Fructose, weight gain, and the insulin resistance syndrome[1–3]

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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/m^2) ≥ 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,

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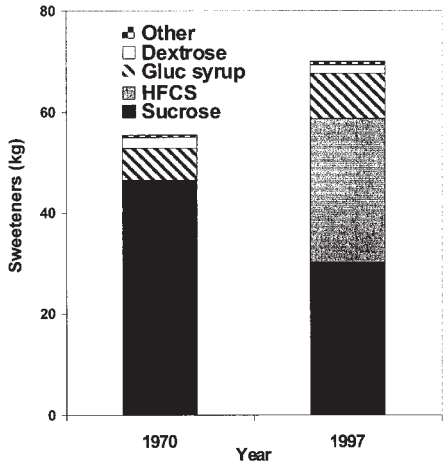

FIGURE 1. Annual per capita use of sucrose, high-fructose corn syrup (HFCS), glucose syrup, dextrose, and other sweeteners (honey, maple syrup, and molasses) in 1970 and 1997 (19). All of the 0.23 kg HFCS used in 1970 contained 42% fructose. In 1997, 38% of the HFCS used contained 42% fructose and 62% of the HFCS contained 55% fructose.

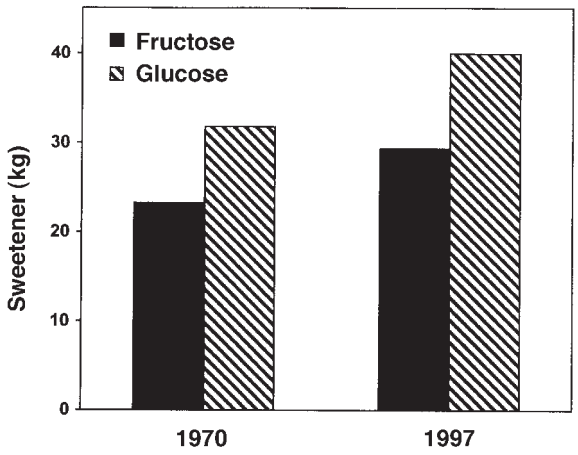

FIGURE 2. Annual per capita use of fructose from sucrose and high-fructose corn syrup (HFCS) and annual per capita use of glucose from sucrose, HFCS, glucose syrup, and dextrose in 1970 and 1997, calculated from the disappearance data for added sweeteners (19). The use of both fructose and glucose increased by 26–27% from 1970 to 1997.

high-fat, particularly high saturated fat, diets induce weight gain, insulin resistance, and hyperlipidemia in humans and animals (15–18). In addition to the known effects of dietary fat, dietary fructose has been shown to produce weight gain and induce insulin resistance, hyperlipidemia, and hypertension in experimental animals. It is therefore possible that increased consumption of fructose could contribute to weight gain and its accompanying metabolic disturbances in humans.

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 ≈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

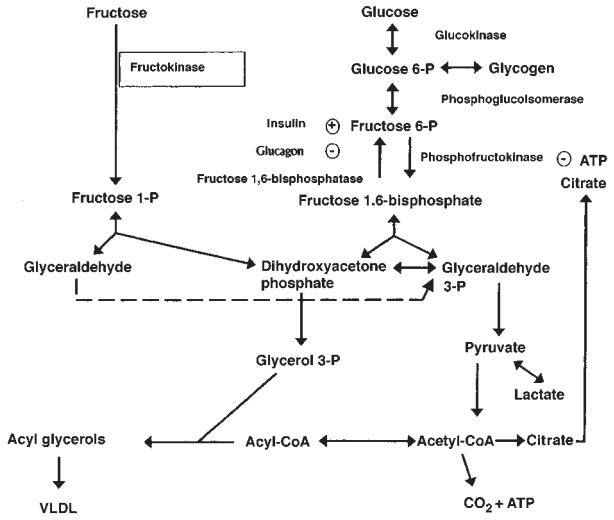

FIGURE 3. Utilization of fructose and glucose in the liver. Hepatic fructose metabolism begins with phosphorylation by fructokinase (EC 2.7.1.4). Fructose carbon enters the glycolytic pathway at the triose phosphate level (dihydroxyacetone phosphate and glyceraldehyde-3-phosphate). Thus, fructose bypasses 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. P, phosphate.

to the liver via the portal vein (23). Fructose is phosphorylated in the liver by adenosine triphosphate to form fructose-1-phosphate. The reaction is catalyzed by the enzyme 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 glycogen 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/d 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

(*see* reviews in references 43 and 44). Briefly, insulin receptors are localized in CNS areas involved in the control of food intake and energy homeostasis. Insulin administration into the CNS inhibits food intake in animals, including nonhuman primates. Insulin does not enter the brain, but is transported into the CNS via a saturable receptor-mediated process. Using compartmental modeling, Kaiyala et al (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 adaptation 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 phosphatidylinositol-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 identified 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 deficiency, 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 circulating leptin concentrations correlate with increased sensations of hunger during prolonged energy restriction in women (60), and leptin 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 adiposity 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 oxidation is involved in the effects of insulin on increases in leptin production. Glucose metabolism has also been suggested to mediate the effects of insulin and glucose infusion to increase leptin production in humans (77). Thus, increases in insulin-stimulated glucose 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 circulating 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 subjects 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 carbohydrate (66). Poppitt et al (81) compared the effects over 6 mo of a low-fat, complex-carbohydrate diet; a low-fat, simple-carbohydrate 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 stimulate 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 of 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. Blakely 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-amylose 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-amylose 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[1]

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

[1] HFCS, high-fructose corn syrup.

children (122) and adolescents (123). In the adolescent population in the United States, total milk consumption decreased by 36% from 1965 to 1996. During the same time period, soft drink consumption increased 287% in boys and 224% in girls (124). The long-term effects of increased consumption of fructose on fasting and postprandial HDL and LDL cholesterol as well as on circulating triacylglycerol concentrations need further investigation. A better understanding of whether the initial responses to increased fructose consumption persist, worsen, or improve with time should result. In addition, the potential role of fructose in the hypertriacyglycerolemia often observed during the consumption of high-carbohydrate, low-fat diets needs to be clarified.

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

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

TABLE 3
Studies reporting the effects of fructose or fructose-containing sweeteners on lipids[1]

Species	Amount fed	Length of study	Effects on lipids	Reference
Rats	68% fructose	100 d	Increased TGs that were reversed when a chow diet was reintroduced	107
Rats (copper-replete or -deficient)	Fructose or starch as the sole carbohydrate source	4 wk	Increased TGs with fructose; increased total cholesterol with fructose plus copper	110
Dogs	60% of energy as fructose or dextrose	20–28 d	Increased fasting TGs with fructose	90
Humans (males with or without hyperinsulinemia)	0%, 7.5%, or 15% of energy as fructose	5 wk each	TGs in hyperinsulinemic men increased as fructose increased	114
Humans (males with or without hyperinsulinemia)	20% of energy as fructose or cornstarch	5 wk each	TGs increased in both groups with fructose but not with cornstarch	115
Humans (males and females aged 13–55 y)	Consumed either sucrose, fructose, or xylitol	2 y	No differences in plasma cholesterol or TGs	116
Humans (males and females)	40 g fat with or without 50 g fructose	10 h	Fat plus fructose led to higher postprandial TGs; increased TGs correlated with baseline TGs	32
Humans (males and females with or without type 2 diabetes)	1 g fat/kg body wt plus 0.75 g/kg body wt of either fructose or starch	6 h	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	33
Humans (males and females)	17% of energy as either fructose or glucose	6 wk	Higher fasting and postprandial TGs in older men with fructose	118
Humans (females)	30% of energy as fructose or glucose with 3 meals	24 h	Higher postprandial TGs with fructose and higher fasting TGs the following day	85

[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[1]

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

[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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interpretation of the quantitative relation between organic anion excretion and dietary UA content only if they were a regular and major component of the daily diet. Estimating NEAP as we did for a large number of preagricultural diets ($n = 159$), with widely differing plant food group distribution ratios, gives a more comprehensive picture of the potential range of preagricultural diet-induced NEAPs, most of which were computed as decidedly negative values (1).

Nothwithstanding their comments, Remer and Manz accept the main conclusion of our article. They end by writing, "Taken together, we also conclude that the average Paleolithic diet principally led to net base production," although they suggest that the average NEAP we reported for 159 diets, −88 mEq/d, might slightly overestimate net base production because of the presence of noncombustible organic acids in some food items. We do not necessarily disagree but doubt that the adjustment is large averaged over 159 different diets, given the small fraction of natural food items with substantial noncombustible organic acid content present in the undissociated acid form. Further limiting the effect of any such noncombustible organic acids, some fraction of those acids in a food item exist in their dissociated organic anion form, the amount depending on the acid's pK_a and the pH of the food. Because such non-bicarbonate-generating organic anions appear as UAs, they get computed both as part of the bicarbonate yield of the food and as part of its contribution to the organic anion excretion rate. Therefore, their effect on the NEAP tends to be cancelled out.

As to meat-eating sweet potato eaters, we concede that odd 2-food item combinations might yield lower estimates of net base load than our reported average for preagricultural diets. We reported several such examples in our paper, even some with net acid loads (1). It seems unlikely that ancestral hominid diets consisting predominately of such odd 2-food item combinations were habitually ingested over millions of years, and therefore it seems unlikely that they played a dominant role in conditioning the genetic makeup of humans.

We end by expressing our appreciation to Remer and Manz for their numerous contributions over many years to our knowledge of diet effects on NEAP and for their trailblazing efforts in tackling the problem of computing the NEAP from diet composition. To the extent that our findings suggest that natural selection likely has adapted human metabolic machinery and integrated organ physiology to habitual ingestion of a net base-producing diet, and not to the modern net acid-producing diet, Remer and Manz merit a share in the discovery.

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Metabolic effects of dietary fructose

Dear Sir:

Elliott et al (1) wrote an interesting article concerning fructose, weight gain, and the insulin resistance syndrome. In that review they concluded that an increased consumption of fructose might be one of the environmental factors contributing to the development of obesity and the accompanying abnormalities of the insulin resistance syndrome. It is true that the prevalence of obesity in the United States and worldwide is increasing, and it is important to identify the acquired causes contributing to this increase. However, several lifestyle factors other than an increased consumption of fructose are much more probable contributors to the development of obesity (eg, a high intake of fat and minimal physical activity).

Elliott et al described a few mechanisms by which the consumption of dietary fructose might influence glucose metabolism and insulin resistance. However, they did not address the prolonged effects of dietary fructose on glucose metabolism, which are worthy of review. Type 2 diabetes (or, adult-onset diabetes) is one of the biggest health problems in the Western world, and it is suggested to be a consequence of increased energy intake and decreased physical activity. In persons with type 2 diabetes, the need for insulin is greater than that able to be produced by the pancreas. Therefore, the foods that produce a lower secretion of insulin (ie, foods that have a low glycemic index) are known to be beneficial for glucose metabolism. Koivisto and Yki-Jarvinen (2) studied the effects of dietary fructose (20% of calories as carbohydrate calories; 45–65 g/d for 4 wk) on insulin concentration and glycated hemoglobin in 10 patients with type 2 diabetes. In that study, subjects were fed—in a double-blind, randomized crossover design—a crystalline fructose or isocaloric complex carbohydrate (control) diet evenly as 4 meals or snacks per day while hospitalized. The mean diurnal blood glucose concentration decreased during both diets, but serum insulin concentration remained unchanged. Glycated hemoglobin, measured to determine glucose balance long term, improved only during the fructose diet (9.0% compared with 8.0%; $P < 0.02$) (2). In that study, insulin sensitivity also increased, by 34% ($P < 0.05$), during the fructose diet but remained unchanged during the control diet.

Even more long-term effects of a fructose diet on glycemic control were studied by Osei et al (3). They performed an outpatient study in 18 patients with type 2 diabetes who consumed either 60 g crystalline fructose/d ($n = 9$) or their usual meals ($n = 9$; control group) for 12 wk. Osei et al reported that both serum glucose and glycated hemoglobin concentrations progressively decreased in the group treated with fructose but had a tendency to increase in the control group during the study. The authors concluded that a slight improvement in glycemic control and alterations in the apoprotein composition that favor a decreased risk of coronary

artery disease may occur with an increased consumption of fructose (3). The conclusion by Elliott et al that dietary fructose has only detrimental metabolic and endocrine effects is somewhat misleading. However, Elliott et al do suggest that much more research is needed to fully understand the metabolic effects of dietary fructose, particularly in humans.

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Reply to TJ Vasankari

Dear Sir:

We agree with Vasankari that dietary fat and inactivity are likely environmental factors contributing to the marked worldwide increase in the prevalence of obesity, and this was noted in our review on the metabolic effects of fructose (1). However, we believe that an increase in fructose consumption also deserves attention as a potential third factor contributing to the escalation of obesity. Because we are not aware of quantitative data regarding the relative contributions of the 3 factors, we consider it premature to conclude that dietary fat and reduced physical activity are "much more probable contributors" to the obesity epidemic. As we and Bray (2) have pointed out, fructose consumption has increased concurrently with the obesity epidemic. Furthermore, because fructose—similarly to dietary fat—does not stimulate insulin secretion, leads to decreased leptin production, and does not suppress the orexigenic gastric hormone ghrelin (3), the lack of effects of long-term fructose consumption on these endocrine systems involved in the regulation of energy homeostasis could lead to increased energy intake, weight gain, and obesity. We therefore regard increased fructose consumption to be a likely contributor to the increased prevalence of obesity in the past 2–3 decades.

Vasankari discusses the inclusion of fructose in the diets of patients with diabetes because of its low glycemic index. In our review we briefly addressed this topic and also cited evidence that the consumption of small catalytic amounts of fructose increases hepatic glucose uptake and reduces glucose excursions after treatment with oral glucose in subjects with type 2 diabetes (1). Thus, we agree that modest amounts of dietary fructose may be beneficial in the dietary management of diabetes. Although we intentionally did not provide an in-depth discussion of or cite additional literature on studies of fructose consumption in diabetes, we believe that certain issues should be considered before high-fructose diets are recommended for diabetic patients. First, when large amounts of fructose are rapidly consumed, a sufficient amount of fructose may escape hepatic uptake to significantly elevate systemic circulating fructose concentrations. Protein fructosylation could contribute to diabetic complications (4), particularly because fructose is a major product of the polyol-sorbitol pathway and because tissue fructose accumulation has been implicated in diabetic neuropathy and other complications of diabetes. It was reported that consumption of a high-fructose diet increases both the formation of cataracts and of oxidative byproducts in the kidneys of streptozotocin-diabetic rats (5). In nondiabetic rats, fructose consumption for 1 y led to increased glycation (fructosamine and glycated hemoglobin) and markers of lipid peroxidation and aging when compared with animals that consumed glucose (6). The effect of dietary fructose on glycation and oxidation-related products deserves further investigation, and it is important to determine whether increased glycation and oxidation occur in humans consuming high amounts of dietary fructose.

In addition, although not all studies have shown an adverse effect of fructose consumption on lipids, several studies (7–9), including our own (3), showed that—compared with glucose—fructose increases postprandial triacylglycerol. Although this effect is likely to be highly dependent on the amount of fructose consumed, evidence exists that fructose-induced hypertriglyceridemia is magnified in subjects with insulin resistance (10) or hypertriglyceridemia (6, 11). Therefore, caution should be exercised when recommending diets high in fructose to patients with the metabolic syndrome or type 2 diabetes. Furthermore, in preliminary studies, we found that overweight women with normal fasting triacylglycerol concentrations who consumed 25% of energy from fructose-sweetened beverages for 10 wk had markedly increased postprandial triacylglycerol concentrations (compared with a baseline diet high in complex carbohydrate) and significantly elevated concentrations of atherogenic apolipoprotein B (12). In contrast, postprandial triacylglycerol and apolipoprotein B concentrations did not increase in subjects who consumed 25% of energy as glucose, which induced larger postprandial circulating glucose and insulin excursions than did the consumption of complex carbohydrate or fructose. Thus, the consumption of glucose-sweetened beverages—which have a high glycemic index—does not result in adverse changes in the postprandial lipid profile.

In summary, the effects of fructose on postprandial triacylglycerol and apolipoprotein B concentrations suggest that long-term consumption of high amounts of fructose could contribute to the risk of cardiovascular disease. As indicated by some studies, this effect is likely to be exacerbated in subjects with preexisting metabolic disease. Finally, as discussed above, the lack of effects on endocrine systems involved in body weight regulation suggests that the long-term consumption of diets high in fructose may lead to weight gain, obesity, and the development of type 2 diabetes. Clearly, much additional research is needed to more fully understand the metabolic effects of high-fructose diets, particularly in subjects at risk of metabolic diseases, ie, obese, insulin-resistant, or hyperlipidemic persons. Limiting fructose consumption may be a desirable objective in the management of obesity and hyperlipidemia in individual persons and in the prevention of weight gain and its metabolic consequences at the population level.

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Erratum

Francois CA, Connor SL, Bolewicz LC, Connor WE. Supplementing lactating women with flaxseed oil does not increase docosahexaenoic acid in their milk. Am J Clin Nutr 2003;77:226–33.

In Table 1 on page 227, the values for fatty acids 18:1n−9 and 20:1n−9 were interchanged. The value for 18:1n−9 should read 20.5% by wt of total fatty acids, and the value for 20:1n−9 should read 0.0% by wt of total fatty acids.