The Journal of Nutrition
Supplement: The State of the Science on Dietary Sweeteners Containing Fructose

Dietary Fructose and Glucose Differentially Affect Lipid and Glucose Homeostasis[1–3]

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Abstract

Absorbed glucose and fructose differ in that glucose largely escapes first-pass removal by the liver, whereas fructose does not, resulting in different metabolic effects of these 2 monosaccharides. In short-term controlled feeding studies, dietary fructose significantly increases postprandial triglyceride (TG) levels and has little effect on serum glucose concentrations, whereas dietary glucose has the opposite effects. When dietary glucose and fructose have been directly compared at ~20–25% of energy over a 4- to 6-wk period, dietary fructose caused significant increases in fasting TG and LDL cholesterol concentrations, whereas dietary glucose did not, but dietary glucose did increase serum glucose and insulin concentrations in the postprandial state whereas dietary fructose did not. When fructose at 30–60 g (~4–12% of energy) was added to the diet in the free-living state, there were no significant effects on lipid or glucose biomarkers. Sucrose and high-fructose corn syrup (HFCS) contain approximately equal amounts of fructose and glucose and no metabolic differences between them have been noted. Controlled feeding studies at more physiologic dietary intakes of fructose and glucose need to be conducted. In our view, to decrease the current high prevalence of obesity, dyslipidemia, insulin resistance, and diabetes, the focus should be on restricting the intake of excess energy, sucrose, HFCS, and animal and trans fats and increasing exercise and the intake of vegetables, vegetable oils, fish, fruit, whole grains, and fiber. J. Nutr. 139: 1257S–1262S, 2009.

Coronary heart disease (CHD)[6] remains a major cause of death, and risk factors include age, male gender, smoking, hypertension, diabetes, elevated total cholesterol and LDL cholesterol (LDL-C), and decreased HDL cholesterol (HDL-C) (1). Dietary factors linked to high CHD mortality include excess intake of energy, saturated fat, cholesterol, and sugars (2). Although age-adjusted CHD morbidity and mortality rates have declined in the United States over the past 50 y in part because of decreased saturated fat intake, better coronary care, smoking cessation, and treatment of elevated blood pressure and cholesterol, there has been a substantial increase in the prevalence of obesity and diabetes (1).

Potential reasons for this epidemic of obesity and diabetes may be sedentary lifestyle, excess energy intake, less cigarette smoking, and an increased intake of refined carbohydrates. It is estimated based on disappearance data in the United States that the consumption of sucrose and high-fructose corn syrup (HFCS) has increased by 27% from 64 g/d in 1970 to 81 g/d in 1997, with total simple carbohydrate consumption now accounting for ~25% of energy intake in the United States (3). However, the intake of total fat and energy has also increased in that time frame. It has been recommended by the National Cholesterol Education Program (NCEP) that saturated fat and cholesterol intake be <10% of energy and 300 mg/d, respectively, in the general population and <7% of energy and 200 mg/d, respectively, in those with elevated LDL-C levels (1). No clear recommendations for type of carbohydrate were provided, even though it has been documented that diets high in refined carbohydrate raise triglyceride (TG) and lower HDL-C levels relative to high-monounsaturated fat diets. Unfortunately, controlled feeding studies in the lipid field have mainly focused on dietary cholesterol and fatty acids and largely ignored or not specified the type of dietary carbohydrate that was used. The

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[6] Abbreviations used: apo, apolipoprotein; CHD, coronary heart disease; HDL-C, HDL cholesterol; HFCS, high-fructose corn syrup; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); TG, triglyceride.

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WHO has recommended that dietary refined carbohydrate intake be restricted to <10% of energy for prevention of chronic disease (4). Our purpose in this review is to focus on the effects of fructose compared with glucose on plasma lipoproteins and glucose homeostasis.

Types of dietary carbohydrate

Dietary carbohydrates consist of polysaccharides, disaccharides, and monosaccharides and account for ~45–70% of energy intake in developed countries. Like protein, carbohydrate contains 4 kcal/g (1 kcal = 4.184 kJ), whereas fat is more energy dense at 9 kcal/g and alcohol contains 7 kcal/g. The major dietary polysaccharides include cellulose and starch, but cellulose cannot be absorbed. Starch is a glucose polymer in plant foods that is not readily digestible in the intestinal tract unless cooked, which disrupts plant cell walls. Cooking foods rich in starch allows water entry, resulting in swelling and separation of the crystalline polymers, making starch digestible via salivary and intestinal amylases. Therefore, eating uncooked plant foods has the benefit of decreasing energy intake from starch.

Disaccharides include: *1*) sucrose (found in sugar cane, sugar beets, honey, and corn syrup), with 1 molecule of glucose and 1 molecule of fructose; *2*) lactose (found in milk) with 1 molecule of glucose and 1 molecule of galactose; and *3*) maltose (found in malt) with 2 molecules of glucose. Monosaccharides include glucose, fructose, galactose, and sorbitol, the alcohol of glucose. The most common naturally occurring monosaccharide is fructose, found in fruits and vegetables. All dietary carbohydrates are absorbed in the intestines as monosaccharides after starch and disaccharides are acted upon by salivary and pancreatic amylases (*5*).

Glucose can be used as fuel (brain and RBC can only use glucose and ketones) and is broken down to form water and carbon dioxide via the tricarboxylic acid cycle. Glucose can also be used to form glycogen stores in the liver and muscle, or it can be converted to fatty acids for deposition as TG in adipose tissue when there is energy excess. After ingestion and absorption of carbohydrate, glucose generally is not removed by the liver from portal blood and is transported to peripheral tissues to be used as energy. Under conditions of energy excess, glucose can also be taken up by the liver and stored as glycogen, or it can be converted to fatty acids and stored as TG. Under conditions of chronic energy excess, muscle and adipose cells become resistant to the effects of insulin and take up less glucose. In this situation, type 2 diabetes develops if the pancreas cannot meet the demand for insulin production. Major sources of glucose in the diet include foods rich in starch, as well as sucrose (table sugar) and HFCS.

In contrast to glucose, fructose is mainly removed by the liver after intestinal absorption into the bloodstream. Fructose in the liver is used to produce glucose, fatty acids, or lactate. Major food sources of fructose include table sugar (sucrose, containing equal amounts of fructose and glucose), HFCS (containing ~42–55% of energy as fructose and the remainder as glucose), fruits, or honey. The compositional data would suggest little difference in the effects of sucrose compared with HFCS, because both these foods have about equal amounts of fructose and glucose. It is estimated that the ingestion of sucrose, HFCS, and other sugars accounts for ~25% of energy consumption in the United States. Such intake may be even higher in children, adolescents, African Americans, and Hispanics, mainly due to increased soft drink consumption (*5*). Added sugar was not a major component of the human diet until the advent of modern food processing. Since that time, there has been a steady increase in sugar consumption, especially in soft drinks and fast foods, as well as an increase in total fat and total energy intake (*5*).

Fructose, glucose, and glycemic index

The concept of glycemic index (GI) was introduced by Jenkins et al. (*6*) as a way to classify dietary carbohydrates based on their ability to raise blood glucose levels. Fifty grams of carbohydrate in a food type, such as white bread, is given orally and serum glucose is measured serially over a 2-h period. The GI for a given food containing 50 g of carbohydrate is calculated as the percentage of the area under the glucose curve relative to the curve obtained after giving the 50 g of glucose in the same subject. Under this classification system, glucose has a GI of 100%, baked potato 85%, cornstarch 70%, and rice 64%. Relatively high-GI foods include watermelon, ice cream, and jellybeans (~70%), whereas relatively low-GI foods include milk, oatmeal, and chick peas (~32–36%). Fructose has a very low GI of 23% and it has therefore been recommended that fructose might be therapeutically useful as a dietary supplement for patients with type 2 diabetes mellitus. Sucrose has a GI of 65% and HFCS has a GI of 73%. To the concept of GI has been added the concept of glycemic load, which is the product of GI of the food and its carbohydrate content. There is a major body of literature indicating that diets with a high GI and glycemic load are more likely to promote increased TG levels, decreased HDL-C levels, and increased indices of insulin resistance over time compared with low-GI diets. Therefore, classification of foods on this basis may be helpful in the prevention and treatment of type 2 diabetes. However, there is much debate about this topic and it can be argued that a focus on specific types of dietary carbohydrates may also have scientific merit and provide more specificity (*5*).

Plasma lipoprotein metabolism

A variety of lipoproteins exist in human plasma that differ in their density, lipid composition, and electrophoretic mobility (*2*). Patients with CHD often have increased total cholesterol, TG, LDL-C, small dense LDL, remnant lipoprotein cholesterol, and lipoprotein (a) [Lp(a)] levels, as well as decreased HDL-C and decreased large HDL particles as compared with controls (*7–15*). After the ingestion of a fat-rich meal, hydrolysis of TG to fatty acids and their absorption, these fatty acids are again placed onto a glycerol backbone in the intestine and packaged into large TG-rich chylomicrons. Chylomicrons contain ~90% of TG by weight and small amounts of protein, mainly as apolipoprotein (apo) B-48, phospholipids, and cholesterol. Their density in plasma is <0.94 kg/L and they migrate at the origin on lipoprotein electrophoresis (*2*). An enzyme-linked immunoassay for apoB-48 is now available, which is specific for this protein (the only available marker for intestinal TG-rich particles or chylomicrons) (*16–18*).

In humans in the fed state, ~2 mg/(kg·d) of apoB-48 is secreted into plasma and its plasma residence time is ~5 h (*2*). apoB-48 made in the intestine contains the first 48% of the amino acids found in apoB-100 secreted by the liver. apoE is necessary for the hepatic uptake of chylomicron remnants, because apoB-48 does not contain the LDL receptor binding domain found on apoB-100. In the setting of human apoE deficiency, the apoE2/2 genotype, or familial combined hyperlipidemia, chylomicron remnants accumulate and premature CHD develops (*19*). CHD patients also often have elevated postprandial TG levels compared with controls (*20*).

The liver secretes VLDL, which contains apoB-100. VLDL are TG-enriched particles of <1.006 kg/L density and have pre-β mobility on electrophoresis (*2*). In humans in the fed state, ~20 mg/(kg·d) of VLDL apoB-100 is secreted, with ~12 mg/(kg·d) being converted to LDL in 4–5 h due to lipolysis, with the

remainder being taken up by the liver directly. In the fed state, VLDL apoB-100 secreted by the liver increases by ~20% (21). Excess fructose and fat uptake by the liver has a deleterious effect on liver metabolism, causing increased liver fat, increased VLDL-TG, and apoB-100 secretion as well as increased secretion of the inflammatory markers C reactive protein, fibrinogen, and serum amyloid A by the liver into the plasma space.

VLDL remnants are produced when VLDL have lost much of the TG and picked up cholesteryl ester and apoE from HDL (2). Remnant lipoprotein cholesterol assays are available, which measure remnant lipoproteins of both liver and intestinal origin (21–24). Moreover, elevated remnant lipoprotein cholesterol levels are elevated in CHD patients compared with controls in both the fasting and fed state, especially in women and in individuals with diabetes (9,10,21–24). The mean residence time of LDL apoB-100 is ~3.5 d and LDL is removed from plasma after binding to the LDL receptor. LDL is the major cholesterol carrying lipoprotein in plasma and contains ~25% apoB-100, 50% as free and esterified cholesterol, 20% phospholipids, and 5% TG by weight.

LDL is the most atherogenic of lipoprotein particles, is enriched in cholesteryl ester, and has been divided into large LDL (1.019–1.043 kg/L density) and small dense LDL (1.044–1.063 kg/L density) (1,2). LDL particle subspecies can be measured by vertical rotor ultracentrifugation, NMR, or gradient gel electrophoresis (8,20). However, all these assays are labor intensive and have not been well standardized. In contrast, assays are now available for direct LDL-C, small dense LDL-C, and HDL-C, which have been well standardized and can be performed on high throughput analyzers. These assays also avoid the problems of calculating LDL-C (25–28). Patients with CHD often have increases in small dense LDL-C as well as remnant lipoprotein cholesterol. The levels of these lipoproteins can be lowered with diet and by statin treatment (28–31). Lowering LDL-C has been associated with decreased CHD risk and specific targets of diet and drug therapy based on level of CHD risk have been established for LDL-C by the Adult Treatment Panel of the NCEP (1). No clear goals for TG or HDL-C levels have been established by the NCEP (1). The American Diabetes Association has recommended that people with diabetes achieve and maintain LDL-C concentrations <2.6 mmol/L or 100 mg/dL, TG concentrations <1.7 mmol/L or 150 mg/dL, and HDL-C concentrations of >1.15 mmol/L or 45 mg/dL (32).

Another atherogenic lipoprotein is Lp(a), which is an apoB-100 particle, usually an LDL particle, with a protein known as apo(a) attached to the terminal region of apoB-100 by a disulfide bond. Apo(a) has significant homology with plasminogen and may interfere with the ability of plasminogen to promote clot lysis. An elevated Lp(a) has been shown to be an independent CHD risk factor and Lp(a) can be lowered with niacin therapy. Lp(a) values in plasma or serum are generally measured by immunoassay, although assays for Lp(a) cholesterol have also been established (12,33).

HDL particles are at least 50% protein and are also rich in phospholipids and their density is between 1.063 and 1.021 kg/L, with mainly α mobility on lipoprotein electrophoresis (2,34). About 12 mg/(kg·d) of HDL apoA-I is secreted into the plasma space in humans and this constituent has a plasma residence time of ~4.5 d. The major function of HDL is to serve as an acceptor of cholesterol from tissues and to deliver it to the liver for excretion from the body in the bile (13–15,34,35). Diets high in saturated fat and cholesterol raise LDL apoB-100 by delaying its fractional clearance and increase HDL apoA-I production in humans (probably a compensatory effect) (2). In contrast, high-carbohydrate diets increase TG levels and decrease HDL-C as well as HDL apoA-I. In this setting, there are greater transfers of HDL and LDL cholesteryl esters to TG-rich lipoproteins via cholesterol ester transfer protein, resulting in smaller, denser LDL and HDL particles (2,35,36). Very little information is available on specific types of dietary carbohydrate on lipoprotein metabolism. Our own data indicate that 4 wk is the minimum time needed to arrive at a new steady state for plasma lipoprotein concentrations under controlled isocaloric conditions when the composition of the diet has been altered (2).

Effects of dietary fructose and glucose on lipid and glucose metabolism

In a literature review of this topic for human studies, >100 publications since 1980 were identified. Here we review the most important and relevant human studies. Hallfrisch and Reiser (37) studied 12 men with normal insulin levels and 12 men with elevated insulin levels and reported that increasing the fructose content (~20% of energy) of the diet was associated with increased TG, total cholesterol, and LDL-C concentrations and that TG increases were significant only in men with hyperinsulinemia. Bosetti et al. (38) compared dietary sucrose and fructose at one-third of the total carbohydrate intake (~17% of energy) for 14 d in normal volunteers and noted no differences in lipids or indicators of insulin resistance between the diets. Reiser (39) reviewed the literature and concluded that individuals with elevated insulin and TG levels were more likely to have deleterious effects on glucose and lipid metabolism from diets high in sucrose and fructose than normal individuals. Steiner (40) came to similar conclusions and indicated that diets high in simple carbohydrates increased VLDL-TG production. Crapo et al. (41) noted that a high-fructose diet induced hypertriglyceridemia in diabetics. These early data suggest that a high intake of fructose (>20% of energy) can have a deleterious effect on lipid levels.

Osei et al. (42) noted no adverse effects on glucose homeostasis or lipid parameters in 9 diabetic participant who received fructose supplementation (60 g/d) for 12 wk in the free-living state. Grigoresco et al. (43) compared the effects of 30 g/d of fructose vs. 30 g/d of starch in well-controlled diabetic patients in the free-living state and noted only moderate elevations in TG levels with the fructose supplementation. Anderson et al. (44) reported that giving diabetics consuming a high-fiber, high-carbohydrate diet 50–60 g/d of fructose did not affect plasma glucose, insulin, or lipid concentrations. Osei et al. (45) reported that supplementing diabetic subjects for 12 mo in the free-living state with 60 g/d of crystalline fructose resulted in significant reductions in glucose and insulin levels, with no significant effects on plasma lipids or body weight. These studies in aggregate indicate that adding 30–60 g/d fructose (120–240 kcal or 6–12% of energy in a 2000-kcal/d diet) to free-living participants had very little effect on lipid levels and may lower glucose levels modestly.

Reiser et al. (46) studied 10 hyperinsulinemic and 11 normoinsulinemic men for 5 wk each in a crossover design using defined controlled diets containing either 20% of energy as fructose or high-amylase cornstarch. In both groups, these investigators noted significantly higher levels of TG, total cholesterol, and uric acid with the high-fructose diet, with significant increases in VLDL-C in the hyperinsulinemic men and significant increases in LDL-C in normoinsulinemic men. They concluded that dietary fructose had a deleterious effect on cardiovascular risk, especially in the men with hyperinsulinemia. Thorburn et al. (47) studied 5 diabetic subjects consuming 13%-

fructose diets compared with baseline and noted no significant effects on plasma TG, VLDL-TG, and parameters of VLDL-TG transport after injection of ^{3}H glycerol.

Swanson et al. (48) studied 14 normal subjects for 28 d each consuming controlled diets containing either 20% of energy as fructose or starch in a crossover design. They noted that the fructose diet resulted in significant increases in total cholesterol and LDL-C compared with the high-starch diet and fasting and postprandial TG, insulin, and glucose levels did not differ. These investigators (49) conducted identical studies in 6 patients with type 1 diabetes and 12 patients with type 2 diabetes. The high fructose resulted in significantly lower levels of glucose (−13%) and glycosylated albumin but significantly higher levels of total and LDL-C (+11%) than the high-starch diet. Similar effects were seen in both types of diabetics. Koivisto and Yki-Jarvinen (50) studied 10 patients with type 2 diabetes and reported improved glycemic control and less insulin resistance after 4 wk of a high-fructose diet (20% of energy) compared with a control diet. These data support the view that dietary fructose at 20% of energy can raise total cholesterol and LDL-C, but can lower glucose and glycosylated albumin, whereas dietary starch at the same level of intake did not affect lipids but was associated with higher levels of glucose, insulin, and glycosylated albumin.

Mayes (51) reviewed the topic and concluded that fructose had deleterious effects on lipids because of its rapid uptake and utilization by the liver, resulting in increased VLDL-TG secretion. Long-term effects include decreased glucose tolerance and insulin resistance and increased uric acid production in animals. Otto et al. (52) studied the acute effects of fiber, xylitol, and fructose and concluded that patients with type 2 diabetes may benefit from replacing glucose with other carbohydrates and fiber. Gerrits and Tsalikian (53) reviewed the topic and concluded that short-term studies indicate that replacing sucrose with fructose improved glycemic control in diabetic subjects, but that long-term studies were needed. Hollenbeck (54) reviewed the topic in the same year and concluded that high-fructose diets appeared to have deleterious effects on TG, VLDL-TG, total cholesterol, VLDL-C, and LDL-C, and that such alterations may be greatest in those at highest CHD risk.

Malerbi et al. (55) studied 16 well-controlled diabetics consuming diets containing 20% of energy as fructose, sucrose, or starch for 28 d each and noted no significant differences in any lipid or glucose homeostasis variables. Abraha et al. (56) documented that acutely dietary fructose as compared with starch (both carbohydrates were given as 0.75 g/kg) resulted in significant postprandial hypertriglyceridemia in both normal and diabetic subjects, especially at 4–6 h after the meal, due to increases in both chylomicron and VLDL-TG. Bantle et al. (57) reported that a 17%-energy fructose diet for 6 wk compared with a 17%-energy glucose diet in 24 subjects with a crossover design resulted in 32% higher daylong TG level in men, but no difference in women, with no significant differences in LDL or HDL-C. Yip et al. (58) reported that meal replacements with Slim Fast either containing lactose, fructose, and sucrose or sugar free with oligosaccharides compared with meal exchange in 75 type 2 diabetic participants for 12 wk resulted in similar weight losses of 6.4% and 6.7% as compared with 4.9% in the exchange plan group and greater reductions in serum glucose with the meal replacements.

Lê et al. (59) reported that 4 wk of feeding a high-fructose diet (1.5 g/kg/d fructose or ~25% of energy) in 7 normal volunteers resulted in significant increases in plasma TG of 36%, VLDL-TG of 72%, lactate of 49%, glucose of 5.5%, and leptin of 48%; body weight and measures of insulin sensitivity, intrahepatocellular lipid, and intramyocellular lipid were not affected (the latter 2 parameters were measured by magnetic resonance imaging). Interestingly, the investigators noted a significant inverse correlation (−0.78) between plasma TG and intrahepatocellular lipid content. Levels of other lipoproteins were apparently measured but not reported. Chong et al. (60) recently reported differential effects of oral fructose compared with glucose given at 0.75 g/kg in test meals also containing 0.5 g/kg fat as an 85% palm oil/15% safflower oil mix on postprandial glucose, insulin, and TG levels in 14 normal volunteers. In these studies, only the glucose meal significantly raised glucose and insulin levels, with peak values occurring at ~60 min after meal ingestion, whereas only fructose raised plasma fructose levels. Both types of meals raised TG levels, but the fructose meal raised VLDL (Sf 20–400 particles) TG, but not chylomicron TG, substantially more than the high-glucose meal, with the greatest differences observed at 6 h after the meal. De novo lipogenesis did not differ between the 2 meals. The authors concluded from their studies that the greater increase in VLDL-TG was not due to excess production but rather to delayed clearance. They speculated that these effects may have been due to less insulin stimulation and less insulin-stimulated increases in lipoprotein lipase activity, but they did not measure this latter parameter (60).

Rutledge et al. (61) reviewed the underlying mechanisms involved in fructose-mediated increases in liver and plasma TG and concluded that fructose should be restricted in the diet to prevent metabolic syndrome. Striegel-Moore et al. (62) reported in a longitudinal study of African American and white adolescent girls that increased soft drink consumption (high in sucrose and HFCS) was significantly associated with increases in body mass over time. McAuley (63) reviewed the topic of nutritional factors and insulin resistance and concluded that excess amounts of dietary energy, saturated fat, fructose, and glucose and lack of fiber have all contributed to the potential for developing insulin resistance.

Conclusions

Investigators began recommending the use of fructose instead of glucose, because acutely, it did not raise blood glucose or insulin levels, in contrast to glucose. However, the price for this potential benefit is rapid uptake by the liver and often conversion into TG. Diets high in fructose are a common way to induce features of metabolic syndrome in rodent models (61). There is sufficient data from controlled dietary studies conducted for at least 4 wk to conclude that diets containing ≥20% energy as fructose are more likely to cause lipid abnormalities (hypertriglyceridemia due to VLDL increases in those with hyperinsulinemia and LDL-C increases in normoinsulinemic subjects) compared with diets containing ≥20% energy as either glucose or starch. Moreover, quite a substantial body of literature indicates that dietary fructose plays a role in causing nonalcoholic liver steatosis (64,65). Howard and Wylie-Rosett (3) writing for the AHA about sucrose, heart disease, diabetes control, and weight loss, concluded that "in the absence of definitive data, recommendations must rely on professional judgement." They did conclude that sugar provides no nutritional value, other than energy, so that sugar use should be minimized in obese and diabetic individuals attempting to lose weight (3). The same statement can be made for HFCS.

Stanhope and Havel (66) have reported in an ongoing study that a high-fructose diet, but not a high-glucose diet, increases visceral adiposity, promotes dyslipidemia, and increases insulin resistance. They postulated that dietary fructose preferentially causes postprandial hypertriglyceridemia, promotes visceral adi-

posity, hepatic lipid accumulation, protein C kinase activation, and hepatic insulin resistance. It should be noted that the fructose content of this diet at 25% of energy is substantially higher than that consumed by individuals in the general population. Stanhope and Havel (67) have recently reported no significant differences between sucrose and HFCS with regard to short-term effects on fasting and postprandial TG, glucose, insulin, leptin, and ghrelin levels.

Forshee et al. (68) have emphasized that pure fructose does not necessarily reflect real-life diets, which generally contain approximately equal amounts of fructose and glucose from fruits, vegetables, nuts, and added sugars such as sucrose, HFCS, and fruit juice concentrates. The level of dietary fructose used in many of the quoted studies is much higher than that found in typical diets. Significant changes were not observed when fructose vs. glucose sweeteners were tested. In addition, the increase in dietary fructose has not been disproportionate to the increase in energy, fat, and cereal grains between the 1970s and the present. Available data suggest that a sedentary lifestyle, an abundance of energy and fast food, smoking cessation, and diets containing excess energy, saturated fat, sucrose, and HFCS have all contributed to our current epidemic of obesity and type 2 diabetes. The food industry can help ameliorate this situation by providing the consumer with better food options that are lower in simple carbohydrate, saturated fat, trans fat, and cholesterol and are richer in essential fatty acids, fiber, and complex carbohydrate.

Other articles in this supplement include (69–78).

Literature Cited

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
2. Schaefer EJ. Lipoproteins, nutrition, and heart disease. Am J Clin Nutr. 2002;75:191–212.
3. Howard BV, Wylie-Rosett J. Sugar and cardiovascular disease. A statement for healthcare professionals from the Committee of the Council on Nutrition, Physical Activity and Metabolism of the American Heart Association. Circulation. 2002;106:523–7.
4. WHO. Diet, nutrition and the prevention of chronic diseases. Geneva: WHO; 2003; WHO Technical Report Series No. 916.
5. Segal MS, Gollub E, Johnson RJ. Is the fructose index more relevant with regards to cardiovascular disease than the glycemic index. Eur J Nutr. 2007;46:406–17.
6. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, et al. Glycemic index of foods: a physiologic basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362–6.
7. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA. 2007;298:776–85.
8. Campos H, Genest JJ Jr, Blijlevens E, McNamara JR, Jenner JL, Ordovas JM, Wilson PW, Schaefer EJ. Low density lipoprotein particle size and coronary artery disease. Arterioscler Thromb. 1992;12:187–95.
9. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PW, Ordovas JM, Schaefer EJ. Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. Atherosclerosis. 2001;154:229–36.
10. Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM, Wilson PW, Framingham Offspring Study. Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham Offspring Study. Diabetes Care. 2002;25:989–94.
11. Siegel RD, Cupples A, Schaefer EJ, Wilson PW. Lipoproteins, apolipoproteins, and low density lipoprotein size among diabetics in the Framingham Offspring Study. Metabolism. 1996;45:1267–72.
12. Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, Adolafia JM, Lippel K, Levy RI. Lipoprotein(a) levels predict coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. JAMA. 1994;271:999–1003.
13. Asztalos BF, Cupples LA, Demissie S, Horvath KV, Cox CE, Batista MC, Schaefer EJ. High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants in the Framingham Offspring Study. Arterioscler Thromb Vasc Biol. 2004;24:2181–7.
14. Asztalos BF, Collins D, Cupples LA, Demissie S, Horvath KV, Bloomfield HE, Robins SJ, Schaefer EJ. Value of high density lipoprotein (HDL) subpopulations in predicting recurrent cardiovascular events in the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol. 2005;25:2185–91.
15. Asztalos BF, Batista M, Horvath KV, Cox CE, Dallal GE, Morse JS, Brown GB, Schaefer EJ. Change in alpha1 HDL concentration predicts progression in coronary artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23:847–52.
16. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ. Postprandial plasma lipoprotein changes in human subjects of different ages. J Lipid Res. 1988;29:469–78.
17. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ. Plasma apolipoprotein changes in the triglyceride-rich lipoprotein fraction of human subjects fed a fat-rich meal. J Lipid Res. 1988;29:925–36.
18. Kinoshita M, Kojima M, Matsushima T, Teramoto T. Determination of apolipoprotein B-48 in serum by a sandwich ELISA. Clin Chim Acta. 2005;351:115–20.
19. Schaefer EJ, Gregg RE, Ghiselli G, Forte TM, Ordovas JM, Zech LA, Brewer HB Jr. Familial apolipoprotein E deficiency. J Clin Invest. 1986;78:1206–19.
20. Schaefer EJ, Audelin MC, McNamara JR, Shah PK, Tayler T, Daly JA, Augustin JL, Seman LJ, Rubenstein JJ. Comparison of fasting and postprandial plasma lipoproteins in subjects with and without coronary heart disease. Am J Cardiol. 2001;88:1129–33.
21. Cohn JS, Wagner DA, Cohn SD, Millar JS, Schaefer EJ. Measurement of very low density and low density lipoprotein apolipoprotein (Apo) B-100 and high density lipoprotein Apo A-I production in human subjects using deuterated leucine: effect of fasting and feeding. J Clin Invest. 1990;85:804–11.
22. Lamon-Fava S, Herrington DM, Reboussin DM, Sherman M, Horvath KV, Cupples LA, White C, Demissie S, Schaefer EJ, et al. Plasma levels of HDL subpopulations and remnant lipoproteins predict the extent of angiographically-defined disease in postmenopausal women. Arterioscler Thromb Vasc Biol. 2008;28:575–9.
23. Miyauchi K, Kayahara N, Ishigami M, Kuwata H, Mori H, Suguichi H, Irie T, Tanaka A, Yamashita S, et al. Development of a homogeneous assay to measure lipoprotein remnant cholesterol. Clin Chem. 2007;53:2128–35.
24. Nakada Y, Kurosawa H, Tohyama J, Inoue Y, Ikewaki K. Increased remnant lipoprotein in patients with coronary artery disease: evaluation utilizing a newly developed remnant assay, remnant lipoprotein cholesterol homogeneous assay (RemL-C). J Atheroscler Thromb. 2007;14:56–64.
25. McNamara JR, Cohn JS, Wilson PW, Schaefer EJ. Calculated values for low-density lipoprotein cholesterol in the assessment of lipid abnormalities and coronary disease risk. Clin Chem. 1990;36:36–42.
26. Sugiuchi H, Irie T, Uji Y, Ueno T, Chaen T, Uekama K, Okabe H. Homogeneous assay for measuring low-density lipoprotein cholesterol in serum with triblock copolymer and alpha-cyclodextrin sulfate. Clin Chem. 1998;44:522–31.
27. Sugiuchi H, Uji Y, Okabe H, Irie T, Uekama K, Kayahara N, Miyauchi K. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated alpha-cyclodextrin. Clin Chem. 1995;41:717–23.
28. Ai M, Otokozawa S, Asztalos BF, Nakajima K, Stein EA, Jones PH, Schaefer EJ. Effects of maximal doses of atorvastatin versus rosuvastatin on small dense low-density lipoprotein cholesterol levels. Am J Cardiol. 2008;101:315–8.
29. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, et al. Cholesterol Treatment Trialists' (CCT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.

30. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48:438–45.
31. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007;297:499–508.
32. American Diabetes Association. Standards of medical care in diabetes–2007. Diabetes Care. 2007;30:S4–41.
33. Seman LJ, DeLuca C, Jenner JL, Cupples LA, McNamara JR, Wilson PW, Castelli WP, Ordovas JM, Schaefer EJ. Lipoprotein(a)-cholesterol and coronary heart disease in the Framingham Heart Study. Clin Chem. 1999;45:1039–46.
34. Schaefer EJ, Lamon-Fava S, Asztalos BF. Nutritional factors and high-density lipoprotein metabolism. In: Fielding CJ, editor. High density lipoproteins: from basic biology to clinical aspects. Weinheim, Germany: Wiley VCH Verlag; 2007. p. 425–42.
35. Schaefer EJ, Asztalos BF. Cholesteryl ester transfer protein inhibition, high density lipoprotein metabolism and heart disease risk reduction. Curr Opin Lipidol. 2006;17:394–8.
36. Schaefer EJ, Levy RI, Ernst ND, Van Sant FD, Brewer HB Jr. The effects of low cholesterol, high polyunsaturated fat, and low fat diets on plasma lipid and lipoprotein cholesterol levels in normal and hypercholesterolemic subjects. Am J Clin Nutr. 1981;34:1758–63.
37. Hallfrisch J, Reiser S, Prather ES. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. Am J Clin Nutr. 1983;37:740–8.
38. Bossetti BM, Kocher LM, Moranz JF, Falko JM. The effects of physiologic amounts of simple sugars on lipoprotein, glucose, and insulin levels in normal subjects. Diabetes Care. 1984;7:309–12.
39. Reiser S. Effect of dietary sugars on metabolic risk factors associated with heart disease. Nutr Health. 1985;3:203–16.
40. Steiner G. Hypertriglyceridemia and carbohydrate intolerance: interrelations and therapeutic implications. Am J Cardiol. 1986;57:G27–30.
41. Crapo PA, Kolterman OG, Henry RR. Metabolic consequence of two-week fructose feeding in diabetic subjects. Diabetes Care. 1986;9:111–9.
42. Osei K, Falko J, Bossetti BM, Holland GC. Metabolic effects of fructose as a natural sweetener in the physiologic meals of ambulatory obese patients with type II diabetes. Am J Med. 1987;83:249–55.
43. Grigoresco C, Rizkalla SW, Halfon P, Bornet F, Fontvielle AM, Bros M, Dauchy F, Tchobroutsky G, Slama G. Lack of detectable deleterious effects on metabolic control of daily fructose ingestion for 2 mo in NIDDM patients. Diabetes Care. 1988;11:546–50.
44. Anderson JW, Story LJ, Zettwoch NC, Gustafson NJ, Jefferson BS. Metabolic effects of fructose supplementation in diabetic individuals. Diabetes Care. 1989;12:337–44.
45. Osei K, Bossetti B. Dietary fructose as a natural sweetener in poorly controlled type 2 diabetes: a 12 month crossover study of effects on glucose, lipoprotein, and apolipoprotein metabolism. Diabet Med. 1989;6:506–11.
46. Reiser S, Powell AS, Scholfield DJ, Panda P, Ellwood KC, Canary JJ. Blood lipids, lipoproteins, apoproteins, and uric acid in men fed diets containing fructose or high-amylose cornstarch. Am J Clin Nutr. 1989;49:832–9.
47. Thorburn AW, Crapo PA, Beltz WF, Wallace P, Witztum JL, Henry RR. Lipid metabolism in non-insulin-dependent diabetes: effects of long-term treatment with fructose-supplemented mixed meals. Am J Clin Nutr. 1989;50:1015–22.
48. Swanson JE, Laine DC, Thomas W, Bantle JP. Metabolic effects of dietary fructose in healthy subjects. Am J Clin Nutr. 1992;55:851–6.
49. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary fructose in diabetic subjects. Diabetes Care. 1992;15:1468–76.
50. Koivisto VA, Yki-Järvinen H. Fructose and insulin sensitivity in patients with type 2 diabetes. J Intern Med. 1993;233:145–53.
51. Mayes PA. Intermediary metabolism of fructose. Am J Clin Nutr. 1993; **58** Suppl 5:S754–65.
52. Otto C, Sönnichsen AC, Ritter MM, Richter WO, Schwandt P. Influence of fiber, xylitol and fructose in enteral formulas on glucose and lipid metabolism in normal subjects. Clin Investig. 1993;71:290–3.
53. Gerrits PM, Tsalikian E. Diabetes and fructose metabolism. Am J Clin Nutr. 1993; **58** Suppl 5:S796–9.
54. Hollenbeck CB. Dietary fructose effects on lipoprotein metabolism and risk for coronary artery disease. Am J Clin Nutr. 1993; **58** Suppl 5: S800–9.
55. Malerbi DA, Paiva ES, Duarte AL, Wajchenberg BL. Metabolic effects of dietary sucrose and fructose in type II diabetic subjects. Diabetes Care. 1996;19:1249–56.
56. Abraha A, Humphreys SM, Clark ML, Matthews DR, Frayn KN. Acute effects of fructose on postprandial lipemia in diabetic and non-diabetic subjects. Br J Nutr. 1998;80:169–75.
57. Bantle JP, Raatz SK, Thomas W, Georgepoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. Am J Clin Nutr. 2000;72:1128–34.
58. Yip I, Go VL, DeShields S, Saltsman P, Bellman M, Thames G, Murray S, Wang HJ, Elashoff R, et al. Liquid meal replacements and glycemic control in obese type 2 diabetes patients. Obes Res. 2001;9 Suppl 4: S341–7.
59. Lê KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, Boesch C, Ravussm E, Tappy L. A 4-week high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. Am J Clin Nutr. 2006;84:1374–9.
60. Chong MF, Fielding BA, Frayn KN. Mechanisms for the acute effect of fructose on postprandial lipemia. Am J Clin Nutr. 2007;85:1511–20.
61. Rutledge AC, Adeli K. Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutr Rev. 2007;65:S13–23.
62. Striegel-Moore RH, Thompson D, Affenito SG, Franko DL, Obarzanek E, Barton BA, Schreiber GB, Daniels SR, Schmidt M, et al. Correlates of beverage intake in adolescent girls: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr. 2006;148:183–7.
63. McAuley K, Mann J. Thematic review series: patient-oriented approach. Nutritional determinants of insulin resistance. J Lipid Res. 2006;47: 1668–76.
64. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for non-alcoholic fatty liver disease. Am J Clin Nutr. 2007;86:285–300.
65. Cave M, Deaciuc I, Mendez C, Song Z, Joshi-Barve S, Barve S, McClain C. Nonalcoholic fatty liver disease: predisposing factors and the role of nutrition. J Nutr Biochem. 2007;18:184–95.
66. Stanhope KL, Havel PJ. Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. Curr Opin Lipidol. 2008;19:16–24.
67. Stanhope KL, Griffen SC, Bair BR, Swarbrick MM, Keim NL, Havel PJ. Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose,-, fructose-,and glucose-sweetened beverages with meals. Am J Clin Nutr. 2008;87:1194–203.
68. Forshee RA, Storey ML, Allison DB, Glinsmann WH, Hein GL, Lineback DR, Miller SA, Nicklas TA, Weaver GA, et al. A critical examination of the evidence relating HFCS and weight gain. Crit Rev Food Sci Nutr. 2007;47:561–82.
69. Jones JM. Dietary sweeteners containing fructose: overview of a workshop on the state of the science. J Nutr. 2009;139:1210S–3S.
70. Borra ST, Bouchoux A. Effects of science and the media on consumer perceptions about dietary sugars. J Nutr. 2009;139:1214S–8S.
71. White JS. Misconceptions about high-fructose corn syrup: is it uniquely responsible for obesity, reactive dicarbonyl compounds, and advanced glycation endproducts? J Nutr. 2009;139:1219S–27S.
72. Marriott BP, Cole N, Lee E. National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. J Nutr. 2009; 139:1228S–35S.
73. Stanhope KL, Havel PJ. Fructose consumption: considerations for future research on its effects on adipose distribution, lipid metabolism, and insulin sensitivity in humans. J Nutr. 2009;139:1236S–41S.
74. Angelopoulos TJ, Lowndes J, Zukley L, Melanson KJ, Nguyen V, Huffman A, Rippe JM. The effect of high-fructose corn syrup consumption on triglycerides and uric acid. J Nutr. 2009;139:1242S–5S.
75. Livesey G. Fructose ingestion: dose-dependent responses in health research. J Nutr. 2009;139:1246S–52S.
76. Moran TH. Fructose and satiety. J Nutr. 2009;139:1253S–6S.
77. John P. Bantle. Dietary fructose and metabolic syndrome and diabetes. J Nutr. 2009;139:1263S–8S.
78. Murphy SP. The state of the science on dietary sweeteners containing fructose: summary and issues to be resolved. J Nutr. 2009;139:1269S–70S.