduced to glycerol-3-phosphate, which is needed for the synthesis of lipids including TGs and phospholipids; and 3) dihydroxyacetone phosphate may be condensed to form fructose-1,6-diphosphate, forming glucose or glycogen. Consequently, pyruvate, lipid, and glycogen are produced. **Figure 1** presents the metabolic pathways of glucose and fructose.

Glucose utilization can be regulated before cleavage, whereas fructose is less regulated. The control of glucose metabolism is related to a phosphorylated derivative of fructose called fructose-2,6-diphosphate (5), which plays an important role in the regulation of glycolysis and gluconeogenesis. Fructose-2,6-diphosphate affects the activity of 2 key regulatory enzymes that control the catabolism and anabolism of carbohydrates in the liver (phosphofructokinase and fructose-1,6-diphosphatase). However, high concentrations of ATP and citrate inhibit phosphofructokinase (6), and AMP stimulates fructose-2,6-diphosphatase, which forms fructose-6-phosphate, lowering the concentrations of fructose-2,6-diphosphate. This reduced concentration of fructose-2,6-diphosphate stimulates fructose-1,6-diphosphatase, favoring the conversion of fructose-1,6-diphosphate to fructose-6-phosphate, an intermediate in gluconeogenesis. In contrast, increased fructose-2,6-diphosphate stimulates 6-phosphofructokinase, which converts fructose-6-phosphate to fructose-1,6-diphosphate, promoting glycolysis. Thus, the main difference between hepatic fructose and glucose metabolism is that fructose molecules bypass the main rate-controlling step in glycolysis involving 6-phosphofructokinase.

Fructose, Lipogenesis, and IR

Initially, fructose attracted great interest as a sweetener for patients with diabetes due to its low glycemic index

compared with glucose (7). However, the consumption of fructose increases concentrations of plasma TGs, the conversion rate of lipids in the liver, and the secretion and removal of TGs (8), which suggests that lipogenesis may be the key biochemical process that is induced by fructose. An increase in the fructose intake rate generates the substrate for de novo lipogenesis (DNL). FAs incorporated into TGs or other lipids are associated with increased VLDL synthesis, which is important in nonalcoholic fatty liver disease (NAFLD) (9). Furthermore, when hepatic DNL is induced, new lipids are synthesized, nonesterified FAs are re-esterified, and hepatic lipid oxidation is downregulated. These events create an imbalance between hepatic lipid “inputs” and “exports,” leading to net intrahepatic fat accumulation. In this sense, lipid metabolism disorders are closely linked to IR, because ectopic lipid deposition may generate toxic lipid-derived metabolites, including diacylglycerol, fatty acyl CoA, and ceramides, and the intracellular accumulation of TGs leads to a higher serine/threonine phosphorylation of insulin receptor substrate 1 (IRS-1), which reduces insulin signaling (10). IR accentuates the lipolysis of TGs in the adipose tissue and inhibits FFA esterification, which increases circulating FFA concentrations that are captured by the liver (11).

Clinical studies on fructose overconsumption. Human studies have shown that fructose intake results in higher rates of DNL than does glucose intake (12). Consequently, fructose is more lipogenic than glucose, an effect that may be exacerbated in patients with hyperlipidemia (13), IR, or type 2 diabetes (14). Furthermore, fructose does not stimulate the production of insulin and leptin, which are involved in energy homeostasis. Indeed, a low insulin concentration after ingesting fructose would be associated with lower mean leptin concentrations than would be seen after ingesting glucose. A clinical trial conducted in 12 women showed that an isocaloric diet with a high fructose content resulted in lower blood glucose and higher serum TGs than a diet

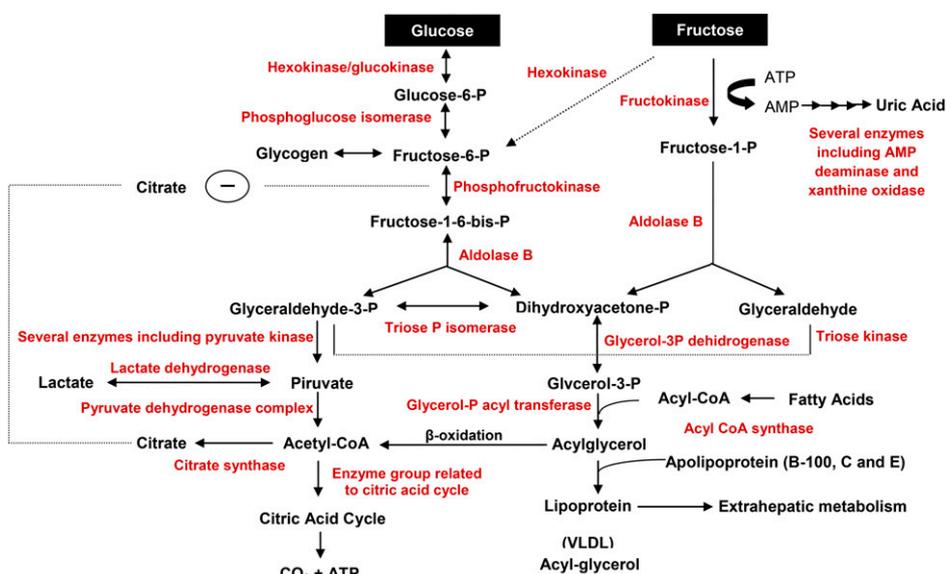


FIGURE 1 Metabolic pathways of dietary glucose and fructose in liver cells. Enzymes are shown in red. P, phosphate.

with high amounts of glucose (15). Dietary fructose during 4 wk in men reduced sensitivity to insulin, increased hepatic steatosis, and increased TG circulation (16). Assy et al. (17) found that patients with NAFLD without the classic risk factors consumed more soft drinks and sweetened juices compared with the control group and showed a correlation between the severity of hepatic steatosis and the quantity of soft drink consumed. Moreover, as expected, IR levels were higher in patients with NAFLD than in controls. Another study showed that the presence of fructose as the only source of carbohydrate in a very-low-calorie diet delayed the expected improvement in plasma glucose and insulin concentrations (18). However, moderate fructose intakes by healthy subjects for 2 wk had no deleterious effects on insulin sensitivity compared with the same amount of sucrose (19). Healthy subjects who consumed up to 1.5 g fructose/kg body weight per day for 4 wk showed increased plasma TG concentrations, but IR was not induced (20).

A high-fructose diet in studies in animals. High-fructose or high-sucrose diets are clearly associated with IR development and disturbed glucose homeostasis in rodents. Rats fed a diet that substituted sucrose for starch developed several alterations in glucose and lipid metabolism over time. The earliest event observed after 1 wk was an increase in hepatic TG content (21). Between 2 and 5 wk, fasting hyperinsulinemia developed, indicating whole-body IR. In rats fed 66% fructose for 3 wk, the insulin receptor mRNA and the numbers of insulin receptors on skeletal muscle were significantly lower than those in rats fed a standard diet (22). In another study, it was found that after 28 d of fructose consumption, there was no change in the concentrations of insulin receptor, but its autophosphorylation, a necessary mechanism for its action, was reduced to 72% in the liver (23). Rats fed a diet containing 35% fructose for 4 wk showed reduced insulin sensitivity associated with impaired hepatic insulin action and glucose availability (24). The effect of a high-fructose diet corroborates its glycemic effect, which was evident in oral-glucose-tolerance tests performed in rats after they were fed 20% fructose for 18 wk (Figure 2). Compared with control rats, blood glucose concentrations

were significantly higher in the fructose-fed rats at 30 wk, and the return to baseline was incomplete during the response tests (Figure 2A). Consequently, the AUCs for glucose were significantly increased in these rats ($P < 0.05$) (Figure 2B).

In addition, fructose also may cause DNL stimulation through the enhanced intrahepatic synthesis of triose phosphate precursors and an increased expression of lipogenic genes. It has been suggested that these mechanisms may involve the inhibition of PPAR- α in liver cells, the stimulation of hepatic DNL, and reduced hepatic lipid oxidation (26). In the early stages of sucrose overfeeding, rodents develop significant changes in their hepatic metabolism, with relatively few changes in their glucose homeostasis, and no significant changes in their extrahepatic insulin sensitivity. In sequence, fructose may increase the expression of key lipogenic enzymes in the liver, and it induces sterol regulatory element-binding protein 1 (SREBP-1) expression, the principal inducer of hepatic lipogenesis (27).

Relations between Fructose, Weight Gain, and Obesity

Fructose may not induce the level of satiety that is observed after a glucose-based meal. Because insulin and leptin provide key signals that convey information about energy intakes and body fat stores to the central nervous system for the long-term regulation of food intakes and energy homeostasis, reduced insulin and leptin production may contribute to increased energy intakes and weight gain in animals and humans. Moreover, ghrelin has been the focus of attention because of its potent effects on stimulating food intake. Compared with dietary glucose, pure fructose consumed with mixed meals reduced circulating insulin and leptin concentrations and attenuated the postprandial suppression of ghrelin (15), which might contribute to increased caloric intakes and ultimately to weight gain and obesity after the chronic consumption of a high-fructose diet.

No evidence of body weight changes. Lê et al. (16) showed that a diet containing 1.5 g fructose/kg administered daily to healthy humans over 4 wk increased plasma TG and glucose

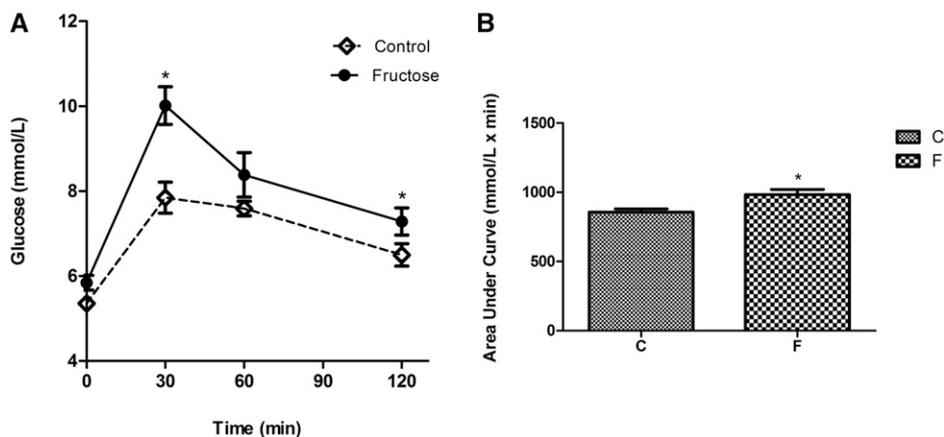


FIGURE 2 Oral-glucose-tolerance test values (A) and the time course AUC (B) in rats fed a high-fructose diet (20% wt:vol fructose solution as a substitute for drinking water for 20 wk). The test was performed, as described in reference 25, 2 wk before the rats ($n = 8$) were killed. Values are means \pm SEMs. * $P < 0.05$ compared with the control group (Student's t test). C, control diet; F, high-fructose diet.

concentrations without any significant changes in body weight, liver and muscle lipid content, or IR. Similarly, a 24-h study did not determine any substantial differences in plasma glucose, insulin, leptin, or ghrelin concentrations when subjects consumed meals containing sucrose or HFCS, and the TG profiles were similar (28). These responses were midway between the lower responses after pure fructose syrup consumption and the higher responses after glucose solution ingestion. No differences in the food intakes were apparent during a meal consumed 50 min later or in the components of the food-intake regulatory mechanisms. Another long-term study undertaken in overweight/obese individuals showed no body weight changes after 10-wk supplementation with glucose or fructose, indicating that the effects of fructose or glucose on food intake might not differ in the long term (29).

Lipid deposition. Although acute fructose consumption can not stimulate leptin secretion, fasting leptin concentrations increased after chronic high-fructose intakes over 1–4 wk in healthy individuals, which indicates that high-fructose feeding may suppress food intakes in the long term (16). Stanhope et al. (29) showed marked differences in the metabolic effects of fructose and glucose during an 8-wk outpatient study when subjects consumed their usual diets ad libitum and either fructose- or glucose-sweetened beverages that comprised 25% of their energy requirements. Fructose-sweetened but not glucose-sweetened beverages promoted intra-abdominal lipid deposition and hepatic lipid production, cholesterol metabolism was shifted unfavorably, and insulin sensitivity was diminished, which suggests that fructose consumption may specifically promote lipid deposition in visceral adipose tissues. DiMeglio and Mattes (30) found that 15 healthy men and women given carbohydrate loads (450 kcal/d) in the form of calorically sweetened soda for 4 wk gained significantly more weight than when the same carbohydrate load was given in a solid form as jelly beans. Ludwig et al. (31) showed that the quantity of sugar-sweetened beverages ingested by adolescents predicted their initial BMI. Furthermore, Raben et al. (32) found that moderately overweight men and women who drank calorically sweetened beverages experienced greater weight gains than those who consumed diet drinks over a 10-wk study period.

Hyperuricemia and Diets Containing Fructose

In the liver, fructose loading drastically stimulates ATP hydrolysis because of its rapid phosphorylation to fructose-1-phosphate, which increases AMP and uric acid synthesis (33). Despite its early designation as an antioxidant (34, 35), uric acid is estimated to be responsible for up to 60% of the antioxidant capacity in plasma (35), and it is now known to have pro-oxidative properties (36). These include the stimulation of vascular smooth muscle cell proliferation, release of inflammatory chemotactic substances (37), induction of monocyte chemotaxis (38), inhibition of proliferation and migration of endothelial cells (39), oxidative stress in adipocytes via the activation of NAD(P)H oxidase

and a reduction in the concentration of NO (36). The latter study showed that the reactive oxygen species produced by NAD(P)H oxidase increased lipid peroxidation, highlighting the relation between uric acid, oxidative stress, and inflammation leading to metabolic syndrome (MeS). Furthermore, high concentrations of uric acid are seen in a wide variety of metabolic diseases (40, 41), which supports the hypothesis that hyperuricemia is a causal factor in the progression of MeS, as shown by Choi and Ford (42).

Fructose contribution to hyperuricemia in human research. Previous studies (43–45) have shown that fructose can induce hyperuricemia; this supports work that has demonstrated an association between a high consumption of high-sugar drinks and an increase in serum uric acid concentrations (46, 47). However, other studies (19, 48, 49) have not found a link between fructose and serum uric acid concentrations. Studies have hypothesized that links exist between fructose intake, hyperuricemia, and IR. Insulin-induced glucose utilization involves the stimulation of key metabolic pathways in insulin-sensitive cells and increases in the blood flow and nutritive circulation to the major insulin-sensitive tissue, skeletal muscle (50). This effect of insulin is caused by its activation of endothelial NO synthase (51). The ability of insulin to produce muscle vasodilation is impaired in obese subjects, and this may contribute to altered glucose homeostasis through “preceptor” IR (52). Because endothelial NO synthase is potently inhibited by uric acid (53), it has been proposed that the inhibition of the vascular effects of insulin by uric acid may be involved in fructose-induced IR. Moreover, it was observed that uric acid is a biomarker for fatty liver (54). A study reported that the prevalence of NAFLD in Chinese individuals was significantly higher in those individuals with hyperuricemia than in those without hyperuricemia (24.75% and 9.54%, respectively; $P < 0.001$) (55). In addition, uric acid concentrations are elevated in the majority of adolescents with hypertension (56), and a prospective study reported that the reduction in uric acid concentrations in patients with kidney disease and hyperuricemia resulted in significantly slower progression of cardiorenal disease (57).

Fructose feeding and hyperuricemia in animals. Fructose-induced increases in uric acid concentrations may contribute to adverse effects (58). Serum uric acid concentrations are elevated in rats fed a diet containing 20% wt:vol fructose in water for 20 wk, and we found a significant direct relation between hyperuricemia and fructose intake (**Figure 3**). Hence, excess fructose ingestion may exert a specific metabolic effect that is dose dependent. Nakagawa et al. (60) showed that lowering uric acid concentrations with a uricosuric agent in rats fed a high-fructose diet prevented IR development, and experimental evidence suggests that chronic hyperuricemia may cause steatosis and hypertriglyceridemia. Experiments with allopurinol-treated rodents showed that the lipogenic effects of fructose may be partially mediated through the direct effects of uric acid, which stimulates

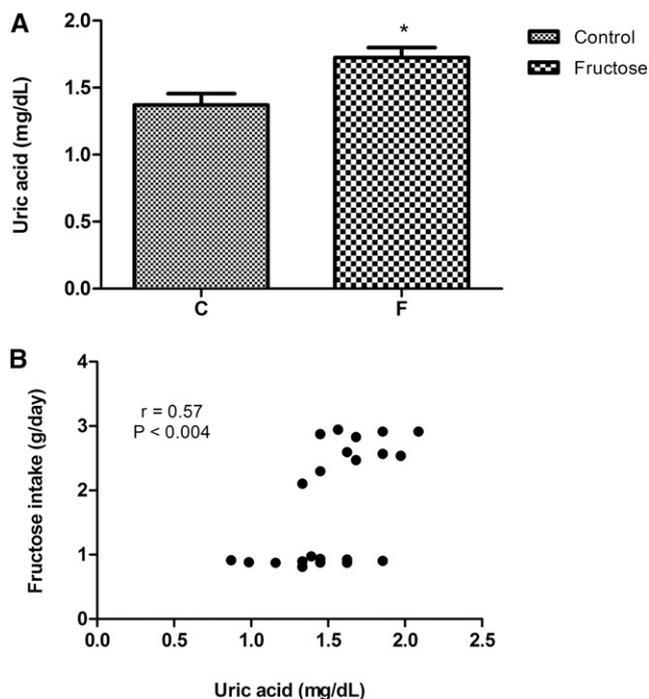


FIGURE 3 Serum uric acid concentrations (A) and Spearman correlations between fructose intakes and uric acid concentrations (B) in rats at 20 wk of treatment with the AIN93M diet and a 20% wt:vol fructose supplementation in drinking water. Values are means \pm SEMs, $n = 11$ rats/group. * $P < 0.05$ compared with control group (Student's t test). Data were derived from reference 59.

hepatic fat accumulation (61, 62). Lanaspá et al. (62) identified a mechanism that involves the translocation of NAD(P)H oxidase to the mitochondria accompanied by the inactivation of aconitase, accumulation of citrate, and the stimulation of fat synthesis. Previous studies showed that hyperuricemia induced by uricase (63) or oxonic acid (64) inhibition led to high serum TG concentrations and steatosis in rats. These additive effects are likely to be fully operational in humans who lack uricase expression, and they act synergistically to induce glomerular hypertension and IR and to elevate hepatic TGs and oxidative stress. Another group documented that high-fructose diets directly cause renal dysfunction, which was based on a study in which rats fed high-fructose diets developed hypertension, hypertriglyceridemia, hyperuricemia, hypertrophy of the kidneys, glomerular hypertension, and reductions in glomerular flows (65). Gersch et al. (66) showed that a diet high in fructose accelerated surgically induced chronic renal failure in rats, an effect that may have been mediated by hyperuricemia or other MeS components, including inflammation or hyperinsulinemia.

Fructose and the Risk of Developing Hypertension

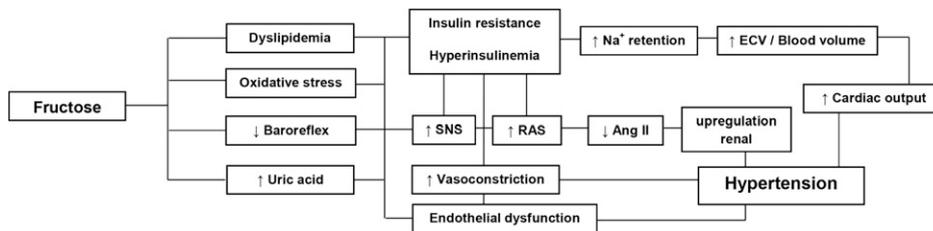
The mechanisms by which fructose causes elevated blood pressure (BP) is not fully known, but some possibilities have been suggested (Figure 4). These include the attenuation of the baroreflex and increased sympathetic nervous

system activity (67), elevation of circulating catecholamines (68), an increase in the activity of the rennin-angiotensin system (69), increased sodium reabsorption (70), increased production of uric acid (60), and endothelial dysfunction (71). There is, however, little evidence that fructose per se directly increases BP.

Human studies on fructose and hypertension. Compared with individuals with normal BP, those with essential hypertension are relatively intolerant to glucose (72). Nevertheless, BP reductions in hypertensive individuals do not necessarily reduce the levels of glucose intolerance and hyperinsulinemia. Fructose supplementation in healthy, normal-weight (16) and overweight subjects (29) with doses amounting to 30% of their total energy requirements failed to significantly alter their BP. Conversely, data collected from almost 2700 persons from 10 US/United Kingdom populations showed direct associations between the consumption of sugar-sweetened beverages and BP increases, which were independent of body weight and height (73). A systematic review of 12 cross-sectional and prospective cohort studies that encompassed >400,000 participants showed that sugar-sweetened beverage intakes were significantly associated with higher BP and an increased incidence of hypertension (74). The authors concluded that intakes of >12 fluid ounces of sugar-sweetened beverages/d increased the risk of hypertension by at least 6%, and these intakes can increase mean systolic BP by at least 1.8 mm Hg over ~18 mo. High fructose intakes may be linked to high calorie intake and weight gain and with IR, and all of these factors are themselves associated with high BP. In individuals with IR, the vasodilatory effect of insulin can be inhibited; these individuals cannot compensate for the decrease in sodium reabsorption in the proximal tubule, thus causing sodium retention (75). Furthermore, a reduction in renal excretion may occur due to various functional or pathologic changes intrinsic to the kidney or to neurohumoral factors, which then influences renal excretion. As a consequence, sodium excretion can be maintained and a change in the glomerular filtration rate or tubular reabsorption may be masked by a high BP. Nevertheless, in prolonged hypertension lasting for months or years, observed pathologic changes in glomerular capillaries result in a decrease in the glomerular filtration rate (requiring an elevated BP) and inhibition of tubular reabsorption in order to maintain sodium homeostasis (76).

Studies in rodents on fructose and hypertension. Many studies have also shown that a high-fructose diet can induce hypertension in rats (77–80). However, there are also other reports that do not show a link between fructose and increased BP (81–83). These conflicting reports could be due to other dietary components fed to the rats (84, 85), the different strains and ages of rats used in the various studies (83), and the different techniques used to measure BP (81, 82). Hwang et al. (77) showed that an adrenergic inhibitor reduced BP, but not IR, in fructose-fed rats. Therefore, if fructose increased sympathetic nervous system activity, then

FIGURE 4 Proposed mechanisms for hypertension resulting from fructose in the diet. Ang II, angiotensin II; ECV, extracellular volume, RAS, renin-angiotensin system; SNS, sympathetic nervous system.



this change is not the cause of the IR, hyperinsulinemia, and hypertriglyceridemia. Suzuki et al. (84) showed that pioglitazone treatment in rats with IR and hypertension resulted in a reduction in glycemic concentrations and in systolic arterial pressure and resulted in the normalization of insulin and TG concentrations. This indicated that the IR was responsible for the development of hypertension in rats fed a diet high in fructose. Chronically, insulin activates the central nervous system and causes an increase in peripheral vascular tone, leading to increased BP. Consequently, this may contribute to IR as a result of vasoconstriction. Vasoconstriction will cause a decrease in blood flow and a reduction in the supply of glucose to the tissues (86). Catena et al. (22) showed that hyperinsulinemia is determined by the number

of insulin receptors in tissues, and that this receptor density is inversely related to salt intake. Therefore, the antinatriuretic effect of the insulin is significantly reduced by a high salt intake, but not in fructose-fed rats, suggesting that the mechanism that normally limits insulin-induced sodium reabsorption is absent in this model (59). Consequently, in the long term, a high salt and fructose intake results in impaired sodium homeostasis, contributing to hypertension. Although much work is focused on fructose-induced IR and cardiorenal disease, not all sources of fructose can cause a deleterious effect. Natural fruit is also rich in antioxidants that may have a beneficial effect (87). Forman et al. (88) reported that fructose intake is not correlated with a high BP when most of the intake is from fruit. Fruit contains other

TABLE 1 Additional intervention studies with fructose administration¹

Route and species	Amount of fructose, %	Time	Effect	Authors (Reference)
Drink				
Mouse	10	3 wk	↑ Fasting glucose (~95%) and ↑ nonfasting insulin (~60%) concentrations	Huang et al. (91)
		2 mo	↑ Glucose (26%), ↑ TG (22%), ↑ insulin (95%) concentrations, and ↑ SBP (22%) values	De Angelis et al. (67)
Rat	30	8 wk	↑ Hepatic TG concentrations (~500%)	Kanuri et al. (92)
	4	14 wk	↑ SBP (~27%)	Vasdev et al. (80)
	10	8 wk	↑ Glucose (8%), ↑ TG (43%) concentrations, and ↑ IR index (20%)	Jalal et al. (93)
		5 wk	↑ TG (162%), ↑ insulin (176%) concentrations, and ↑ IR index (238%)	Xu et al. (94)
		6 wk	↑ TG (149%), ↑ insulin (75%) concentrations, and ↑ SBP (10%) values	Suzuki et al. (84)
		2 and 5 wk	↑ Insulin (28%), TG (108%) concentrations, ↑ IR index (48%), and ↑ SBP (12%) values	Zhao et al. (79)
	20	20 wk	↑ Glucose (48%), ↑ insulin (62%) concentrations, and ↑ IR index (128%)	Dornas et al. (59)
		30 d	↑ TG concentrations (~55%)	Motoyama et al. (95)
Guinea pig	10	19 d	↑ TG concentrations in relation to glucose treatment (155%)	Bar-On and Stein (8)
Food				
Rat	56.8	6 wk	↑ TG (~500%) and ↑ insulin (~23%) concentrations	Faure et al. (96)
	60	4 wk	↑ Insulin (45%) and ↑ uric acid (84%) concentrations	Nakagawa et al. (60)
		8 and 9 wk	↑ TG (~140%) concentrations and ↑ SBP (~14%) values	
		30 d	↑ Glucose (19%), ↑ insulin (67%) concentrations, and ↑ IR index (72%)	Nandhini et al. (97)
		6 wk	↑ Glucose (45%), ↑ TG (233%), ↑ insulin (130%) concentrations, and ↑ IR index (240%)	Liu et al. (25)
		35 d	↑ Glucose (20%), ↑ TG (277%), ↑ insulin (239%) concentrations, and ↑ IR index (307%)	El Mesallamy et al. (98)
	65	2 wk	↑ Glucose (54%), ↑ TG (441%) concentrations, and ↑ SBP (12%) values	Kim et al. (78)
		4 wk	↑ TG (112%), ↑ hepatic TG (75%), and ↑ insulin (63%) concentrations	Busserolles et al. (99)
	66	2 wk	↑ Glucose (~30%), ↑ TG (~146%), ↑ insulin (~118%) concentrations, and ↑ SBP (~16%) values	Hwang et al. (77)
	66	8 wk	↑ Glucose (42%), ↑ TG (30%), and ↑ insulin (157%) concentrations	D'Angelo et al. (81)
Hamster	60	2 wk	↑ TG (~215%) and ↑ insulin (~146%) concentrations	Taghibiglou et al. (100)
Dog	60	20–28 d	↑ TG (160%), ↑ insulin (210%) concentrations, and ↑ 22% MBP values	Martinez et al. (101)
Human	15	5 wk	↑ Insulin concentrations (14%) in hyperinsulinemic and glucose-intolerant subjects (235%)	Hallfrisch et al. (102)
	20	5 wk	↑ TG (47%) in hyperinsulinemic and (20%) nonhyperinsulinemic subjects	Reiser et al. (103)

¹ IR, insulin resistance; MBP, mean blood pressure; SBP, systolic blood pressure; ↑, increase.

compounds such as vitamin C, quercetin, and resveratrol, which may alter the metabolic activities of fructose. Accordingly, fructose in natural foods exists at lower concentrations and is completely different from the predominant fructose sources in the American diet, which comprise processed products with high amounts of added sugars and high proportions of fructose; these problems should be targeted more explicitly in dietary guidelines to support cardiometabolic and general health (89, 90).

Conclusions

There is no doubt that high-fructose feeding can cause several adverse effects (**Table 1**), because fructose stimulates DNL more than other carbohydrate sources. However, this review's conclusions should be viewed with caution, because it is unclear whether the effects of dietary fructose that have been observed in animals occur in humans. The relative doses of fructose consumed in animal experiments are much larger than those consumed by humans. Conversely, it has been reported that lower sucrose intakes by rodents also lead to IR development; therefore, such modest doses of fructose may require longer durations of exposure to induce effects relating to insulin sensitivity. Although some studies in humans have shown that high fructose doses can result in IR, postprandial hypertriglyceridemia, intra-abdominal fat accumulation, hyperuricemia, and elevated BP, it is important to determine the doses of sugar that alter health outcomes and thus identify populations who are particularly susceptible or protected from the adverse health effects of high-sugar diets. Investigating these important questions may provide a more complete understanding about how excess fructose consumption can cause disease and how the incidence rates of diet-related diseases can be reduced. This will help to reconcile the seemingly inconsistent results and will provide more reliable data for the design of randomized trials. We hope that this work will encourage investigators to focus on fructose and generate the data needed to address the questions in this review.

Acknowledgments

All authors read and approved the final manuscript.

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