

Sucrose, High-Fructose Corn Syrup, and Fructose, Their Metabolism and Potential Health Effects: What Do We Really Know?^{1,2}

James M. Rippe^{5*} and Theodore J. Angelopoulos⁶

⁵University of Central Florida Medical School, Orlando, FL and Rippe Lifestyle Institute, Shrewsbury, MA; and ⁶Laboratory of Applied Physiology, Department of Health Professions, University of Central Florida, Orlando, FL

ABSTRACT

Both controversy and confusion exist concerning fructose, sucrose, and high-fructose corn syrup (HFCS) with respect to their metabolism and health effects. These concerns have often been fueled by speculation based on limited data or animal studies. In retrospect, recent controversies arose when a scientific commentary was published suggesting a possible unique link between HFCS consumption and obesity. Since then, a broad scientific consensus has emerged that there are no metabolic or endocrine response differences between HFCS and sucrose related to obesity or any other adverse health outcome. This equivalence is not surprising given that both of these sugars contain approximately equal amounts of fructose and glucose, contain the same number of calories, possess the same level of sweetness, and are absorbed identically through the gastrointestinal tract. Research comparing pure fructose with pure glucose, although interesting from a scientific point of view, has limited application to human nutrition given that neither is consumed to an appreciable degree in isolation in the human diet. Whether there is a link between fructose, HFCS, or sucrose and increased risk of heart disease, metabolic syndrome, or fatty infiltration of the liver or muscle remains in dispute with different studies using different methodologies arriving at different conclusions. Further randomized clinical trials are needed to resolve many of these issues. The purpose of this review is to summarize current knowledge about the metabolism, endocrine responses, and potential health effects of sucrose, HFCS, and fructose. *Adv. Nutr.* 4: 236–245, 2013.

Introduction

Over the past decade, considerable scientific debate and controversy have arisen concerning the metabolism, endocrine response, and potential health effects of sucrose, high-fructose corn syrup (HFCS), and fructose (1–17).

Although an enormous body of scientific literature has been available on all 3 of these sugars for many years (18–23), in retrospect, the recent controversy seems to have started with the publication of a commentary in the *American Journal of Clinical Nutrition* (AJCN) in 2004 (3), suggesting that HFCS in beverages might play a unique role

in the epidemic of obesity currently being experienced in the United States and many other countries. Although the authors of this commentary clearly stated that they were only describing a temporal association and not a cause-and-effect relationship, a heated debate concerning the metabolism and potential health effects of sucrose, HFCS, and fructose subsequently ensued. This debate has involved not only the scientific community but also major media outlets, the public at large, and policymakers. Controversies concerning these 3 sugars have been fueled by conditions that, in our view, created a “perfect storm” for confusion and mistaken identity. Even though the original authors of the AJCN commentary were clear that they were simply offering a hypothesis, other investigators, food manufacturers, and the public at large have contributed to this controversy, often without distinguishing between an association and cause and effect, while frequently confusing the sugars used in research studies, or exaggerating the implications of animal work.

In addition, several other factors appear to have contributed to the ongoing controversy about these 3 sugars. The historic choice of the name “high-fructose” corn syrup certainly

¹ Presented at the symposium “Fructose, Sucrose and High-Fructose Corn Syrup. Modern Scientific Findings and Health Implications,” held April 22, 2012, at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2012 in San Diego, CA. The symposium was sponsored by the American Society for Nutrition and supported in part by an educational grant from the Corn Refiners Association. A summary of the symposium “Fructose, Sucrose and High-Fructose Corn Syrup. Modern Scientific Findings and Health Implications” was published in the September 2012 issue of *Advances in Nutrition*.

² Author disclosures: J. M. Rippe, consulting fees from ConAgra Foods, PepsiCo International, Kraft Foods, the Corn Refiners Association, and Weight Watchers International. T. J. Angelopoulos, no conflicts of interest.

* To whom correspondence should be addressed. E-mail: jrippe@rippelifestyle.com.

contributed to the confusion, even though HFCS contains virtually the same amount of fructose as sucrose. Furthermore, over the past decade, a number of researchers reported results based on experiments comparing metabolic and health effects of pure fructose with those of pure glucose, which brought other issues into the debate (13,17).

Not surprisingly, the public and media have found it difficult to distinguish between studies conducted with pure fructose versus pure glucose, neither of which is commonly consumed in the human diet and the more commonly consumed HFCS and sucrose, which contain both fructose and glucose. Finally, because the United States and many other countries are in the midst of an obesity epidemic, further impetus was added to these discussions because the premise of limiting consumption of added sugars seemed to many an attractive option for potentially affecting the increasing prevalence of obesity.

With all of this as background, the purpose of the current review is to discuss the metabolism and the endocrine responses to consumption of sucrose, HFCS, and fructose. We also attempt to elucidate the strengths and weaknesses of the evidence supporting the putative link between the consumption of these sugars and potential adverse health consequences. We then discuss results of recent randomized, controlled trials using various levels of fructose, HFCS, and sucrose. We address these issues by asking and attempting to answer a series of questions related to the metabolism, endocrine responses, and health effects of these 3 sugars.

Current status of knowledge

Is there a unique link between HFCS and obesity?

In their commentary in *AJCN* in 2004, Bray et al. (3) argued that increased use of HFCS in the United States mirrored the rapid increase in obesity. Data to support this hypothesized connection were presented in graphic form, as illustrated in **Figure 1**. These authors argued that the digestion, absorption, and metabolism of fructose compared with glucose differed in ways that promoted the likelihood of increased energy consumption, resulting in an increased likelihood of obesity and diabetes, metabolic syndrome, and cardiovascular disease (3,24–29).

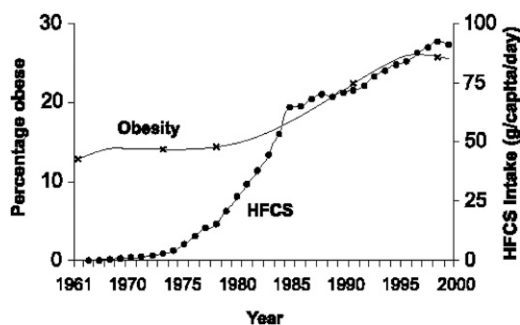


Figure 1 Temporal association between increased consumption of high-fructose corn syrup (HFCS) and prevalence of obesity. Adapted from (3) with permission.

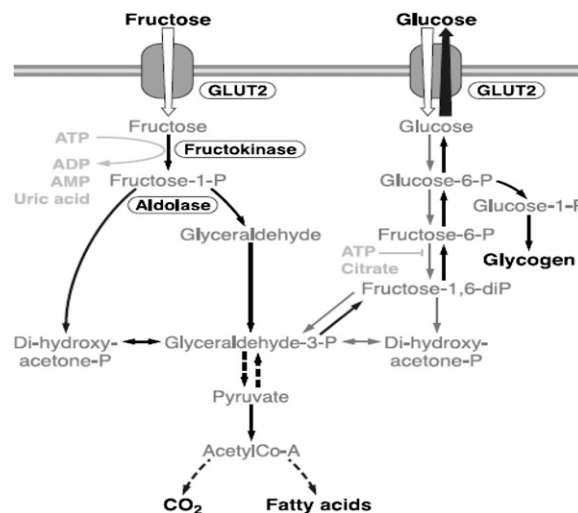


Figure 2 Metabolism of fructose and glucose in the liver. Reproduced from (41) with permission.

In retrospect, the argument that HFCS is uniquely linked to obesity failed to take into consideration a number of important issues. Although consumption of HFCS in the United States dramatically increased from the early 1970s when it first came into use until about 1999, over the past decade the consumption of HFCS has decreased (30), whereas obesity has increased or remained at the same levels in most population groups (31). Moreover, as HFCS consumption increased in the United States, there was a commensurate, dramatic decrease in the amount of sucrose consumed (30).

Although total caloric sweetener consumption in the United States has increased since 1970, sucrose remains the leading added sugar consumed in the American diet and the leading source of fructose (32). According to the USDA's Economic Research Service, between 1970 and 2005, sugars and sweeteners available for consumption increased 76 kcal/d per person from 400 kcal to 476 kcal (33). Furthermore, worldwide consumption of sucrose is 9 times as much as HFCS, and there are epidemics of obesity and diabetes in areas where little or no HFCS is available (e.g., Mexico, Australia, and Europe).

Research studies since the 2004 *AJCN* article have also refuted the idea that HFCS is metabolically different from sucrose (15,34–36). Studies published from our research group demonstrated that acute responses to HFCS and sucrose are virtually identical with regard to glucose, insulin, leptin, ghrelin, and appetite in both normal weight (34) and obese (37) women. Studies by Stanhope et al. (36) showed findings similar to those that we reported in both men and women and also demonstrated no difference in postprandial triglycerides after consumption of either HFCS or sucrose at 25% of energy (36). Studies by Soenen and Westerterp-Plantenga (35) showed no differences in satiety or energy intake after HFCS, sucrose, or milk preloads.

These studies and other scientific literature persuaded the American Medical Association (8) and the Academy of

Nutrition and Dietetics (9) to issue statements indicating that there were no differences between HFCS and sucrose in their likelihood of causing obesity. In addition, the ASN recently released a consensus statement on energy balance noting its complexity and arguing specifically against isolation of 1 component of the diet as uniquely responsible for weight gain and obesity (38).

Perhaps the prevailing scientific consensus relating to the metabolic equivalence of HFCS and sucrose was best summarized by G. Harvey Anderson (39) when he wrote:

The hypothesis that the replacement of sucrose by HFCS in beverages plays a positive role in obesity is not supported on the basis of its composition, biologic actions, or short-term effects on food intake. Had the hypothesis been phrased in the converse, namely that replacing HFCS with sucrose in beverages would be seen as a solution to the obesity epidemic, its merit would have been seen more clearly. Put simply, a proposal that a return to sucrose containing beverages would be a credible solution to the obesity epidemic would have been met with outright dismissal.

Although this debate has largely been resolved within the scientific community, multiple articles in the lay press and Internet postings still maintain that HFCS is somehow uniquely linked to obesity. Furthermore, a number of food and beverage manufacturers have touted removal of HFCS from their products as though it somehow makes these products “healthier.” These examples serve as a reminder that scientific debate on issues that the public cares about does not take place in a vacuum and that misperceptions may linger long after the scientific debate has largely been resolved.

Is research comparing fructose with glucose relevant to human nutrition?

Several studies have compared the metabolism, endocrine response, and health effects of pure fructose with those of pure glucose. Often these studies have compared amounts of either fructose or glucose delivered as 25% of energy as components of mixed nutrient diets (13,17,40). The theoretical justification for such research trials rests on the well-established difference in hepatic metabolism of fructose and glucose in the liver. The routes of hepatic metabolism of fructose and glucose are depicted in [Figure 2](#) (41).

Fructose metabolism differs from that of glucose in 2 major ways (41,42). First, there is nearly complete hepatic extraction of fructose. Second, as illustrated in [Figure 2](#), there are different enzymatic reactions in the initial steps of the metabolism of fructose and glucose.

These differences in hepatic metabolism could theoretically lead to a variety of different short- and long-term effects of fructose compared with glucose. Teff et al. (17) reported that when either fructose or glucose were consumed as 25% of energy, glucose caused higher spikes in blood glucose and insulin as well as greater increases in leptin and more suppression of ghrelin levels than did fructose. However, when these conditions were repeated in our research laboratory comparing 30% of energy from HFCS versus sucrose, all of these

differences disappeared ([Fig. 3](#)) (15). Our findings were subsequently confirmed by Stanhope et al. (36) and extended to men ([Fig. 4](#)).

Stanhope et al. (36) reported that consuming fructose-sweetened, but not glucose-sweetened beverages at the same levels of energy consumption (25% of energy), increased visceral adiposity and lipids, and decreased insulin sensitivity in overweight or obese individuals. Initial research in our laboratory did not support these findings (43). Subsequent research in our laboratory involving 352 overweight or obese individuals who consumed either HFCS or sucrose at levels up to the 90th percentile population consumption level for fructose (30% of energy from either HFCS or sucrose) did not show any changes in either systolic or diastolic blood pressure or glucose. HDL cholesterol decreased by <1 mg/dL and triglycerides increased 10% (104.1 ± 51.8 mg/dL to 114.1 ± 67.4 mg/dL) ($P < 0.05$) (unpublished observations).

Recent research reviews by Dolan et al. (44,45) reported that no adverse effect on triglycerides or weight was observed in multiple trials using fructose at up to the 95th percentile population consumption level. Meta-analyses by Ha et al. (46) also documented that no increases in blood pressure or propensity toward obesity occurred at up to the 90th percentile population consumption levels of fructose (47). It should be emphasized that these meta-analyses included only studies exploring consumption of fructose in isolation. Stanhope et al. (36) also did not find increases in blood pressure when obese individuals consumed as much as 25% of energy as either fructose or glucose.

It should be noted that fructose and glucose are rarely consumed in isolation in the human diet. Thus, studies comparing pure fructose with pure glucose, particularly at high levels, should be treated with caution, particularly because studies comparing the more commonly consumed sucrose and HFCS have yielded different results.

Does fructose, HFCS, or sucrose consumption increase the risk of heart disease?

With the recognition that fructose versus glucose experiments do not reflect typical human nutrition, increased scrutiny has been focused on the fructose moiety of both HFCS and sucrose. Sucrose is composed of 50% glucose and 50% fructose, whereas the forms of HFCS used in most foods and beverages are typically composed of 55% fructose and 45% glucose (this is the common form used in beverages) or 42% fructose and 58% glucose (the form commonly used in baked goods and other food applications) (48).

Because soft drinks are a major source of added sugar consumption in the American diet, a number of studies have explored soft-drink consumption and its potential association with a variety of metabolic and health issues. Cross-sectional studies in humans have linked soft-drink consumption with less optimum nutrition, greater body weight, and higher energy intake (49,50). It has also been suggested that excessive fructose consumption from added

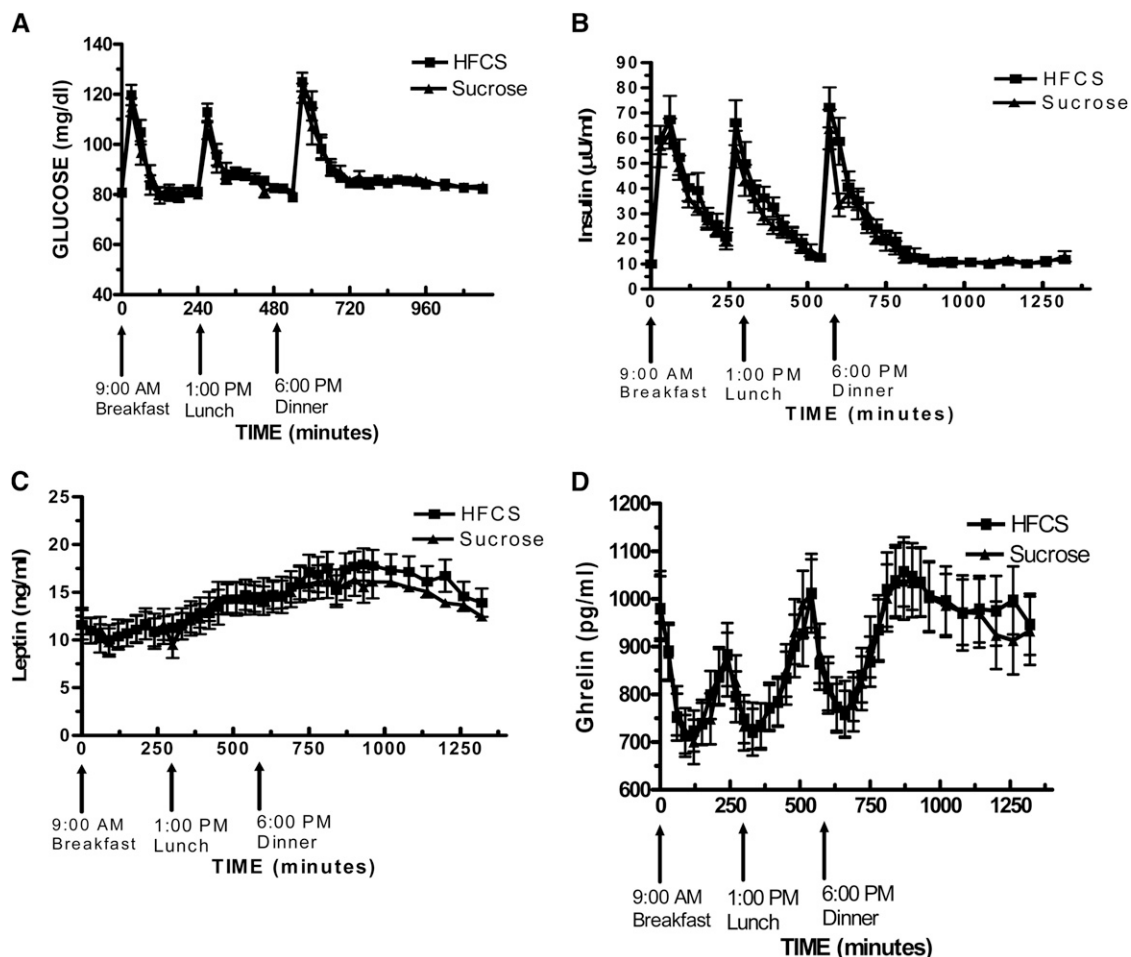


Figure 3 Comparison of high-fructose corn syrup (HFCS) and sucrose effects on glucose (A) and short-term energy-regulating hormones (B, C, D) in normal weight females. Reproduced from (34) with permission.

sugars may play a role in epidemics of heart disease, insulin resistance, type 2 diabetes, hypertension, dyslipidemia, and obesity (51–55). In addition, some studies have suggested that fructose ingestion may lead to increased indices of inflammation and oxidative stress (56–59), whereas other studies have not confirmed these findings (60).

With this body of information as background, the AHA has issued a scientific statement recommending that American women consume no more than 100 kcal/d and American men consume no more than 150 kcal/d from added sugars (61). The AHA acknowledged that these recommendations are much lower than other guidelines for added sugars such as those from the Dietary Guidelines for Americans (62) and the Institute of Medicine–recommended daily allowances (63). Moreover, the AHA recognized that these recommendations were largely based on epidemiologic studies or animal data and acknowledged the need for randomized clinical trials in this area.

The AHA recommendations for upper limits of added sugar consumption, which are currently exceeded by >90% of the population, should be taken with caution. Recent research reviews have reported that fructose consumption at up to the 90th percentile population consumption level in

either healthy weight or obese individuals does not result in increased triglycerides or weight gain (44,45). Moreover, studies in our research laboratory at levels of 2 to 3 times those recommended by the AHA did not show any adverse impact on lipids (64). A recently completed trial in our research laboratory involving 352 overweight or obese individuals who consumed up to the 90th percentile population consumption levels for fructose as part of mixed-nutrient, eu-caloric diets did not show any adverse effect on total cholesterol ($P = 0.88$) or LDL cholesterol ($P = 0.85$). A significant 14% increase in triglycerides was noted, although it must be emphasized that triglyceride levels remained within the normal range both before and after measurement (65).

Other investigators have reported results in which sugar consumption increased lipids in human subjects. In particular, Stanhope et al. (66), using a model in which 25% of energy consumption from fructose was compared with 25% energy consumption from glucose in acute experiments showed increases in triglycerides. Once again, however, it should be noted that pure fructose and pure glucose are rarely consumed in the human diet and that the reported levels were within established population norms. Other investigators including Raben et al. (67), Marckmann (68),

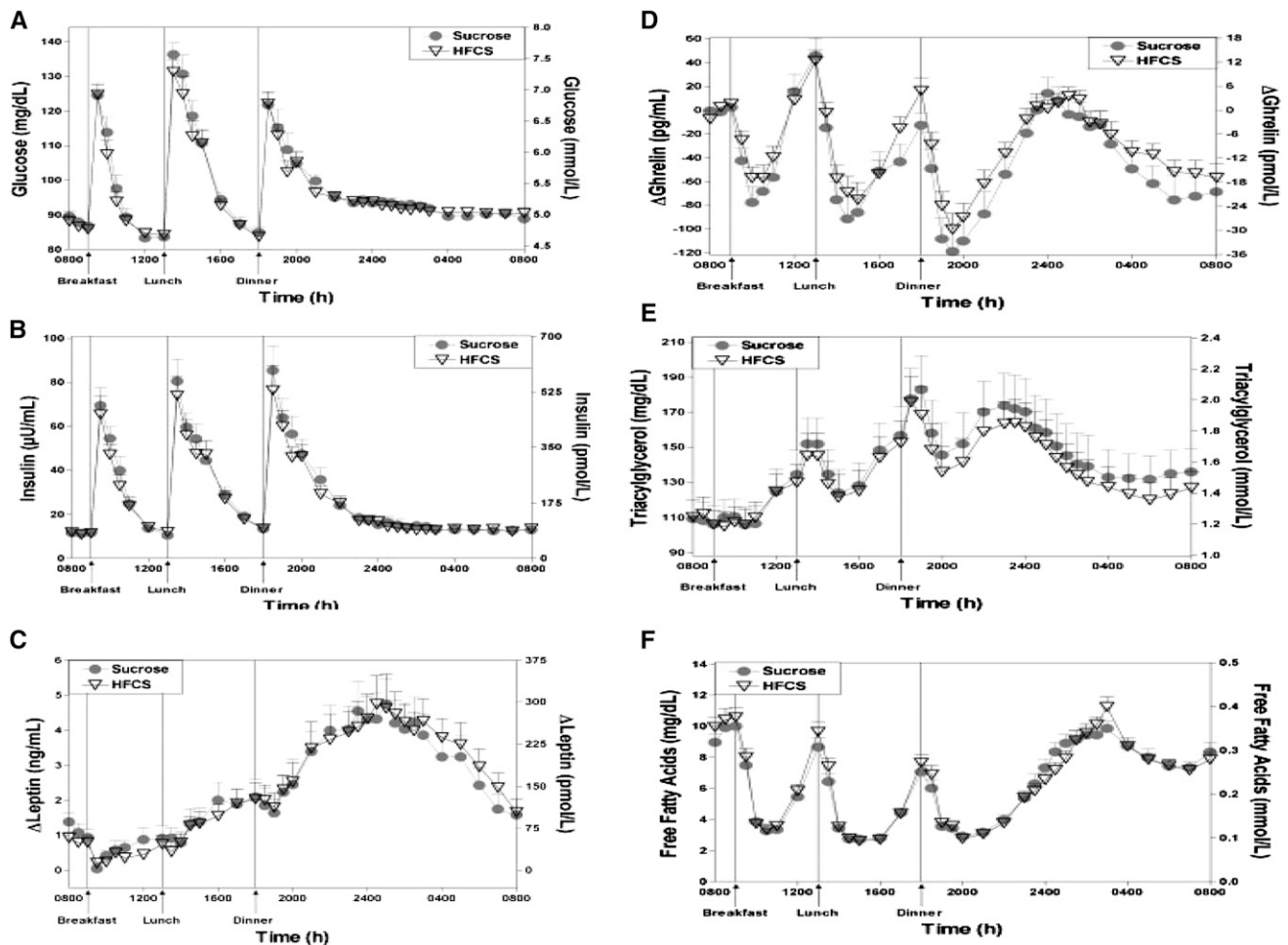


Figure 4 Comparison of high-fructose corn syrup (HFCS) and sucrose effects on glucose (A), triglycerides (E), free fatty acids (F) and short-term energy-regulating hormones (B, C, D) in men and women. Reproduced from (36) with permission.

Maersk et al. (69), and Stanhope et al. (70) also reported a variety of increased lipid measurements in individuals after sugar consumption.

We also reported that levels of added sugar consumption higher than those recommended by the AHA do not adversely affect weight (71) or blood pressure (72). Stanhope et al. (13) did not report an adverse effect on blood pressure from consumption of 25% of energy from added sugars. The meta-analysis by Ha et al. (46) came to similar conclusions. Additional randomized, controlled trials are needed to sort out the impact of added sugars on lipids, blood pressure, obesity, and other established risk factors for heart disease.

Does consumption of sucrose, HFCS, or fructose increase risk factors for metabolic syndrome?

It has been postulated that consumption of fructose may increase risk factors for metabolic syndrome. Johnson et al. (73) suggested that fructose consumption can cause an increase in uric acid as a waste product in its metabolism due to degradation of ATP (73–75). This increase in uric acid, in turn, according to this theory, may lead to endothelial dysfunction, which may contribute to high blood pressure (73,76,77).

Other investigators have suggested that increased inflammatory markers secondary to fructose consumption may also contribute to increased risk of metabolic syndrome (78). Furthermore, the increase in triglycerides, often found with increased carbohydrate consumption, may increase the risk of metabolic syndrome (17,79). Finally, Stanhope et al. (13) found that individuals who consumed 25% of their energy in fructose had increased visceral adiposity, another risk factor for the development of metabolic syndrome, compared with obese diabetic individuals who consumed 25% of their energy as glucose.

The literature linking fructose consumption to the risk of metabolic syndrome must be treated with caution. As already indicated, several research reviews do not support the concept that fructose consumption at normal population levels increased levels of obesity or triglycerides (44,45). Furthermore, Sun et al. (80) analyzed NHANES data and did not find increased levels of uric acid related to fructose consumption. A further meta-analysis of NHANES data by this same team did not show a link between different levels of fructose consumption and either uric acid levels or metabolic syndrome (81). Research in our laboratory showed

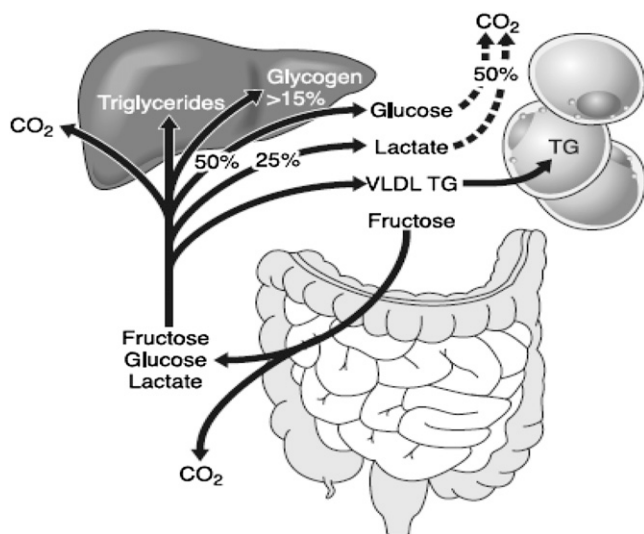


Figure 5 The metabolic fate of an oral fructose load in healthy subjects. TG, triglyceride. Reproduced from (41) permission.

that consumption of HFCS or sucrose at up to the 50th percentile population consumption level for fructose did not show increases in either systolic or diastolic blood pressure, uric acid, waist circumference, or triglycerides (72). A subsequent research trial in our laboratory involving 352 overweight or obese subjects who consumed up to the 90th percentile population consumption level of fructose confirmed these findings for systolic and diastolic blood pressure and waist circumference, although triglycerides increased by ~10% ($P < 0.05$). Thus, no consensus has yet been achieved on whether fructose, HFCS, or sucrose increases risk factors for metabolic syndrome.

Does fructose, HFCS, or sucrose increase the risk of fatty infiltration in the liver or muscle?

As already indicated, the theoretical argument concerning the potential adverse metabolic effects of fructose consumption is based on the well-established differences in hepatic metabolism between fructose and glucose (41,42). As illustrated in Figure 1, there are significant differences between fructose and glucose metabolism in the liver. It is important, however, to point out that the metabolic pathways for fructose and glucose in the liver are interactive.

As illustrated in Figure 5, the vast majority of the fructose that is metabolized in the liver is converted into glucose, glycogen, lactate, and carbon dioxide. As depicted in Figure 5, ~50% of fructose is converted in the liver to glucose (82–84), 25% to lactate (85,86), and 15% to 18% to glycogen (87,88), and a few percent is metabolized to carbon dioxide. Only a very small percentage (on the order of 1%–5% depending on the specific conditions used and underlying nutritional and metabolic status of individuals studied) is converted to free fatty acids (89–91).

It has been argued by some investigators that the fact that fructose and glucose are invariably consumed together could drive creation of increased free fatty acids through the process of de novo lipogenesis (DNL) (92,93). This argument is

based on the concept that, in this setting, glucose dominates the glycogenetic pathway, leaving fructose no alternative but to be converted into FFA. However, most research in this area does not support DNL as a significant quantitative producer of FFA (94,95). As depicted in Figure 6, the metabolic pathways related to DNL also inhibit the oxidation of FFA. It has been estimated by Hellerstein (94) that only 1% to 3% of VLDL generated in individuals consuming a normal Western diet is a result of DNL.

Even in settings of extreme carbohydrate overload, only a small percentage of carbohydrates is converted into fats in the process of DNL. In 1 experiment in which individuals were fed >1500 extra kcal/d in excess carbohydrates (total consumption of 700 g of carbohydrate/d), only 3.3 g of fat were generated (96). Studies by Lê et al. (97) showed that healthy individuals who were fed 1 g/kg of fructose did not experience increased liver fat. Silbernagel et al. (98) found similar results in individuals who consumed 30% of energy from fructose over a 4-wk timeframe.

Research in our laboratory has not shown any increase in liver fat or ectopic deposition of muscle fat at levels at up to 30% of energy from either HFCS or sucrose over a 10-wk period of consumption (S. Bravo, J. Lowndes, S. Sinnett, Z. Fullerton, J. Rippe, unpublished observations).

Other researchers, however, have suggested that consumption of large amounts of fructose can increase DNL. Lê et al. (99) reported that infusion of 3.5 g of fructose/kg of fat free mass increased ectopic deposition of fats in the liver and muscle in offspring of diabetic patients. Stanhope et al. (13) reported increased DNL in individuals consuming 25% of energy from fructose compared with individuals consuming 25% of energy from glucose. It must be emphasized that the levels of fructose consumption in these 2 experiments are 2 to 3 times the 95th population consumption of fructose from all sources. Maersk et al. (69) reported ectopic deposition of fat in the liver and muscle when comparing individuals who consumed 1 L of sugar-sweetened cola versus 1 L of diet beverages, 1 L of milk, or 1 L of water each day. This finding, however, as the authors noted, is confounded by the fact that the sugar-sweetened cola-consuming group also increased absolute body weight and total fat mass.

The disparities in findings from these studies may be attributed to differences in research design or failure to make a distinction between qualitative increases in DNL and quantitative increases. Although numerous studies have shown that increased consumption of fructose may result in *qualitative* increases in DNL, considerable *quantitative* increases appear unlikely. Although DNL does not appear to generate significant quantities of fat, it may contribute to other metabolic abnormalities through changes in signaling mechanisms, hormonal regulation, or promoting dyslipidemia. Further, randomized, controlled trials are needed to sort out this issue moving forward.

Conclusions

So, what do we really know about the metabolism, endocrine responses, and health effects of sucrose, HFCS, and

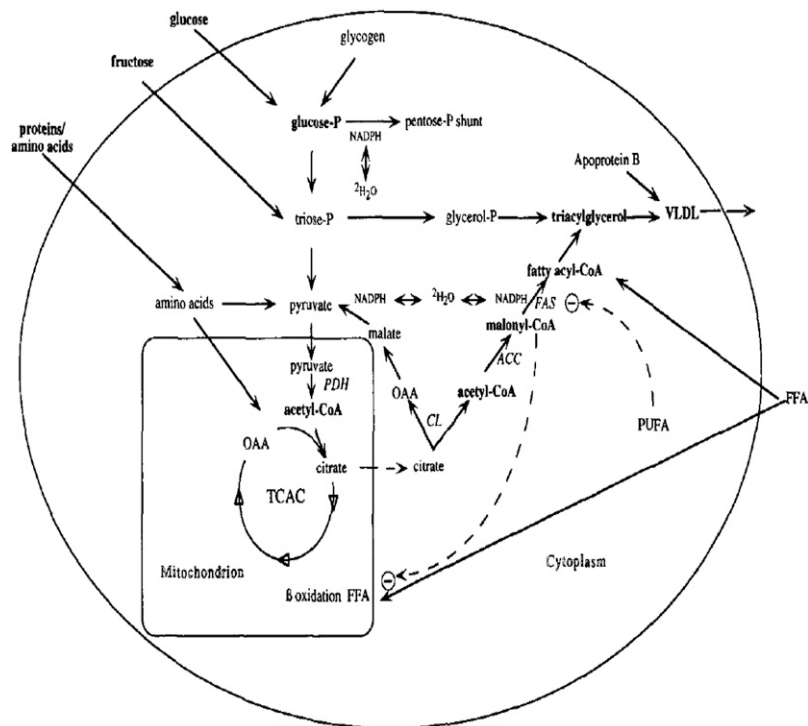


Figure 6. Metabolic pathways related to de novo lipogenesis. A liver cell is shown, with VLDL secretory pathway and fructose uptake; otherwise, the pathways also apply in adipocytes. Circled minus sign, inhibitory action. ACC, acetyl-CoA carboxylase; CFT-1, carnitine palmitoyl transferase 1; CL, ATP:citrate lyase; FAS, fatty acid synthetase; OAA, oxaloacetate; P, phosphate; PDH, pyruvate dehydrogenase; TCAC, tricarboxylic acid cycle. Reproduced from (95) with permission.

fructose? At present, we believe that the following conclusions are warranted. First, there is no unique relationship between HFCS and obesity. Second, there is broad scientific consensus that there are no significant metabolic or endocrine response differences or differences in health-related effects between HFCS and sucrose. Third, the metabolism and health effects of both HFCS and sucrose are different from those observed in studies that compare pure fructose with pure glucose, neither of which is consumed to any appreciable degree in the human diet. Fourth, recent randomized clinical trials have suggested that there are no adverse effects on total cholesterol, LDL cholesterol or HDL cholesterol at amounts ranging up to the 90th percentile level of fructose consumption, although other investigators have shown increases in cholesterol and/or LDL cholesterol in subjects consuming either sucrose or HFCS (66,68–70), so further research studies are needed to clarify this issue. There is, however, a reliable increase in triglycerides from consumption of elevated levels of carbohydrates (particularly simple sugars), which merits further exploration.

Cox et al. (100) reported that fructose consumption at 25% of calories compared with glucose at 25% of calories acutely increased uric acid profiles. However, research in our laboratory comparing HFCS with sucrose yielded identical responses and no increases in acute levels of uric acid in either normal weight or obese women (101,102). Moreover, a recently completed trial in our research laboratory in which individuals consumed up to 30% of calories (90th percentile population consumption level for fructose) over a 10-wk period did not show any increase in uric acid. Thus, the issue of whether increased fructose consumption results in increases in uric acid or blood pressure remains

in dispute. It should be pointed out that Maersk et al. (69) reported increased visceral adipose tissue in response to 6 wk of consumption of 1 L/d of sucrose-sweetened cola. Increased visceral adipose tissue is an established risk factor for metabolic syndrome. However, research in our laboratory did not confirm these findings. Whether fructose consumption results in increased risk factors for metabolic syndrome also remains in dispute. Studies exploring whether fatty infiltration of the liver or muscle occurs in response to fructose consumption have produced disparate findings. Differences in duration of these studies (research studies varying in length from 4 to 10 wk) have not shown any increases in liver or muscle fatty infiltration in response to fructose consumption, whereas the Maersk et al. 6-mo study did show this phenomenon. This indicates that further research studies, perhaps of longer duration, are required to resolve this issue.

Taken together, these findings suggest that we must be very cautious when attributing adverse health consequences to the consumption of fructose, HFCS, or sucrose, particularly at normal population consumption levels. More randomized, controlled trials at normal levels of consumption using commonly consumed sugars are necessary to resolve these issues. In the meantime, it is important to recognize that scientific debates of this nature do not take place in a vacuum. These discussions have enormous potential to confuse and alarm the public, making the need to frame results with appropriate caution and minimize speculation imperative.

Acknowledgments

Both authors have read and approved the final manuscript.

Literature Cited

1. Bray GA. Fructose: pure, white, and deadly? fructose, by any other name, is a hazard health. *J Diabetes Sci Technol*. 2010;4:1003–7.
2. Rippe JM. The health implications of sucrose, high-fructose corn syrup, and fructose: what do we really know? *J Diabetes Sci Technol*. 2010;4:1008–11.
3. Rippe JM. The health implications of sucrose, high fructose corn syrup, and fructose: What do we really know? *J Diabetes Technol*. 2010; 4. Issue 4.
4. Fulgoni V. High fructose corn syrup: everything you wanted to know, but were afraid to ask. *Am J Clin Nutr*. 2008;88: suppl:1715S.
5. Stanhope KL, Havel P. Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup. *Am J Clin Nutr*. 2008;88: suppl:1733S.
6. White JS. Straight talk about high-fructose corn syrup: what it is and what it ain't. *Am J Clin Nutr*. 2008;88: suppl:1716S.
7. 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.
8. American Medical Association. Report 3 of the Council on Science and Public Health 2008 (A-08).
9. Academy of Nutrition and Dietetics. Use of nutritive and nonnutritive sweeteners. *J Am Diet Assoc*. 2004;104:255–75.
10. Bray GA. Fructose: should we worry? *Int J Obes (Lond)*. 2008;32: S127–31.
11. Johnson RJ, Gower T, Gollub E. The sugar fix, the high-fructose fall-out that is making you fat and sick. New York: Rodale, 2008.
12. Popkin B. the world is fat: the fads, trends, policies, and products that are fattening the human race. New York: Penguin Group, 2008.
13. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119:1322–34.
14. Sánchez-Lozada LG, Le M, Segal M, Johnson RJ. How safe is fructose for persons with or without diabetes? *Am J Clin Nutr*. 2008;88:1189–90.
15. White J, Foreyt J, Melanson K, Angelopoulos T. High-Fructose Corn Syrup: Controversies and Common Sense. *Am J Lifestyle Med*. 2010; 4:515–20.
16. Bray GA. Fructose and risk of cardiometabolic disease. *Curr Atheroscler Rep*. 2012;14:570–8.
17. Teff KL, Elliott SS, Tschöp M, Kieffer TJ, Rader D, Heiman M, Townsend RR, Keim NL, D'Alessio D, Havel PJ. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J Clin Endocrinol Metab*. 2004;89:2963–72.
18. Yudkin J. Pure, white and deadly. London: Penguins Books; 1986.
19. Life Sciences Research Office. SCOGS-50: evaluation of the health aspects of corn sugar (dextrose), corn syrups, and invert sugar as food ingredients. Bethesda, MD: Federation of American Societies for Experimental Biology, 1976.
20. Glinsmann WH, Irausquin H, Park YK. Evaluation of health aspects of sugars contained in carbohydrate sweeteners: report of Sugars Task Force, 1986. *J Nutr*. 1986;116:S1–216.
21. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr*. 2004;79:537–43.
22. Glinsmann WH, Bowman BA. The public health significance of dietary fructose. *Am J Clin Nutr*. 1993;58:820S–3S.
23. Buck AW. High fructose corn syrup. In: Nabors LO, editor. *Alternative sweeteners*. 3rd ed. New York, NY: Marcel Dekker, 2001:391–411.
24. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr*. 2006;84: 274–88.
25. Olsen NJ, Heitmann BL. Intake of calorically sweetened beverages and obesity. *Obes Rev*. 2009;10:68–75.
26. Curry DL. Effects of mannose and fructose on the synthesis and secretion of insulin. *Pancreas*. 1989;4:2–9.
27. Malik V, G.A. Bray, B.M. Popkin, J.P. Despres, F.B. Hu. sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diab Care*. 2010;33:2477–83
28. Nakagawa T, Tuttle KR, Short RA, Johnson RJ. Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. *Nat Clin Pract Nephrol*. 2005;1:80–6.
29. Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. *Am J Clin Nutr*. 2000; 72:1128–34.
30. USDA Economic Research Service. U.S. per capita loss-adjusted food availability: “Total Calories.” CDC, 2010 National Center for Health Statistics.
31. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010;303:235–41.
32. Buzby J, Wells HF. Loss-adjusted food availability data: calories. USDA-Economic Research Service, 2007. Available from: www.ers.usda.gov/Data/FoodConsumption/spreadsheets/foodloss/Calories.xls. Accessed March 15, 2007.
33. Wells HF, Buzby JC. Dietary assessment of major trends in US food consumption, 1970–2005. Economic Research Service, US Department of Agriculture; March 2008. Economic Information Bulletin No. 33. Available from: <http://www.ers.usda.gov/Publications/EIB33>. Accessed January 4, 2009.
34. Melanson KJ, Zukley L, Lowndes J, Nguyen V, Angelopoulos T, Rippe J. Effects of high fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women nutrition. *Nutrition*. 2007;23:103–12.
35. Soenen S, Westerterp-Plantenga MS. No differences in satiety or energy intake after high fructose corn syrup, sucrose, or milk preloads. *Am J Clin Nutr*. 2007;86:1586–94.
36. Stanhope KL, Griffen S, Bair B, Swarbrick M, Keim N, Havel P. Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, fructose-, and glucose-sweetened beverages with meals. *Am J Clin Nutr*. 2008;87:1194–203.
37. Zukley L, Lowndes J, Nguyen V, Brosnahan J, Summers A, Melanson K, Angelopoulos T, Rippe J. Consumption of beverages sweetened with high fructose corn syrup and sucrose produce similar levels of glucose, leptin, insulin and ghrelin in obese females. *FASEB* 2007;21:538.
38. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and its components: implications for body weight regulation. *Am J Clin Nutr*. 2012;95:989–94.
39. Anderson GH. Much ado about high-fructose corn syrup in beverages: the meat of the matter. *Am J Clin Nutr*. 2007;86:1577–8.
40. Cox CL, Stanhope KL, Schwarz JM, Graham JL, Hatcher B, Griffen SC, Bremer AA, Berglund L, McGahan JP, Havel PJ, et al. Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. *Eur J Clin Nutr*. 2012;66:201–8.
41. Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev*. 2010;90:23–46.
42. Mayes PA. Intermediary metabolism of fructose. *Am J Clin Nutr*. 1993;58: Suppl:754S–65S.
43. Lowndes J, Kawiecki D, Angelopoulos TJ, Melanson K, Rippe JM. Components of metabolic syndrome are not affected by regular consumption of sucrose or high fructose corn syrup. *Endocr Rev*. 2010;31 Suppl 1:S141.
44. Dolan LC, Potter SM, Burdock GA. Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals. *Crit Rev Food Sci Nutr*. 2010;50:53–84.
45. Dolan LC, Potter SM, Burdock GA. Evidence-based review on the effect of normal dietary consumption of fructose on blood lipids and body weight of overweight and obese individuals. *Crit Rev Food Sci Nutr*. 2010;50:889–918.
46. Ha V, Sievenpiper JL, de Souza RJ, Chiavaroli L, Wang DD, Cozma AI, Mirrahimi A, Yu ME, Carleton AJ, Dibouono M, et al. Effect of fructose on blood pressure: a systematic review and meta-analysis of controlled feeding trials. *Hypertension*. 2012;59:787–95.

47. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, Chiavaroli L, Di Buono M, Jenkins AL, Leiter LA, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. *Ann Intern Med.* 2012;156:291–304.
48. White JS, Foreyt JP, Melanson KJ, Angelopoulos TJ. High-fructose corn syrup: controversies and common sense. *Am J Lifestyle Med.* 2010;4:515–20.
49. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health.* 2007;97:667–75.
50. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr.* 1990;51:963–9.
51. Lê KA, Tappy L. Metabolic effects of fructose. *Curr Opin Clin Nutr Metab Care.* 2006;9:469–75.
52. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev.* 2005;63:133–57.
53. Gross LS, Li S, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr.* 2004;79:774–9.
54. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr.* 2002;76:911–22.
55. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation.* 2007;116:480–8. Published correction appears in: *Circulation.* 2007;116:e557.
56. Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002;75:492–8.
57. Price KD, Price CS, Reynolds RD. Hyperglycemia-induced ascorbic acid deficiency promotes endothelial dysfunction and the development of atherosclerosis. *Atherosclerosis.* 2001;158:1–12.
58. Scribner KB, Pawlak DB, Ludwig DS. Hepatic steatosis and increased adiposity in mice consuming rapidly vs. slowly absorbed carbohydrate. *Obesity (Silver Spring).* 2007;15:2190–9.
59. Ceriello A, Bortolotti N, Crescentini A, Motz E, Lizzio S, Russo A, Ézsol Z, Tonutti L, Taboga C. Antioxidant defences are reduced during the oral glucose tolerance test in normal and non-insulin-dependent diabetic subjects. *Eur J Clin Invest.* 1998;28:329–33.
60. Ma SW, Tomlinson B, Benzie IF. A study of the effect of oral glucose loading on plasma oxidant: antioxidant balance in normal subjects. *Eur J Nutr.* 2005;44:250–4.
61. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J, the AHA Nutrition Committee of the Council on Nutrition, PA, and Metabolic and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation.* 2009;120:1011–20.
62. Dietary Guidelines for Americans. 2010. Available from: <http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm>. Accessed Nov 1, 2012.
63. Institute of Medicine. 2002. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. [cited 2012 Nov 1]. Available from: <http://www.iom.edu/Reports/2002/Dietary-Reference-Intakes-for-Energy-Carbohydrate-Fiber-Fat-Fatty-Acids-Cholesterol-Protein-and-Amino-Acids.aspx>.
64. Lowndes J, Kawiecki D, Angelopoulos T, Rippe J. Fructose containing sugars do not result in an atherogenic lipid profile when consumed as part of a eucaloric (weight-stable) diet. *Circulation.* 2010;122:A10906.
65. Lowndes J, Sinnett S, Yu Z, Rippe J. Effects of fructose containing sugars on lipids, blood pressure and uric acid when consumed at up to 90th percentile population consumption levels. *Circulation.* 2012;126:A13066.
66. Stanhope KL, Bremer AA, Medici V, Nakajima K, Ito Y, Nakana T, Chen G, Fong TH, Lee V, Menorca RI, Keim NL, Havel PJ. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *J Clin Endocrinol Metab.* 2011;96:E1596–605.
67. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr.* 2002;76:721–9.
68. Marckmann P. Dietary treatment of thrombogenic disorders related to the metabolic syndrome. *Br J Nutr.* 2000;83: Suppl 1:S121–6.
69. Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, Pedersen SB, Astrup A, Richelsen B. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. *Am J Clin Nutr.* 2012;95:283–9.
70. 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.
71. Lowndes J, Kawiecki D, Angelopoulos T, Rippe J. Fructose containing sugars do not cause changes in weight, body composition or abdominal fat when consumed as part of a eucaloric (weight-stable) diet. *Obesity.* 2010;18: Suppl 2:S51.
72. Lowndes J, Kawiecki D, Angelopoulos TJ, Melanson K, Rippe JM. Components of the metabolic syndrome are not affected by regular consumption of sucrose or high fructose corn syrup. *Endocr Rev.* 2010;31 Suppl 1:S1411.
73. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kung DH, Gersch MS, Benner S, Sanchez-Lozada LG. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr.* 2007;86:899–906.
74. Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet.* 1967;2:528–31.
75. Stirpe F, Della Corte E, Bonetti E, Abbondanza A, Abbati A, De Stefano F. Fructose-induced hyperuricaemia. *Lancet.* 1970;2:1310–1.
76. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol.* 2005;16:3553–62.
77. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. *Kidney Int.* 2005;67:1739–42.
78. Sørensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr.* 2005;82:421–7.
79. 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.
80. Sun SZ, Flickinger BD, Williamson-Hughes PS, Empie MW. Lack of association between dietary fructose and hyperuricemia risk in adults. *Nutr Metab (Lond).* 2010;7:16.
81. Sun SZ, Anderson GH, Flickinger BD, Williamson-Hughes PS, Empie MW. Fructose and non-fructose sugar intakes in the US population and their associations with indicators of metabolic syndrome. *Food Chem Toxicol.* 2011;49:2875–82.
82. Bjorkman O, Crump M, Phillips RW. Intestinal metabolism of orally administered glucose and fructose in Yucatan miniature swine. *J Nutr.* 1984;114:1413–20.
83. Tounian P, Schneiter P, Henry S, Jéquier E, Tappy L. Effects of infused fructose on endogenous glucose production, gluconeogenesis and glycogen metabolism in healthy humans. *Am J Physiol.* 1994;267: E710–7.
84. Tounian P, Schneiter P, Henry S, Delarue J, Tappy L. Effects of dexamethasone on hepatic glucose production and fructose metabolism in healthy humans. *Am J Physiol Endocrinol Metab.* 1997;273: E315–20.
85. Burns SP, Murphy HC, Iles RA, Bailey RA, Cohen RD. Hepatic intralobular mapping of fructose metabolism in the rat liver. *Biochem J.* 2000;349:539–45.
86. Dietze G, Wicklmayr M, Grunst J, Stiegler S, Mehert H. Utilization of glucose and fructose in human liver and muscle. *Int Z Vitam Ernahrungsforsch Beih.* 1976;15:31–43.
87. Koo HY, Wallig MA, Chung BH, Nara TY, Cho BH, Nakamura MT. Dietary fructose induces a wide range of genes with distinct shift in

- carbohydrate and lipid metabolism in fed and fasted rat liver. *Biochim Biophys Acta*. 2008;1782: 341–348.
88. Nilsson LH, Hultman E. Liver and muscle glycogen in man after glucose and fructose infusion. *Scand J Clin Lab Invest*. 1974;33:5–10.
 89. Chong MF, Fielding BA, Frayn KN. Mechanisms for the acute effect of fructose on postprandial lipemia. *Am J Clin Nutr*. 2007;85:1511–20.
 90. McDevitt RM, Bott SJ, Harding M, Coward WA, Bluck LJ, Prentice AM. De novo lipogenesis during controlled overfeeding with sucrose or glucose in lean and obese women. *Am J Clin Nutr*. 2001;74:737–46.
 91. Parks EJ, Skokan LE, Timlin MT, Dingfelder CS. Dietary sugars stimulate fatty acid synthesis in adults. *J Nutr*. 2008;138:1039–46.
 92. Lustig RH. Letter to the editor. *J Am Diet Assoc*. 2011;111:990–3.
 93. Hudgins LC, Parker TS, Levine DM, Hellerstein MK. A dual sugar challenge test for lipogenic sensitivity to dietary fructose. *J Clin Endocrinol Metab*. 2011;96:861–8.
 94. Hellerstein MK. No common energy currency: de novo lipogenesis as the road less traveled. *Am J Clin Nutr*. 2001;74:707–8.
 95. Hellerstein MK, Schwarz JM, Neese RA. Regulation of hepatic de novo lipogenesis in humans. *Annu Rev Nutr*. 1996;16:523–57.
 96. Schwarz JM, Neese RA, Turner S, Dare D, Hellerstein MK. Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. *J Clin Invest*. 1995;96:2735–43.
 97. Lê KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, Boesch C, Ravussin E. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. *Am J Clin Nutr*. 2006;84:1374–9.
 98. Silbernagel G, Machann J, Unmuth S, Schick F, Stefan N, Häring HU, Fritsche A. Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: an exploratory trial. *Br J Nutr*. 2011;106:79–86.
 99. Lê KA, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, Boesch C, Tappy L. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. *Am J Clin Nutr*. 2009;89:1760–5.
 100. Cox CL, Stanhope KL, Schwarz JM, Graham JL, Hatcher B, Griffen SC, Bremer AA, Berglund L, McGahan JP, Keim NL, et al. Consumption of fructose- but not glucose-sweetened beverages for 10 weeks increases circulating concentrations of uric acid, retinol binding protein- 4, and gamma-glutamyl transferase activity in overweight/obese humans. *Nutr Metab (Lond)*. 2012;9:68.
 101. Lowndes J, Zukley L, Nguyen V, Rippe JM. The effect of high-fructose corn syrup on uric acid levels in normal weight women. *Obesity*. 2008; 16:(Suppl. 1)S150.
 102. Lowndes J, Zukley L, Nguyen V, Angelopoulos T, Rippe J. The effect of high-fructose corn syrup on uric acid levels in obese women. *Obesity (Suppl)*. 2007;15:498-P.