

Fructose Consumption: Considerations for Future Research on Its Effects on Adipose Distribution, Lipid Metabolism, and Insulin Sensitivity in Humans^{1,2}

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Abstract

Results from a recent study investigating the metabolic effects of consuming fructose-sweetened beverages at 25% of energy requirements for 10 wk demonstrate that a high-fructose diet induces dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity. The purpose of this review is to present aspects of the study design which may be critical for assessment of the metabolic effects of sugar consumption. Collection of postprandial blood samples is required to document the full effects of fructose on lipid metabolism. Fasting triglyceride (TG) concentrations are an unreliable index of fructose-induced dyslipidemia. Differences in the short-term (24-h) and long-term (>2 wk) effects of fructose consumption on TG and apolipoprotein-B demonstrate that acute effects can differ substantially from those occurring after sustained fructose exposure. Investigating the effects of fructose when consumed ad libitum compared with energy-balanced diets suggest that additive effects of fructose-induced de novo lipogenesis and positive energy balance may contribute to dyslipidemia and decreased insulin sensitivity. Increases of intra-abdominal fat observed in subjects consuming fructose, but not glucose, for 10 wk indicate that the 2 sugars have differential effects on regional adipose deposition. However, the increase of fasting glucose, insulin, and homeostasis model assessment-insulin resistance at 2 wk and the lack of increase of 24-h systemic FFA concentrations suggest that fructose decreases insulin sensitivity independently of visceral adiposity and FFA. The lower postprandial glucose and insulin excursions in subjects consuming fructose and increased excursions in those consuming glucose do not support a relationship between dietary glycemic index and the development of dyslipidemia, decreased insulin sensitivity, or increased visceral adiposity. *J. Nutr.* 139: 1236S–1241S, 2009.

Introduction

Although there is convincing evidence that diets high in fructose can produce obesity, insulin resistance/glucose intolerance, and dyslipidemia in animals, direct experimental evidence that sustained consumption of fructose promotes the development of metabolic syndrome in humans has been much less well

documented (1–5). However, results from our recent study comparing the metabolic effects of 10 wk of fructose and glucose consumption demonstrate that a high-fructose diet induces dyslipidemia, insulin resistance, and increased visceral adiposity (6). The strength of the data, particularly with regards to the effects on lipid metabolism, leads to the question of why results from many earlier investigations of fructose consumption in humans have been inconclusive. The purpose of this review is to address this question, focusing on several aspects of study design that are important when investigating the effects of fructose, and likely many other dietary factors, on lipid and carbohydrate metabolism. In addition, we will highlight some of the issues raised by the results that we think should be considered in the design and interpretation of future clinical research on the role of fructose in the development of metabolic syndrome.

Overview of study design

The study was designed as a prospective, blinded diet intervention with a 2-wk baseline period on a high-complex carbohydrate, moderate-fat diet and a 10-wk diet intervention phase

¹ Published in a supplement to *The Journal of Nutrition*. Presented at the conference “The State-of-the-Science on Dietary Sweeteners Containing Fructose,” held in Beltsville, MD, March 18–19, 2008. The conference was cosponsored by the Technical Committee on Carbohydrates of the International Life Sciences Institute North America and the USDA, Agricultural Research Service. The views expressed in these papers are not necessarily those of the USDA, the Agricultural Research Service, or the supplement coordinators. Supplement coordinators for this supplement were David M. Klurfeld, USDA, Agricultural Research Service, and Molly Kretsch, USDA, Agricultural Research Service. Supplement coordinator disclosure: D. Klurfeld and M. Kretsch: no relationships to disclose.

² Author disclosures: K. L. Stanhope, P. J. Havel, funding to support travel to the 18–19 March, 2008 workshop “The State of the Science on Dietary Sweeteners Containing Fructose” and the writing of this resulting manuscript was provided by the International Life Sciences Institute, North American Branch.

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TABLE 1 Study design

Study period	Setting	Duration	Diet
Baseline	Inpatient	2 wk	Energy balance diet: 55% complex carbohydrate, 30% fat, 15% protein
Intervention	Outpatient	8 wk	Ad libitum usual diet and sugar-sweetened beverages providing 25% of energy requirement
Intervention	Inpatient	2 wk	Energy balance diet: 25% sugar-sweetened beverage, 30% complex carbohydrate, 30% fat, 15% protein

(Table 1) during which overweight to obese (BMI 25–35) men and women (43–70 y) consumed either fructose- or glucose-sweetened beverages providing 25% of energy requirements [calculated by the Mifflin equation (7)]. Metabolic inpatient studies were performed during the baseline period and the final 2 wk of the intervention phase. During the inpatient baseline and intervention periods, energy-balanced (weight-maintaining) meals were provided (55% of energy as carbohydrate, 30% fat, 15% protein), with the intervention meals being as identical as possible to the baseline meals (55% complex carbohydrate) with the exception that the carbohydrate energy was provided 30% as complex carbohydrate and 25% as fructose- or glucose-sweetened beverages. During the first 8 wk of the intervention period, the subjects resided in their own homes and were provided with 3 servings/d of fructose- or glucose-sweetened beverages that were consumed along with a self-selected ad libitum (usual) diet.

A number of procedures were performed during the inpatient baseline and intervention periods, including abdominal computerized tomography scans for quantification of intra- and extra-abdominal fat area, and oral glucose tolerance tests and deuterated glucose disposal for assessment of insulin sensitivity. In addition, 24-h blood collections, consisting of 36 samples collected from 0800 to 0800 the following morning, were performed during baseline and wk 2, 8, and 10 of intervention. The baseline and intervention wk 10 collections were preceded by 10 d of consumption of an energy-balanced (weight maintaining) diet and the collections at intervention wk 2 and 8 were preceded by periods of ad libitum feeding. The purposes of this combined inpatient/outpatient design were to compare the effects of the high-fructose and -glucose diets under well-controlled metabolic conditions (at baseline and intervention wk 10) and to also investigate the potentially additive or synergistic interactions between the consumption of sugar-sweetened beverages with components of the subjects' typical diets consumed ad libitum that might lead to greater effects on lipid metabolism and insulin sensitivity/glucose tolerance (at intervention wk 2 and 8).

Postprandial blood sampling

There are aspects of the design of this study that we consider critical to adequately assess the metabolic effects of sugar consumption. Collection of blood samples during the postprandial period is one of the most important. Bantle et al. (8) were first to report that 24-h triglyceride (TG)³ postprandial profiles increased in men after consuming a 6-wk diet providing 17% energy as fructose compared with a diet providing 17% energy from glucose; however, this difference was not apparent in

women. We subsequently reported pronounced and consistent effects of both short-term (9,10) and long-term (6) fructose consumption to increase TG area under the curve (AUC) during 14- or 24-h blood sampling in both men and women. In our recent study, the 23-h TG AUC were increased by ~100% in subjects consuming fructose and tended to be decreased in subjects consuming glucose. However, despite the marked increases in the 23-h TG AUC, fasting TG concentrations did not increase after 2, 8, or 10 wk of fructose consumption (6). This is not an entirely unexpected finding. We and other investigators have reported that long-term consumption (≥ 2 wk) of fructose at 20–25% of energy did not increase fasting TG concentrations in older overweight women (11), in healthy male and female subjects (12), in hyperinsulinemic female subjects (13), in male and female patients with type 2 diabetes (14,15), and in men with hypertriglyceridemia (16). In other studies, however, consumption of fructose for ≥ 2 wk at 15–20% of energy has been reported to increase fasting TG concentrations in healthy (8,17–19) and hyperinsulinemic male subjects (19,20) and in patients with hypertriglyceridemia and type 2 diabetes (21). The reasons underlying these conflicting results are not clear but are likely to be less important than the observation that fasting TG concentrations are not a reliable indicator of fructose-induced dyslipidemia. There is growing evidence linking increased postprandial TG concentrations with a proatherogenic state (22–27). This association may be mediated by the remodeling of lipoproteins induced by postprandial hypertriglyceridemia (28–30). Accordingly, in addition to increased concentrations of postprandial TG, the participants consuming fructose in our recent study exhibited marked and significant increases in fasting and postprandial apolipoprotein-B (apoB), fasting small dense LDL (sdLDL), and postprandial remnant lipoprotein concentrations (6). The observation that fasting TG concentrations were unaffected in this setting contrasts with the markedly increased postprandial TG concentrations and other adverse changes of lipid parameters measured in these subjects during fructose consumption. It also substantiates the growing concern that standard clinical profiling, as well as many clinical studies investigating lipid levels and cardiovascular disease risk, do not include measurements of TG levels in the postprandial state (25,31).

Sustained fructose exposure

We have observed prominent differences in the effects of fructose consumption during short-term (24-h) compared with long-term studies (+2 wk). These results have led us to conclude that long-term studies are necessary to reliably determine the sustained metabolic effects of fructose consumption. In 24-h studies, we have consistently observed that consumption of fructose beverages with each meal for 1 d results in increased fasting TG concentrations of ~25% the following morning (9,10). As discussed above, fasting TG concentrations were unchanged

³ Abbreviations used: apoB, apolipoprotein-B; AUC, area under the curve; DNL, de novo lipogenesis; GI, glycemic index; HFCS, high-fructose corn syrup; sdLDL, small dense LDL; TG, triglyceride.

during our previous (11) and recent long-term studies after 2, 8, or 10 wk of fructose consumption (6). Another difference between the effects of short-term and long-term exposure to fructose-containing beverages is in the effects on plasma apoB concentrations. In participants from our recent long-term study, both fasting and postprandial apoB concentrations were increased by ~25% after 2, 8, and 10 wk of fructose consumption (6). However, in 24-h studies, consumption of fructose-sweetened beverages with 3 meals resulted in significant decreases of postprandial apoB concentrations (–10% at 2200 h) compared with fasting levels (9). This decrease is surprising given it is observed concurrently with marked increases of postprandial TG concentrations. Delineating the mechanism behind this transitory decrease of apoB may provide new insight into the regulation of VLDL production. Nonetheless, a more immediate point is that the effects of acute exposure to dietary fructose can be markedly different from those observed after sustained fructose exposure. Long-term studies are also necessary for identifying progressive effects of sustained fructose consumption. An example is provided by the sdLDL results from our recent study. Fasting sdLDL concentrations increased progressively during fructose consumption: by 20% after 2 wk, 30% after 8 wk, and 40% after 10 wk (6). Long-term studies with both fasting and postprandial measurements are clearly required to fully evaluate the metabolic effects of prolonged consumption of fructose on lipid metabolism.

Positive energy balance

Participants in our recent study consumed sugar-sweetened beverages (at 25% of weight-maintaining energy requirements) along with their usual ad libitum diets during an 8-wk outpatient period (Table 1). During this period, both groups were in positive energy balance, gaining an average of ~1.4 kg (6). Clearly, the adverse effects of fructose consumption on lipid metabolism and insulin sensitivity cannot be explained solely by positive energy balance or weight gain, because these effects were absent in the participants who consumed glucose-sweetened beverages despite a comparable amount of weight gain. However, this does not preclude the possibility of an interaction of positive energy balance and/or weight gain with fructose consumption resulting in greater effects on lipid and carbohydrate metabolism than if the subjects had been studied only in a state of neutral energy balance. It is possible that such an interaction may have contributed to the impairment of glucose tolerance and reduced insulin sensitivity in the participants consuming fructose.

Insulin resistance

The participants consuming fructose exhibited increased fasting glucose and insulin concentrations as well as an increase of the homeostasis model assessment-insulin resistance. In addition, increased glucose and insulin excursions during the oral glucose tolerance test and decreased insulin sensitivity as assessed by deuterated glucose disposal (32) were observed (6). In contrast, it has been reported that the substitution of fructose at 18% of the energy requirement to an energy-balanced, moderate-fat diet in 7 young, normal-weight men for 4 wk increased fasting glucose levels; however, other indices of insulin resistance, as well as hepatic TG content, were unaffected (18). Study design differences, including the amount (18 vs. 25% of energy requirement) and duration (4 vs. 10 wk) of fructose exposure, could contribute to the conflicting results. In addition, differences in the ages of the subjects (23 vs. 53 y) or in their baseline insulin sensitivity (fasting insulin, 58 vs. 101 pmol/L) may have

rendered the participants in our study more susceptible to the effects of fructose to induce insulin resistance.

Positive energy balance and insulin resistance

It is also likely that the 8-wk exposure to positive energy balance contributed to the decrease of insulin sensitivity in the participants consuming fructose. It has been proposed that hepatic TG accumulation is a major mediator of hepatic insulin resistance (33,34). TG accumulates in the liver when TG production exceeds FFA oxidation and VLDL production and secretion (35). We suggest that participants who consumed fructose and excess energy from other foods concurrently may have produced enough TG, via fructose-induced de novo lipogenesis (DNL), to exceed the liver's capacity for FFA oxidation and VLDL production and secretion, thus resulting in increased liver TG content and insulin resistance. Supporting this suggestion was our observation that energy intake measured during the preceding day was significantly correlated to the fructose-induced increases of postprandial apoB and TG concentrations (6), outcomes that are directly affected by increased hepatic lipid availability (36). In contrast, in the study by Le et al. (18) in which the 7 young men consumed fructose in the context of an energy-balanced diet, DNL may have increased; however, in the absence of positive energy balance, insufficient TG was produced to exceed FFA oxidation and VLDL production and secretion. Thus, these subjects did not exhibit increases of liver TG content or insulin resistance (18). It also follows that the participants consuming glucose in our study in the setting of positive energy balance did not produce sufficient TG to exceed FFA oxidation and VLDL production and secretion, because the glucose-sweetened beverages did not result in increased DNL. It is possible that both increases of DNL and positive energy balance are required to increase liver TG and thus promote the development of insulin resistance in participants consuming fructose, which may explain the differences between our results (6) and those of Le and Tappy (18). Additional studies will be required to further test the hypothesis that fructose-induced DNL, in a setting of positive energy balance, induces insulin resistance by increasing the intrahepatic TG pool.

Future clinical research on development of metabolic syndrome

In addition to having potentially important public health implications, we believe the results from our recent study can influence the direction of future clinical research on development of metabolic syndrome. The data regarding intra-abdominal fat deposition, FFA levels, and glycemic exposure are of particular interest.

Fructose and intra-abdominal fat deposition

As noted above, during the 8-wk outpatient period, when the subjects in the study consumed their usual diets ad libitum along with either fructose- or glucose-sweetened beverages at 25% of energy requirements, the subjects gained an average of 1.4 kg. Surprisingly, intra-abdominal fat area (measured by computerized tomography) significantly increased in participants consuming fructose but was unchanged in participants consuming glucose. In contrast, the extra-abdominal (subcutaneous) fat area significantly increased in the participants consuming glucose and not in those consuming fructose (6). These results suggest that fructose consumption may specifically promote lipid deposition in visceral adipose tissue. We observed increased expression of the lipogenic genes stearoyl-CoA desaturase-1, fatty acid desaturase 1, and fatty acid desaturase 2 in subcuta-

neous gluteal fat of the participants who consumed glucose for 10 wk, whereas the expression of these genes was unchanged in the participants consuming fructose (6). These data also suggest differences in the effects of the fructose and glucose on regional adipose deposition. The mechanism(s) underlying the differences are unclear but could involve the differential effects of the 2 sugars on postprandial exposure to TG and remnant lipoproteins. Votruba and Jensen (37) recently reviewed what is known about regional differences in adipose tissue TG uptake and concluded that the contribution of VLDL-TG uptake by different depots to regional body fat distribution is unknown and requires future study. The differential effects of fructose and glucose on insulin sensitivity and/or glucose-induced postprandial insulin excursions (discussed below) could also be involved. Insulin has been demonstrated to increase lipoprotein lipase expression in human subcutaneous compared with omental adipose tissue *ex vivo* (38). Clearly, the effect of fructose consumption to preferentially increase visceral adipose deposition compared with glucose consumption is an interesting observation that warrants further mechanistic investigation.

Fructose and FFA

As discussed above, consumption of a diet high in fructose, but not one high in free glucose, promoted dyslipidemia, insulin resistance, and increased visceral adiposity (6). These results suggest that this investigation and future such studies may lead to a better understanding of the sequence of events leading to the development of metabolic syndrome. The portal hypothesis of insulin resistance (39) has been proposed as an explanation for the association among central obesity and insulin resistance and the pathogenesis of metabolic syndrome. Bergman et al. (40) have recently concluded that FFA per se are among the most important products of the visceral adipocyte contributing to insulin resistance and hence metabolic syndrome and that the anatomical position of the visceral adipose depot (i.e. portal drainage to the liver) plays an important role in the pathogenesis of metabolic syndrome. However, an interesting and potentially important finding from our study is that fasting and 24-h systemic FFA profiles were unchanged in participants consuming fructose, whereas those consuming glucose had modest but significantly increased 24-h circulating FFA concentrations (6). Based on this observation and on the observation that fructose consumption appears to impair insulin resistance in as few as 2 wk, we proposed that a high-fructose diet, which provides substrate for DNL, can produce a lipid overload in the liver that results in hepatic insulin resistance independently of increased visceral adiposity and FFA levels (41). Additional studies are necessary to further investigate the mechanism underlying fructose-induced insulin resistance.

Glycemic exposure/glycemic index

The results from this study also illustrate some important relationships between glycemic exposure and dyslipidemia, cardiovascular disease risk, and insulin resistance. It has been proposed that elevated postprandial glucose excursions may increase the risk of cardiovascular disease even in nondiabetic persons (42). Glycemic index (GI) is used to categorize carbohydrate-containing food by the 2-h blood glucose response to a specified amount of the food relative to the response to an isocaloric amount of pure glucose or white bread. High GI diets have been associated with the development of cardiovascular disease (43–46), insulin resistance (47), and type 2 diabetes (48,49). However, there are also a number of conflicting reports indicating that high GI diets are not associated with the

development of cardiovascular disease (50), insulin resistance (51), or type 2 diabetes (52,53). The following reasons for these inconsistent results have been suggested: 1) the 2-h glycemic response to mixed meals may not reflect the chronic physiological effects; 2) glycemic responses to the same meal can vary considerably when consumed serially throughout the day and there is also a large degree of interindividual variation; and 3) the impact of protein and fat in the overall diet on the glycemic response is the subject of debate (54).

Glycemic exposure and the effects of glucose and fructose consumption

A further implication of our recent data is that dietary fructose may be an important contributor to the inconsistent reported effects of dietary GI on metabolic disease risk. The GI of fructose is 23 compared with 100 for glucose and the calculated relative GI of the baseline high-complex carbohydrate diet and the high-glucose and high-fructose intervention diets consumed during the 24-h blood collections in our study were 64, 83, and 38, respectively (based on the glucose standard). As expected, the glucose and insulin excursions (mean amplitude of the 3 postmeal glucose peaks) of the 3 diets paralleled the GI, with exposure being highest with the glucose diet, intermediate with the complex carbohydrate diet, and lowest with the fructose diet. However, it was the participants who consumed the high-fructose diet, the diet that had the lowest GI (GI = 38) and that produced the least glycemic exposure, who developed a more atherogenic lipoprotein profile, glucose intolerance, and decreased insulin sensitivity (6). In contrast, when participants substituted the high-glucose diet (GI = 83) for the complex carbohydrate diet (GI = 64), postprandial plasma glucose and insulin excursions increased substantially; however, postprandial TG exposure, apoB, sLDL, remnant lipoproteins, and insulin sensitivity remained unchanged (6). Thus, these results do not support the hypothesis that elevated postprandial glucose and/or insulin excursions contribute to dyslipidemia, insulin resistance, an increased risk of cardiovascular disease, or type 2 diabetes in older overweight/obese men and women. These results also demonstrate that studies investigating the relationship of dietary carbohydrates to the development of metabolic diseases must carefully distinguish between and accurately determine dietary glucose and fructose contents. It has recently been suggested that a fructose index may be more relevant with respect to cardiovascular disease risk than the GI (55).

Summary and conclusions

In summary, studies of the metabolic effects of dietary fructose should include postprandial sampling (24 h when possible) and an intervention of sufficient length to evaluate the impact on lipid metabolism and insulin sensitivity. The effects of whether the participants are in a neutral or positive energy balance needs to be considered and both male and female participants should be studied, because there appear to be important gender differences in the metabolic responses to fructose consumption. While our recent investigation generated important new data regarding the long-term effects of consuming glucose and fructose-sweetened beverages, there are a number of additional questions to be addressed: 1) What are the effects of consuming fructose at 25% of energy requirements to promote dyslipidemia and to decrease glucose tolerance/insulin sensitivity in different populations, including younger normal-weight adults compared with overweight/obese adults?; 2) Are these effects present in normal-weight or overweight/obese participants when lower (10–15% of energy) or intermediate (15–20% of energy)

amounts of fructose are consumed?; and 3) What are the metabolic effects of consuming high-fructose corn syrup (HFCS) or sucrose, the predominant sweeteners in the U.S. food supply, which are a mixture of glucose and fructose (HFCS contains 42–55% fructose and sucrose contains 50% fructose) at low, intermediate, and high levels?

We are currently conducting a dose-response study of the effects of consuming both fructose and HFCS at 3 different levels on lipid metabolism, glucose tolerance/insulin sensitivity, and hepatic TG content in normal-weight insulin-sensitive, and overweight/obese insulin-resistant men and women under the age of 40 y. In conducting these studies, we expect to obtain the data needed to address the questions raised above. Also needed are studies of the metabolic effects of fructose and HFCS/sucrose consumption in pediatric populations, including both children and adolescents.

Other articles in this supplement include references (56–65).

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