Fructose, weight gain, and the insulin resistance syndrome1–3

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ABSTRACT

This review explores whether fructose consumption might be a contributing factor to the development of obesity and the accompanying metabolic abnormalities observed in the insulin resistance syndrome. The per capita disappearance data for fructose from the combined consumption of sucrose and high-fructose corn syrup have increased by 26%, from 64 g/d in 1970 to 81 g/d in 1997. Both plasma insulin and leptin act in the central nervous system in the long-term regulation of energy homeostasis. Because fructose does not stimulate insulin secretion from pancreatic β cells, the consumption of foods and beverages containing fructose produces smaller postprandial insulin excursions than does consumption of glucose-containing carbohydrate. Because leptin production is regulated by insulin responses to meals, fructose consumption also reduces circulating leptin concentrations. The combined effects of lowered circulating leptin and insulin in individuals who consume diets that are high in dietary fructose could therefore increase the likelihood of weight gain and its associated metabolic sequelae. In addition, fructose, compared with glucose, is preferentially metabolized to lipid in the liver. Fructose consumption induces insulin resistance, impaired glucose tolerance, hyperinsulinemia, hypertriacylglycerolemia, and hypertension in animal models. The data in humans are less clear. Although there are existing data on the metabolic and endocrine effects of dietary fructose that suggest that increased consumption of fructose may be detrimental in terms of body weight and adiposity and the metabolic indexes associated with the insulin resistance syndrome, much more research is needed to fully understand the metabolic effect of dietary fructose in humans. Am J Clin Nutr 2002;76:911–22.

KEY WORDS Fructose, leptin, weight gain, insulin resistance, triacylglycerol, hypertension, obesity, review

INTRODUCTION

The prevalence of obesity in the United States and worldwide is increasing (1, 2). More than one-half of US men and women aged ≥ 20 y are considered overweight [ie, a body mass index (BMI; in kg/m²) ≥ 25], and nearly one-fourth are clinically obese (BMI ≥ 30) (3, 4). Although extreme obesity has received the most attention in the clinical setting, most obesity in the population can be described as moderate to marked. However, even moderate obesity can contribute to chronic metabolic abnormalities characteristic of the insulin resistance syndrome, such as dyslipidemia, hypertension, insulin resistance, and glucose intolerance (1), particularly when it is associated with intraabdominal fat deposition (ie, central obesity) (5). Although it is likely that no single factor is responsible for the increased prevalence of moderate obesity, environmental elements—interacting with predisposing genetic factors—clearly must be involved (1). Identification of the acquired causes contributing to an increase in the prevalence of obesity is necessary to develop public health policy and dietary and physical activity recommendations that are both comprehensive and effective in reversing the current trend.

The purpose of this review is to explore whether the increased consumption of dietary fructose might be one of the environmental factors contributing to the development of obesity and the accompanying abnormalities of the insulin resistance syndrome. The insulin resistance syndrome is a cluster of related variables that appears to be of major importance in the pathogenesis of coronary artery disease. The syndrome originally included resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, hypertension, dyslipidemia characterized by high triacylglycerol concentrations, and low concentrations of HDLs (6). More recently, the list of abnormalities has been expanded to include central obesity (7); small, dense LDLs (8); increased uric acid concentrations (9); higher circulating concentrations of plasminogen activator inhibitor 1 (10); and decreased circulating concentrations of adiponectin (11). In addition, a link between local adipose steroid metabolism and the insulin resistance syndrome has been suggested by reports that the activity of 11β-hydroxysteroid dehydrogenase (EC 1.1.1.146) is increased in the adipose tissue of obese humans (12). Increased expression of this enzyme, specifically in adipose tissue, was shown recently to induce visceral obesity, insulin-resistant diabetes, and hyperlipidemia in a transgenic mouse model (13).

The terms syndrome X, metabolic syndrome, and insulin resistance syndrome have been used in the literature to describe the observed clustering of metabolic abnormalities. It has been hypothesized that insulin resistance, which may affect 25% of middle-aged adults in this country (14), is the common etiologic factor in the syndrome (6). The macronutrient content of the diet has been linked to the insulin resistance syndrome. For example,
FRUCTOSE CONSUMPTION
Changes in diet have been studied as contributing factors to the development of obesity. Along with an increase in total energy consumption over the past few decades (19), there has been a shift in the types of nutrients consumed in the American diet. The consumption of fructose has increased, largely because of an increased consumption of soft drinks and many other beverages that are high in fructose and because of the consumption of foods such as breakfast cereals, baked goods, condiments, and prepared desserts sweetened with sucrose and high-fructose corn syrup (HFCS). HFCS is produced by the enzymatic isomerization of dextrose to fructose (20). The commercial use of HFCS began to increase in the 1970s and, by 1985, HFCS accounted for approximately 35% of the total amount of sweeteners by dry weight in the food supply (21). Although HFCS can contain up to 90% fructose (22), most of the HFCS used in beverages contains ≈55% fructose.

In a 1993 article, the authors estimated the mean individual consumption of fructose in adolescents and adults to be 40 g/d, the range being 29–54 g/d (21). Thirteen of the 40 g of dietary fructose is estimated to come from naturally occurring sources of fructose, and 27 g is estimated to come from added sources of fructose. Young males (15–18 y of age) reported the highest fructose intakes with a 90th percentile intake of fructose from all sources of nearly 100 g/d. However, these intakes were based on the 1977–1978 US Department of Agriculture Nationwide Food Consumption Survey and are likely to seriously underestimate current consumption, because the consumption of HFCS-sweetened beverages has increased markedly during the intervening time. In addition, at the time that the article by Park and Yetley (21) was written, the use of crystalline fructose had just been expanded to the general food supply. To our knowledge, aside from the food disappearance data discussed below, there are no more recent data available on the amount of fructose currently consumed in the United States.

Food disappearance data serve as indicators of trends in consumption over time (19). As depicted in Figure 1, although the per capita use of sucrose decreased moderately from 46.4 kg (102 lb) in 1970 to 30.5 kg (67 lb) in 1997, the per capita use of HFCS increased from a negligible 0.23 kg (0.5 lb) in 1970 to 28.4 kg (62.4 lb) in 1997 (19). The use of glucose syrup also increased, whereas the contribution of other sweeteners—supplied as honey, molasses, and maple syrup—remained constant at ≈1% (Figure 1). The use of glucose and fructose calculated from sweetener disappearance increased in parallel during this time period (Figure 2). Calculated on a daily basis, the per capita use of added fructose, obtained by combining the disappearance data for the fructose contained in sucrose and in HFCS, increased by 26%, from 64 g/d in 1970 to 81 g/d in 1997. This represents an average daily energy intake from added fructose of ≈1356 kJ (324 kcal). In addition, a 19% increase in fruit and vegetable consumption was observed between 1982 and 1997 (19). This could lead to a small (2.5 g/d) increase in naturally occurring fructose in the diet, raising the estimated amount of naturally occurring fructose in the diet to ≈15–16 g/d for an average total fructose use of 97 g/d (1624 kJ, or 388 kcal) in 1997. Just two 355-mL (12-oz) soft drinks can supply up to 50 g fructose (~840 kJ, or 200 kcal) or >10% of the energy requirements for an average-weight woman, without considering any other dietary sources of fructose. Thus, fructose consumption makes up a significant proportion of energy intake in the American diet, and an increased fructose consumption has coincided with an increase in the prevalence of obesity over the past 2 decades. It therefore is prudent to ask whether current fructose intakes could contribute to weight gain and its metabolic sequelae.

FRUCTOSE METABOLISM
The hepatic metabolism of fructose has important effects on both glucose and lipid metabolism. Absorbed fructose is delivered...
Hepatic fructose metabolism begins with phosphorylation by fructokinase (EC 2.7.1.4). Fructose carbon enters the glycolytic pathway at the triose phosphate level (dihydroxyacetone phosphate and glyceraldehyde-3-phosphate). Thus, fructose bypasses the major control point by which glucose carbon enters glycolysis (phosphofructokinase; EC 2.7.1.11), where glucose metabolism is limited by feedback inhibition by citrate and ATP. This allows fructose to serve as an unregulated source of both glycerol-3-phosphate and acetyl-CoA for hepatic lipogenesis. Phosphate.

**FIGURE 3.** Utilization of fructose and glucose in the liver. Hepatic fructose metabolism begins with phosphorylation by fructokinase (EC 2.7.1.4). Fructose-1-phosphate is split by aldolase B (EC 4.1.2.13) into glyceraldehyde and dihydroxyacetone phosphate. Both can be converted to glyceraldehyde-3-phosphate. Thus, the fructose molecule is metabolized into 2 triose phosphates that bypass the main rate-controlling step in glycolysis, 6-phosphofructokinase (EC 2.7.1.11) (Figure 2). In contrast, hepatic glucose metabolism is limited by the capacity to store glucose as glycogen and, more importantly, by the inhibition of glycolysis and further glucose uptake resulting from the effects of citrate and ATP to inhibit phosphofructokinase (Figure 3). The products of fructose metabolism in the glycolytic pathway of the liver are glucose, glycogen, lactate, and pyruvate. Because fructose uptake by the liver is not inhibited at the level of phosphofructokinase, fructose consumption results in larger increases of circulating lactate than does consumption of a comparable amount of glucose.

Infusing small amounts of fructose intraportally in dogs appears to have a catalytic action that increases hepatic glucose uptake (24), an effect likely to be mediated by hepatic glucokinase. More recently, a low-dose infusion of fructose has been shown to increase carbon flux through glycerogen synthase (EC 2.4.1.11) and thereby stimulate glycogen synthesis in humans (25). Low-dose fructose has also been found to restore the ability of hyperglycemia to regulate hepatic glucose production (26), and the addition of 7.5 g fructose to the standard 75 g glucose reduced the glycemic response to oral-glucose-tolerance tests in adults with type 2 diabetes (27). Thus small (catalytic) amounts of oral fructose may be beneficial in improving glycemic control in type 2 diabetes. In addition, fructose ingestion results in smaller postprandial glycemic excursions compared with glucose and glucose-containing carbohydrates (starches) that are rapidly absorbed as glucose (28); however, increased blood fructose concentrations could also contribute to glycation and diabetic complications.

In contrast with low doses of fructose, when much larger amounts of fructose are consumed (eg, in sucrose- and HFCS-sweetened beverages), fructose continues to enter the glycolytic pathway distal to phosphofructokinase (Figure 3), and hepatic triacylglycerol production is facilitated. Fructose can provide carbon atoms for both the glycerol and the acyl portions of acylglycerol molecules (23). Thus, unlike glucose metabolism, in which the uptake of glucose is negatively regulated at the level of phosphofructokinase, high concentrations of fructose can serve as a relatively unregulated source of acetyl-CoA. Indeed, studies in human subjects have shown that fructose ingestion results in markedly increased rates of de novo lipogenesis (29, 30), whereas de novo lipogenesis does not increase in response to eucaloric glucose ingestion (31). Thus, fructose is more lipogenic than is glucose, an effect that might be exacerbated in subjects with existing hyperlipidemia (32) or insulin resistance or type 2 diabetes (33). In addition, as discussed below, fructose does not stimulate the production of 2 key hormones, insulin and leptin, which are involved in the long-term regulation of energy homeostasis. Therefore, the decrease in insulin responses to meals and leptin production associated with chronic consumption of diets high in fructose may have deleterious long-term effects on the regulation of energy intake and body adiposity.

**FRUCTOSE, ENERGY INTAKE, AND WEIGHT GAIN**

Although energy intake, body weight, and adiposity all increase in animals consuming high-fructose diets (34–36), considerably less information is available about humans. The effects of dietary fructose on weight gain have been reported in 3 studies in human subjects. Drinking 1150 g soda sweetened with HFCS for 3 wk resulted in significant increases in ad libitum energy intake and body weight compared with the same amount of soda with aspartame in male and female subjects (37). Body weight also increased in a group of 14 middle-aged men, 11 with type 2 diabetes mellitus and 3 with type 1 diabetes mellitus, who incorporated 50–60 g fructose into their diets for 24 wk (38). More recently, the effects of consumption of either sucrose, which consists of 50% fructose, or an artificial sweetener on ad libitum food intake and body weight were measured in overweight volunteers. Individuals who consumed large amounts of sucrose (28% of energy) showed an increase in energy intake, body weight, fat mass, and blood pressure after the 10-wk intervention (39). Thus, in these limited studies of fructose or sucrose feeding in humans, the subjects did not compensate for energy consumed as fructose by reducing ad libitum energy intake from other sources. Although these studies were not designed to test the effects of fructose on weight gain, the observation of increased body weight associated with fructose ingestion is of interest. One explanation for this observation could be that fructose ingestion did not increase the production of 2 hormones, insulin and leptin, that have key roles in the long-term regulation of food intake and energy expenditure.

Fructose, unlike glucose, does not stimulate insulin secretion from pancreatic β cells (40, 41). The lack of stimulation by fructose is likely due to the low concentrations of the fructose transporter GLUT5 in β cells (42). Insulin is involved in the regulation of body adiposity via its actions in the central nervous system (CNS) to inhibit food intake and increase energy expenditure.
In humans, plasma leptin decreases after fasting (67) or tin administration can reduce appetite in humans (61). Together, the hunger during prolonged energy restriction in women (60), and leptin concentrations correlate with increased sensations of increased body adiposity in humans (59). Decreases in circulatciency, associated with heterozygous leptin gene mutations, was posity resulting from leptin deficiency (58). Relative leptin defi- to produce leptin (56) or from defects in the leptin receptor (57), fied with hyperphagia and marked obesity, resulting from a failure effects in primates. In addition, human subjects have been identi- food intake and activates the sympathetic nervous system in rhesus appear to share a common signaling pathway via activation of phos- expenditure (50, 51). The effects of insulin and leptin on food intake limit adiposity by inhibiting food intake and increasing energy of the defective gene (45) showed that the obesity induced by a high-fat diet was associated with a 60% reduction of the transport of insulin into the CNS in dogs. This impairment of central insulin transport was inversely related to an increase in body weight in response to high-fat feeding. Specifically, knocking out the insulin receptor in neurons results in hyperphagia and obesity in mice (46). Thus, reduced insulin delivery into the CNS or disruption of the insulin-signaling pathways in the CNS may result in weight gain and the development of obesity.

As discussed above, there is considerable evidence in support of the hypothesis that insulin signaling in the CNS lowers food intake and that insulin functions as a negative feedback signal of recent energy intake and body adiposity. However, because of the known anabolic effects of insulin to simulate lipid synthesis and promote fat storage, there is a widespread belief that insulin induces weight gain and obesity. This misconception has led to the promotion of numerous diets suggesting that weight loss can be achieved by avoiding foods that stimulate insulin secretion. However, the proponents of such diets do not distinguish between normal insulin responses to meals in which circulating insulin concentrations increase and quickly return to fasting concentrations and the chronic hyperinsulinemia secondary to β cell adap- tion to insulin resistance. Note that reduced glucose-stimulated insulin secretion has been shown to be prognostic of greater future weight gain; therefore, increased insulin secretion in response to meals is unlikely to contribute to weight gain and obesity (47).

A major breakthrough in obesity research came with the cloning of the defective gene (ob) responsible for hyperphagia and obesity in an obese diabetic mouse strain (48). The gene is expressed in adipose tissue (49) and its protein product, leptin, functions as a circulating signal from body fat stores to the CNS, where it acts to limit adiposity by inhibiting food intake and increasing energy expenditure (50, 51). The effects of insulin and leptin on food intake appear to share a common signaling pathway via activation of phos- phatidylinositol-3-kinase (EC 2.7.1.137) (52). The increase in energy expenditure in rodents may be mediated by activation of the sympathetic nervous system (53). Leptin administration decreases food intake and activates the sympathetic nervous system in rhesus monkeys (54, 55), indicating that leptin has similar biological effects in primates. In addition, human subjects have been identi- fied with hyperphagia and marked obesity, resulting from a failure to produce leptin (56) or from defects in the leptin receptor (57), and leptin administration decreases the hyperphagia and body adiposity resulting from leptin deficiency (58). Relative leptin defi- ciency, associated with heterozygous leptin gene mutations, was also shown recently to have a significant biological effect, resulting in increased body adiposity in humans (59). Decreases in circulat- ing leptin concentrations correlate with increased sensations of hunger during prolonged energy restriction in women (60), and lep- tin administration can reduce appetite in humans (61). Together, the available evidence strongly suggests an important role for leptin in the regulation of energy balance in humans (11, 62).

Plasma leptin concentrations are strongly correlated with adi- posity in rodents (63, 64), nonhuman primates (65), and humans (64, 66). In humans, plasma leptin decreases after fasting (67) or energy restriction (68) to a much greater degree than would be expected from modest changes in body adiposity. However, meal ingestion does not increase plasma leptin concentrations in short- term (2–4 h) studies (67), indicating that leptin functions as a medium- to long-term regulator of energy balance rather than as a short-term satiety factor such as cholecystokinin (see review in reference 69). There is a diurnal pattern of plasma leptin concentrations in humans, with peak concentrations occurring 6–8 h after the evening meal (70). The nocturnal increase in leptin is entrained by meal timing (71) and does not occur if the subjects are fasted (72). Insulin stimulates leptin gene expression and secretion and appears to have a major role in the physiologic regulation of leptin production and in determining the magnitude of its diurnal fluctuation (11). Insulin infusions producing physiologic increments in plasma insulin have been found to increase circulating leptin concentrations in humans after several hours (73).

Studies in isolated adipocytes have provided evidence that increases in glucose transport and metabolism are key steps in insulin-stimulated leptin expression and secretion in vitro (74). A blockade of glucose transport or inhibition of glycolysis inhibits insulin-induced leptin secretion and ob gene expression, and the activation of the leptin promoter (75) in proportion to the inhibition in adipocyte glucose utilization. Furthermore, results from these and other experiments (76) indicate that anaerobic glucose metabolism does not stimulate leptin secretion, suggesting that glucose oxida- tion is involved in the effects of insulin on increases in leptin pro- duction. Glucose metabolism has also been suggested to mediate the effects of insulin and glucose infusion to increase leptin pro- duction in humans (77). Thus, increases in insulin-stimulated glu- cose metabolism after meals would be expected to influence the diurnal pattern of circulating leptin concentrations (71, 78, 79).

If, as suggested by the in vitro studies, leptin secretion is dependent on insulin-mediated adipocyte glucose transport and metabolism, then meals high in carbohydrate, which induce larger postprandial insulin and glucose excursions, should increase cir- culating leptin more than would low-carbohydrate meals. When the ratio of dietary carbohydrate to fat was altered, consumption of 3 meals with a high proportion of glucose carbohydrate enhanced insulin secretion, produced larger glucose excursions, and increased plasma leptin concentrations over 24 h relative to high- fat, low-carbohydrate meals (80). In another study, when women were placed on a weight-maintaining regimen, such that energy intake was adjusted to offset weight loss or weight gain, the sub- jects needed to be fed significantly more energy (500 ± 125 kJ/d, or 120 ± 30 kcal/d) when the fat content of the diet was lowered from 35% to 15% of energy and was replaced with complex carbohy- drate (66). Poppitt et al (81) compared the effects over 6 mo of a low-fat, complex-carbohydrate diet; a low-fat, simple-carbo- hydrate diet; and a control diet in overweight volunteers with ≥3 risk factors for metabolic syndrome. Weight loss was greatest in the low-fat, complex-carbohydrate group. These data suggest that low-fat, high-carbohydrate feeding may have altered the regulated level of adiposity, an effect that could be mediated in part by a long-term increase in leptin production. Conversely, decreased leptin secretion could contribute to the reported effect of high-fat diets, ie, weight gain and obesity (82–84).

As previously discussed, fructose, unlike glucose, does not stim- ulate insulin secretion (41). Although high-carbohydrate meals stimulate leptin production in humans relative to high-fat meals (80), if the carbohydrate provided in this study had been fructose rather than glucose, the results would probably have been different.
because of the dissimilar effects of the 2 sugars on insulin secretion. To compare the effects of glucose and fructose on leptin production, plasma leptin concentrations were measured in rhesus monkeys after intravenous infusion with saline, glucose, or fructose. Glucose infusion markedly increased plasma glucose and insulin concentrations and progressively increased plasma leptin 4–8 h into the infusions. In contrast, an intravenous infusion of the same amount of fructose only modestly increased plasma glucose and did not stimulate insulin secretion or increase circulating leptin concentrations over an 8-h period (65). To test whether ingested fructose would produce results similar to those of fructose infusion, 12 women were studied during the randomized consumption of 3 meals accompanied by fructose-containing beverages on 1 d and 3 meals accompanied by glucose-containing beverages on a separate day. The sweetened beverages supplied 30% of the total energy provided during the test days. As predicted, the consumption of fructose-containing beverages with the meals resulted in smaller postprandial glucose and insulin excursions than did the consumption of glucose-containing beverages. In addition, the consumption of 3 high-fructose meals resulted in lower circulating leptin concentrations over 24 h than did the consumption of 3 high-glucose meals (85). Furthermore, during consumption of meals accompanied by glucose beverages, circulating concentrations of the orexigenic gastric hormone ghrelin (see review in reference 86) clearly decreased 1–3 h after each meal, whereas ghrelin was much less suppressed after meals with fructose-containing beverages (85). Because insulin and leptin, and possibly ghrelin, function as key signals to the CNS in the long-term regulation of energy balance (see review in reference 69), the observed decreases in circulating insulin and leptin and increases in ghrelin could lead to increased energy intake and thereby contribute to weight gain, obesity, and its metabolic consequences during long-term consumption of diets high in energy derived from fructose.

FRUCTOSE CONSUMPTION AND INSULIN RESISTANCE

Diets high in fructose induce insulin resistance in rodents (87–89) and in dogs (90). For example, Thorburn et al (91) fed rats a diet containing 35% of energy as fructose for 4 wk and found reduced insulin sensitivity associated with impaired hepatic insulin action and whole-body glucose disposal. Both copper-deficient and copper-replete rats showed adverse changes in glucose metabolism when fed diets containing fructose for 2 wk, whereas rats fed a comparable amount of starch had no observable effects (92). In a study in hamsters fed a diet with either a high-fructose or a high-sucrose carbohydrate source for 2 wk, the rate of glucose disappearance after intravenous glucose administration decreased to a greater degree after fructose consumption than after consumption of the sucrose diet, which supplied only 50% as much fructose (36). Although fructose does not stimulate insulin secretion in the short term (41), the insulin resistance and obesity induced by long-term fructose feeding in experimental animals induces compensatory hyperinsulinemia. Blakeley et al (93) showed significant increases in fasting serum insulin and fasting serum glucose concentrations in rats that consumed 15% of energy as fructose for 15 mo compared with cornstarch-fed rats, even though no differences in body weight or food intake between the 2 groups were observed. The effects of dietary fructose on insulin action in humans are not as well documented. In 1980, Beck-Nielsen et al (94) investigated whether the reduction in insulin sensitivity induced by sucrose consumption is related to the glucose or fructose components of the diet. They found that 7 d of high-glucose feeding induced no significant changes in insulin sensitivity, whereas high-fructose feeding was accompanied by both reductions in insulin binding and insulin sensitivity. Other investigators found that diets containing 15% of energy as fructose produced undesirable changes in glucose metabolism in both normal and hyperinsulinemic men (95).

The classic relation between insulin resistance, increased fasting plasma insulin concentrations, and glucose intolerance has been hypothesized to be mediated by changes in ambient nonesterified fatty acid concentrations (see review in reference 96). Elevated nonesterified fatty acid concentrations are one of the metabolic consequences of a chronic positive energy balance and increased body adiposity (97). If, as discussed above, fructose consumption leads to increased body weight as a result of decreased insulin secretion and reduced leptin production, an increase in circulating nonesterified fatty acids might follow. The exposure to increased concentrations of nonesterified fatty acids may reduce insulin sensitivity by increasing the intramyocellular lipid content (98). Increased portal delivery of nonesterified fatty acids, particularly from visceral adipose tissue, could also lead to impaired carbohydrate metabolism, because elevated portal nonesterified fatty acid concentrations increase hepatic glucose production (99, 100). In addition, over time, increased nonesterified fatty acid concentrations may have a deleterious effect on β cell function (101).

An increased supply of nonesterified fatty acids in the liver also leads to an increase in the production of VLDL triacylglycerol (102). Fructose consumption has been shown to induce hypertriacylglycerolemia (as discussed below). Because insulin resistance and reduced insulin binding have been reported in hypertriacylglycerolemic persons (103), this may be one mechanism by which fructose diets promote insulin resistance. Administration of benfluorex, a hypolipidemic agent, reversed the insulin resistance induced by fructose feeding in rats. The improvement was associated with the normalization of triacylglycerol concentrations (104). However, 3 mo of gemfibrozil administration to 24 persons with endogenous hypertriacylglycerolemia resulted in marked decreases in both plasma triacylglycerol and nonesterified fatty acid concentrations but did not enhance insulin-mediated glucose disposal and did not lower plasma insulin concentrations (105). Therefore, the role of triacylglycerol in the development of insulin resistance remains controversial. On the other hand, postprandial hypertriacylglycerolemia after fructose ingestion is exacerbated in subjects with higher fasting insulin concentrations (33), suggesting an interaction between insulin resistance and the lipogenic effects of fructose (see below).

Another potential mechanism leading to insulin resistance could involve decreased production of the adipocyte protein, adiponectin, because reduced circulating concentrations of this hormone are associated with insulin resistance independently of body adiposity (11, 106). We are currently investigating the effects of dietary fructose compared with those of glucose on circulating adiponectin concentrations. Whatever the underlying mechanism, it is clear that fructose feeding induces insulin resistance and glucose intolerance in rodents. Given the increase in fructose consumption in the American diet, it is important to examine whether fructose has similar effects on insulin action and glucose tolerance in humans, particularly those persons who are likely to be susceptible to insulin resistance and impaired glucose metabolism.
FRUCTOSE CONSUMPTION AND LIPIDS

There are numerous studies in which dietary fructose has been shown to induce hyperlipidemia in rodents (104, 107–109). Herman et al (107) reported that rats fed a high-fructose diet had sustained elevations in serum triacylglycerol. Circulating triacylglycerol concentrations rose and remained elevated during the entire time fructose was fed (100 d) and fell promptly when a standard chow diet was instituted. The same investigators also concluded that there was a greater capacity of human liver to metabolize fructose to lipid compared with glucose because high-sucrose diets led to elevated serum triacylglycerol concentrations in humans, whereas the same amount of glucose resulted in lower concentrations of serum triacylglycerol (107). Fields and Lewis (110) fed rats copper-adequate or copper-deficient, high-fat diets with fructose or starch as the sole carbohydrate source. The combination of the high-fat diet with fructose resulted in increased circulating triacylglycerol, and fructose with copper deficiency resulted in significant increases in blood cholesterol. Hyperlipidemia did not develop when starch was combined with a high-fat diet (110). As previously discussed, the 2 monosaccharides—glucose and fructose—are metabolized differently. Hellerstein (111) showed that there is little de novo lipogenesis from glucose under eucaloric conditions in humans. In contrast, Schwarz et al (29, 30, 112) reported 3- to 15-fold increases in fractional de novo lipogenesis from fructose above fasting concentrations in obese and lean subjects (29, 30) and nearly 30% of circulating triacylglycerol palmitate after fructose ingestion resulted from de novo lipogenesis derived from fructose (112).

Fructose is the component of sucrose that is considered to be responsible for some of the adverse effects of this disaccharide on blood triacylglycerol (113). After extensive work on the metabolic effects of sucrose at the Beltsville Human Nutrition Research Center, the investigators focused on fructose specifically. Hallfrisch et al (114) fed 12 hyperinsulinemic men and 12 male control subjects diets containing 0%, 7.5%, and 15% of energy from fructose for 5 wk each in a crossover study. Total plasma cholesterol and LDL-cholesterol concentrations were higher when the men consumed 7.5% or 15% of energy as fructose than as starch. Plasma triacylglycerol concentrations in the hyperinsulinemic subjects increased as the amount of fructose increased. In 1989 Reiser et al (115) reported results from another 5-wk crossover study in which 10 hyperinsulinemic and 11 nonhyperinsulinemic men consumed diets containing 20% of energy as fructose or as high-amylase cornstarch. Triacylglycerol and cholesterol concentrations increased in both groups of subjects when they consumed fructose, but not cornstarch. Thus, consumption of fructose compared with the same amount of high-amylase cornstarch produced undesirable changes in cardiovascular risk factors in both hyperinsulinemic and nonhyperinsulinemic men.

Not all studies that have evaluated the effects of fructose have reported increased lipids. In the Turku sugar studies (116), the effect of chronic consumption of sucrose, xylitol, and fructose was studied for 2 y in 127 healthy subjects. Substituting fructose or xylitol for sucrose did not influence plasma cholesterol or triacylglycerol concentrations. Effects on body weight were not reported. It is important to note, however, that an effect of fructose alone may have been obscured by comparing its effects with those of sucrose, which is composed of 50% fructose. In a review article on the effects of dietary fructose on lipid metabolism, Hollenbeck (117) concluded that there is strong evidence that fructose consumed at ≈20% of total energy results in an increase in total and LDL-cholesterol concentrations but added that the effect of dietary fructose on triacylglycerol concentrations is less clear. Because most studies reported fasting plasma triacylglycerol concentrations, differences in postprandial triacylglycerol excursions in response to dietary changes may have been missed in some of the reported studies.

In a recent study in which 17% of energy was consumed as either crystalline fructose or glucose for 6 wk, both fasting and postprandial triacylglycerol concentrations were measured (118). The fructose diet produced significantly higher fasting, postprandial, and daylong plasma triacylglycerol values in older men, although this effect of fructose was not seen in younger (< 40 y of age) men or in the older (≥40 y of age) women included in the study. The fructose diet had no significant effects on fasting plasma cholesterol, HDL cholesterol, or LDL cholesterol in either men or women. In healthy persons, increases in triacylglycerol concentrations can decrease over time as a result of metabolic adaptation, but there does appear to be a subset of individuals who are particularly sensitive to dietary fructose, including those with hyperinsulinemia (28). We recently compared the effects of fructose- and glucose-sweetened beverages (providing 30% of total energy) consumed with 3 meals over 24 h in 12 young, normal-weight women without hypertriacylglycerolemia (119). Plasma triacylglycerol concentrations increased more rapidly and peaked at higher concentrations after consumption of fructose-containing than after glucose-containing beverages. Plasma triacylglycerol concentrations remained elevated after fructose but declined to or below fasting concentrations several hours after glucose consumption. In addition, fasting triacylglycerol concentrations the morning after fructose consumption were increased above baseline concentrations and were elevated compared with fasting triacylglycerol concentrations after glucose consumption. Evidence exists that this effect of fructose (ie, an increase in postprandial triacylglycerol concentrations) may be exacerbated in subjects with hypertriacylglycerolemia (32) or insulin resistance (33).

In a comprehensive review of carbohydrate-induced hypertriacylglycerolemia, Parks and Hellerstein (120) reviewed potential biological mechanisms for the phenomenon in humans. The authors concluded that elevated triacylglycerol concentrations observed with increased consumption of dietary carbohydrates result from elevated triacylglycerol synthesis and, in some persons, from reduced triacylglycerol clearance. The increased synthesis of triacylglycerol results primarily from both increases in the VLDL particle secretion rate by the liver and in VLDL particle size. Reductions in triacylglycerol clearance may be due in part to reductions in lipoprotein lipase (EC 3.1.1.34) activity (119). Using a fructose-fed Syrian golden hamster animal model, Taghibiglou et al (121) investigated mechanisms potentially responsible for the overproduction of VLDL in the insulin-resistant state. They found evidence for enhanced lipoprotein assembly, reduced intracellular apolipoprotein B degradation, and increased expression of microsomal triacylglycerol transfer protein. Together, these findings help to explain the increased assembly and secretion of apolipoprotein-B–containing lipoprotein particles in a fructose-fed, insulin-resistant animal model (121).

In summary, there is an abundance of data in rodents that show that fructose feeding causes chronic hyperlipidemia. Several short-term studies in humans have implicated fructose consumption as a factor promoting unfavorable lipid profiles. Many persons consume sucrose and fructose at amounts in the range of 30% of energy intake (113). This appears to be particularly true for...
TABLE 1
Studies reporting the effects of fructose or fructose-containing sweeteners on weight gain

<table>
<thead>
<tr>
<th>Species</th>
<th>Amount fed</th>
<th>Length of study</th>
<th>Effects on weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>15% of energy as fructose or</td>
<td>15 mo</td>
<td>No differences in body weight or relative food intake</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>cornstarch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamsters</td>
<td>60% fructose or sucrose</td>
<td>2 wk</td>
<td>Increased energy intake, weight gain, and adiposity with fructose</td>
<td>36</td>
</tr>
<tr>
<td>Humans (males and females)</td>
<td>1150 g soda sweetened with</td>
<td>3 wk</td>
<td>Increased energy intake and body weight with soda sweetened with HFCS</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>HFCS (~80 g fructose) or artificial sweetener</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans (middle-aged males)</td>
<td>50–60 g fructose fed</td>
<td>24 wk</td>
<td>Increased body weight</td>
<td>38</td>
</tr>
<tr>
<td>Humans (overweight males and females)</td>
<td>28% of energy as sucrose or</td>
<td>10 wk</td>
<td>Increased energy intake, body weight, and fat mass with sucrose intake</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>artificial sweetener</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1HFCS, high-fructose corn syrup.

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FRUCTOSE AND HYPERTENSION

Similar to insulin resistance and hyperlipidemia, many published experiments have shown that high-fructose diets induce hypertension in animals, including rodents (125–128) and dogs (90). In fact, fructose-fed rats are frequently used as a model for studying the effects of pharmacologic agents for treating hypertension (> 50 studies during the past 5 y). The mechanism of fructose-induced hypertension is not well understood, but such factors as uric acid production (113), hyperinsulinemia (129), aldehyde formation (130), and altered vascular reactivity (131) have been implicated. Takagawa et al (132) showed that long-term (40 wk) fructose feeding impaired vascular relaxation in the mesenteric arteries of male Sprague-Dawley rats. Fructose feeding induced hypertension in normal-fed and high-salt–fed rats and was associated with an increased expression of the angiotensin II type 1 receptor in adipose tissue (133).

Compared with individuals with normal blood pressure, persons with high blood pressure are relatively glucose intolerant (6). Additionally, lowering blood pressure in hypertensive individuals does not necessarily reduce the degree of glucose intolerance and hyperinsulinemia. Two potential explanations for how insulin resistance and hyperinsulinemia could lead to an increase in blood pressure are as follows: 1) increases in sympathetic neural outflow and plasma catecholamine concentrations associated with increased plasma insulin concentrations, and 2) insulin action at the level of the proximal tubule to increase fluid reabsorption (6). Because hypertension is a well-known comorbidity associated with obesity, insulin resistance, hyperinsulinemia, and hyperlipidemia, it is important to determine the effects of fructose consumption on blood pressure in human subjects.

TABLE 2
Studies reporting the effects of fructose or fructose-containing sweeteners on insulin resistance and glucose metabolism

<table>
<thead>
<tr>
<th>Species</th>
<th>Amount fed</th>
<th>Length of study</th>
<th>Effects on insulin resistance and glucose metabolism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>54% of energy as sucrose or</td>
<td>11–13 wk</td>
<td>Increased insulin response to meals and reduced insulin sensitivity with sucrose</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>cornstarch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>35% of energy as fructose or</td>
<td>4 wk</td>
<td>Reduced insulin sensitivity with fructose</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>15% of energy as fructose</td>
<td>15 mo</td>
<td>Increased fasting serum insulin and fasting serum glucose with fructose</td>
<td>93</td>
</tr>
<tr>
<td>Rats (copper-replete or -deficient)</td>
<td>62% fructose or starch</td>
<td>2 wk</td>
<td>Increased plasma insulin with no reduction of plasma glucose with fructose</td>
<td>92</td>
</tr>
<tr>
<td>Rats</td>
<td>66% of energy as fructose</td>
<td>2 wk</td>
<td>Plasma glucose and insulin responses to oral glucose load greater in fructose-fed rats</td>
<td>132</td>
</tr>
<tr>
<td>Hamsters</td>
<td>60% fructose or sucrose</td>
<td>2 wk</td>
<td>Decrease in glucose disappearance rate with fructose feeding</td>
<td>36</td>
</tr>
<tr>
<td>Dogs</td>
<td>60% of energy as fructose or</td>
<td>20–28 d</td>
<td>Fasting insulin concentrations increased and insulin sensitivity decreased with fructose</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>dextrose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans (males and females)</td>
<td>4.18 MJ (1000 extra kcal) as</td>
<td>7 d</td>
<td>Reductions in insulin binding and insulin sensitivity with fructose</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>fructose or glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans (males with or without hyperinsulinemia)</td>
<td>0%, 7.5%, and 15% of energy as fructose</td>
<td>5 wk each</td>
<td>15% fructose resulted in higher insulin and glucose responses than did the other 2 diets</td>
<td>95</td>
</tr>
</tbody>
</table>
TABLE 3
Studies reporting the effects of fructose or fructose-containing sweeteners on lipids

<table>
<thead>
<tr>
<th>Species</th>
<th>Amount fed</th>
<th>Length of study</th>
<th>Effects on lipids</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>68% fructose</td>
<td>100 d</td>
<td>Increased TGs that were reversed when a chow diet was reintroduced</td>
<td>107</td>
</tr>
<tr>
<td>Rats (copper-replete or -deficient)</td>
<td>Fructose or starch as the sole carbohydrate source</td>
<td>4 wk</td>
<td>Increased TGs with fructose; increased total cholesterol with fructose plus copper</td>
<td>110</td>
</tr>
<tr>
<td>Dogs</td>
<td>60% of energy as fructose or dextrose</td>
<td>20–28 d</td>
<td>Increased fasting TGs with fructose</td>
<td>90</td>
</tr>
<tr>
<td>Humans (males with or without hyperinsulinemia)</td>
<td>0%, 7.5%, or 15% of energy as fructose</td>
<td>5 wk each</td>
<td>TGs in hyperinsulinemic men increased as fructose increased</td>
<td>114</td>
</tr>
<tr>
<td>Humans (males or females aged 13–55 y)</td>
<td>Consumed either sucrose, fructose, or xylitol</td>
<td>2 y</td>
<td>No differences in plasma cholesterol or TGs</td>
<td>116</td>
</tr>
<tr>
<td>Humans (males and females)</td>
<td>40 g fat with or without 50 g fructose</td>
<td>10 h</td>
<td>Fat plus fructose led to higher postprandial TGs; increased TGs correlated with baseline TGs</td>
<td>32</td>
</tr>
<tr>
<td>Humans (males and females with or without type 2 diabetes)</td>
<td>1 g fat/kg body wt plus 0.75 g/kg body wt of either fructose or starch</td>
<td>6 h</td>
<td>TGs rose more slowly but were higher after fructose than after starch 4–6 h after the meal; increased TGs positively correlated with fasting insulin</td>
<td>33</td>
</tr>
<tr>
<td>Humans (males and females)</td>
<td>17% of energy as either fructose or glucose</td>
<td>6 wk</td>
<td>Higher fasting and postprandial TGs in older men with fructose</td>
<td>118</td>
</tr>
<tr>
<td>Humans (females)</td>
<td>30% of energy as fructose or glucose with 3 meals</td>
<td>24 h</td>
<td>Higher postprandial TGs with fructose and higher fasting TGs the following day</td>
<td>85</td>
</tr>
</tbody>
</table>

1 TG, triacylglycerol.

CONCLUSIONS

The intake of dietary fructose has increased markedly as a result of the steady increase in added sugars in the American diet (134). In the past, fructose was considered to be beneficial in the dietary management of diabetes mellitus and insulin resistance because fructose ingestion results in smaller postprandial glycemic and insulin excursions than do glucose and complex carbohydrates (28). In light of the information presented here, a cautionary note is warranted. Obesity is a growing epidemic in the United States. In terms of feedback to the CNS regarding energy status in peripheral tissues, fructose consumption results in decreased production and, therefore, decreased signaling to the CNS from 2 hormones (leptin and insulin) involved in the long-term regulation of energy homeostasis and body adiposity (11, 69). The same observation applies to dietary fat. Thus, the long-term consumption of diets high in fat and fructose is likely to lead to increased energy intake, weight gain, and obesity. The potential for weight gain from increased fructose consumption may only represent one aspect of its metabolic consequences (Tables 1–4).

Fructose has been implicated as a contributor to nearly all of the classic manifestations of the insulin resistance syndrome. Insulin resistance, impaired glucose tolerance, hyperinsulinemia, hypertension, and hyperlipidemia are associated with fructose intake in animal models. The data in humans are less clear, perhaps in part because the effects of fructose are often compared with those of sucrose, which is composed of 50% fructose. Other complicating factors obscuring the effect of dietary fructose on metabolic indexes include the duration of the studies, the age and the sex of the subjects tested, and the state in which the measurements are made (ie. fasting or postprandial).

A considerable amount of research needs to be done to more completely appreciate the effect of fructose in the American diet. In the meantime, a prudent approach concerning recommendations for dietary fructose would consider the following 2 points. First,

TABLE 4
Studies reporting the effects of fructose or fructose-containing sweeteners on blood pressure

<table>
<thead>
<tr>
<th>Species</th>
<th>Amount fed</th>
<th>Length of study</th>
<th>Effects on blood pressure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>35% of energy as fructose and 35% as starch or 70% starch or 59% fat</td>
<td>4 wk</td>
<td>Increased mean arterial pressure with fructose</td>
<td>104</td>
</tr>
<tr>
<td>Rats</td>
<td>5%, 10%, or 20% fructose in drinking water</td>
<td>≥1 wk</td>
<td>Fructose-induced hypertension with 10% solution by end of 1 wk</td>
<td>124</td>
</tr>
<tr>
<td>Rats</td>
<td>66% of energy as fructose with or without sodium chloride</td>
<td>3 wk</td>
<td>Systolic BP increased in fructose-fed rats receiving the high-salt diet</td>
<td>132</td>
</tr>
<tr>
<td>Dogs</td>
<td>60% of energy as fructose or dextrose</td>
<td>20–28 d</td>
<td>Mean arterial pressure increased with fructose</td>
<td>90</td>
</tr>
<tr>
<td>Humans (males with or without hyperinsulinemia)</td>
<td>0%, 7.5%, or 15% of energy as fructose</td>
<td>5 wk each</td>
<td>Systolic BP slightly higher with 0% fructose; no difference in diastolic BP</td>
<td>114</td>
</tr>
</tbody>
</table>

1 BP, blood pressure.
added fructose (in the forms of sucrose and HFCS) does not appear to be the optimal choice as a source of carbohydrate in the diet. Small amounts of added fructose are probably benign and may even have some favorable metabolic effects. However, on the basis of the available data regarding the endocrine and metabolic effects of consuming large quantities of fructose and the potential to exacerbate components of the insulin resistance syndrome, it is preferable to primarily consume dietary carbohydrates in the form of glucose (free glucose and starch). This may be particularly important in subjects with existing hyperlipidemia or insulin resistance who could be more susceptible to the adverse metabolic effects of fructose. Second, the concerns raised about the addition of fructose to the diet as sucrose or HFCS should not be extended to naturally occurring fructose from fruit and vegetables. The consumption of fruit and vegetables should continue to be encouraged because of the resulting increased intake of fiber, micronutrients, and antioxidants. In addition, the intake of naturally occurring fructose is low, ~15 g/d, and is unlikely to contribute significantly to the untoward metabolic consequences associated with the consumption of large amounts of fructose. Certainly, it would be desirable to have more precise data regarding the current amounts and patterns of fructose consumption. Unfortunately, to our knowledge, no accurate data on fructose consumption more recent than 1977–1978 are available. Although fructose disappearance data show a clear-cut pattern toward increased consumption of fructose, more definitive measurements of intake in different populations require large-scale surveys. In addition, it is important to gain a better understanding of the effects and mechanisms of fructose consumption on metabolic indexes such as insulin sensitivity and lipid metabolism, including triacylglycerol production.

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REFERENCES

10. Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) of syndrome X? A viewpoint strongly against. Curr Opin Lipidol 1997;8:23–7.


