REVIEW

Fructose-Containing Sugars and Cardiovascular Disease[1,2]

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ABSTRACT

Cardiovascular disease (CVD) is the single largest cause of mortality in the United States and worldwide. Numerous risk factors have been identified for CVD, including a number of nutritional factors. Recently, attention has been focused on fructose-containing sugars and their putative link to risk factors for CVD. In this review, we focus on recent studies related to sugar consumption and cardiovascular risk factors including lipids, blood pressure, obesity, insulin resistance, diabetes, and the metabolic syndrome. We then examine the scientific basis for competing recommendations for sugar intake. We conclude that although it appears prudent to avoid excessive consumption of fructose-containing sugars, levels within the normal range of human consumption are not uniquely related to CVD risk factors with the exception of triglycerides, which may rise when simple sugars exceed 20% of energy per day, particularly in hypercaloric settings. *Adv Nutr* 2015;6:430–9.

Keywords: sugars, fructose, high-fructose corn sugar, sucrose, metabolism

Introduction

Cardiovascular disease (CVD)[7] is the single largest cause of mortality in the United States and worldwide (1). CVD represents 37% of all annual mortality in the United States, and when combined with stroke, these 2 manifestations of atherosclerotic vascular disease represent more than half of all annual mortality in the United States (2). Multiple underlying risk factors for heart disease have been identified including dyslipidemias (3), elevated blood pressure (4, 5), an inactive lifestyle (6), obesity (7), diabetes (8), and cigarette smoking (9).

Nutritional patterns clearly play an important role in the development of CVD (10–12). Historically, much of the emphasis on the relation between nutrition and CVD has focused on intake of certain types of fats, level of sodium consumption, overall energy density, and calorie consumption (13). Dietary sugars have come under scrutiny because of epidemiologic studies suggesting a possible link between intake of fructose, high-fructose corn sugar (HFCS), sucrose, and CVD (14–17). Much of this literature focuses on the potential relation between fructose-containing sugars and risk factors for heart disease such as diabetes, obesity, hypertension, and dyslipidemias rather than heart disease itself (18–21). However, many of the randomized research trials cited in an attempt to establish these links have relied on abnormally high doses of added sugars beyond those consumed in the human diet, the use of pure fructose vs. pure glucose models (neither of which is commonly consumed in the human diet), or rodent studies that may have little relevance to human nutrition. In particular, de novo lipogenesis in rodents is quite different from human beings. Under conditions of long-term, high-carbohydrate feeding, de novo lipogenesis accounts for 60–70% of FAs in rodents (22). Moreover, in rodents high fructose exposure increases expression of lipogenic enzymes, FA synthase, and acetyl-CoA carboxylase. These enzymes appear activated in rodents through the hexosamine biosynthesis pathway, which does not occur in humans. Finally, most rodent studies have given a fructose dosage 4–5 times the 95th percentile intake in humans (23). Such extreme dosing may alter the ratio of glucose to fructose (24).

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[7] Abbreviations used: CVD, cardiovascular disease; DGAC, Dietary Guidelines for Advisory Committee; HFCS, high-fructose corn sugar; MetS, metabolic syndrome; SACN, Scientific Advisory Committee on Nutrition; SSB, sugar-sweetened beverage.

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This review will focus largely on putative links between fructose-containing sugars and CVD risk factors rather than CVD itself, where much less information exists. We will focus on the biological effects of fructose-containing sugars in the context of dosage, with a particular emphasis on studies using levels within the normal range of human consumption and employing those added sugars normally consumed in the human diet (e.g., sucrose and HFCS). We will attempt to summarize this literature and offer our opinion as to what constitutes a scientifically defensible upper limit of added sugar consumption with regard to risk of CVD.

Perhaps the most important emerging risk factor for heart disease is the dramatic increase in worldwide obesity. The WHO estimates that there were 1.1 billion overweight or obese adults in the world in 2004 (25). This is estimated to grow to 1.5 billion individuals by the year 2030 (26, 27). The emerging pandemic of obesity has caused numerous investigators to focus on nutritional aspects of this problem.

Whether or not the consumption of sugar makes a substantial contribution to weight gain and obesity remains in dispute. More research has focused on excessive total calorie consumption, which the Dietary Guidelines for Americans, 2010 lists as the largest nutritional problem facing the United States (28). According to the USDA Economic Research Service, caloric consumption in the United States increased from a mean of 2169 kcal/(person · d) in 1970 to 2594 kcal/(person · d) in 2009 (29). This increase represents an additional 425 kcal or ~20% more energy consumed than in 1970. This increase of 425 kcal includes an increase of added fats of 184 kcal/(person · d) (43% of the total), flour, and cereal products (44% of total), whereas all added sugars combined increased by 39 kcal/(person · d) (9% of total) (29). As an overall percentage of energy consumed, added sugars declined from 19% in 1970 to 17% in 2009.

Nutrition and CVD

It is important to put issues related to sugar consumption and CVD into a broader nutritional perspective. The AHA included nutritional factors as one of 7 key components of its overall strategic plan for 2020 entitled "Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction" (11). The AHA listed 5 dietary goals to improve nutrition and lower the risk of CVD. They are the following:

- Fruits and vegetables: ≥4.5 cups (1067 mL)/d
- Fish: ≥2 2.5-oz servings/wk (preferably oily fish) (~57 g)
- Fiber-rich whole grains: ≥1.1-g fiber per 10-g carbohydrates [≥3 1-oz (28 g) equivalent servings/d]
- Sodium: ≤1500 mg/d
- Sugar-sweetened beverages (SSBs): ≤450 kcal (1044 mL)/wk

Although limiting sugar consumption in the form of SSBs is included in the list, this is only one of multiple recommendations from the AHA to improve cardiovascular health through positive nutritional behaviors.

Sugar Consumption in the United States

Sugars are a common component of the food supply in the United States, both as a naturally occurring component of many foods and as added during processing or preparation. Naturally occurring sugars include sucrose, lactose, and fructose and are found in dairy products, fruits, vegetables, and many grain products (28). Added sugars add sweetness to many products. When they are present in nutrient-rich foods (e.g., low-fat chocolate milk), sugars may actually contribute to improved dietary quality, while having no adverse effect on weight by displacing energy-dense, nutrient-poor foods (30).

The 2 leading added sugars in the diet of Americans are sucrose and HFCS. Each year in the United States, more sucrose is consumed than HFCS (31). Worldwide, >10 times as much sucrose is consumed as HFCS (31). Total consumption of sugars has declined by 25% in the 15-y period between 1998 and 2012 (32). The mean amount of sugar consumed in the United States among the population >4 y of age was estimated by Marriott et al. (33) at 332 kcal/(person · d) using data from the NHANES 2003–2006. Because sucrose and HFCS are made up of roughly equal amounts of fructose and glucose, this represents a mean of roughly 166 kcal/(person · d) of each of these monosaccharaides consumed each day.

Fructose, Glucose, HFCS, and Sucrose

A common error is to equate fructose with HFCS (24). A more proper comparison is HFCS and sucrose. Fructose, as the name implies, is composed of 100% fructose. The 2 major forms of HFCS are composed of either 55% fructose and 45% glucose or glucose polymers (HFCS-55) or 42% fructose and 58% glucose or glucose polymers (HFCS-42). Sucrose is composed of 50% glucose and 50% fructose.

In HFCS the fructose and glucose exist separately; whereas, in sucrose the 2 monosaccharaides are connected by a covalent bond. As a practical matter, however, both are absorbed identically as free fructose and free glucose because the bond between glucose and fructose in sucrose is immediately hydrolyzed by the enzyme sucrase in the brush border of the intestine. Moreover, in acidic environments (e.g., soft drinks) much of the bond between fructose and glucose (i.e., sucrose) has already hydrolyzed by a process called inversion before the product is consumed. This process is accelerated both by warmth and an acidic environment. Thus, in many carbonated soft drinks sweetened with sucrose much of this disaccharide may have already inverted to its components, glucose and fructose, before ingestion.

It is also important to understand that neither pure fructose nor pure glucose is consumed in any appreciable degree in isolation in the human diet. They are almost invariably consumed together in nutritive sweeteners such as sucrose, HFCS, honey, concentrated fruit juices, etc., or in a wide variety of fruits and vegetables. Finally, it should be noted that the amount of glucose in the diet is substantially greater than the amount of fructose. Estimates as high as 7 times as much glucose compared with fructose in the American diet have been given (24). This is not surprising given that glucose is a primary fuel for virtually every somatic cell.

Concern over fructose in sugars is based on the well-known differences in hepatic metabolism between fructose

and glucose (34, 35). A small percentage of fructose may be converted into FFAs and ultimately TGs in the liver. In humans, 1–5% of fructose may go through this pathway of de novo lipogenesis (36). Furthermore, the pathways of metabolism of fructose and glucose in the liver are interactive with >90% of fructose being converted to glucose, glycogen, or lactate (37, 38). A detailed discussion of fructose and glucose metabolism is beyond the scope of this article and handled in considerable detail in multiple reviews and one recent academic textbook (37–39).

Sugars and CVD Risk Factors

To our knowledge, no randomized controlled trials have explored the relation between sugars and CVD per se. Thus, most of the literature in this area relates to sugars and CVD risk factors.

Effects of dietary sugars on lipids. A number of studies have demonstrated that diets high in simple sugars (>20% of kcal) may result in elevated fasting TGs, a known risk factor for CVD (40–53) (**Table 1**). It is for this reason that the AHA scientific statement on TGs lists avoiding excess fructose as one nutritional mechanism for preventing hypertriglyceridemia (56). Diets high in simple sugars have also often resulted in a decrease in HDL cholesterol (57–62). Elevations in fasting TGs may be particularly marked in those individuals with sedentary lifestyles or metabolic syndrome (MetS) and are more marked in men than women. Increased hepatic TG synthesis as well as de novo lipogenesis in the liver and reduced peripheral TG clearance have all been attributed to increased fructose metabolism (56, 62).

These findings should be treated with caution, however, because several recent systematic reviews and meta-analyses have reported that when fructose is substituted isocalorically for other carbohydrate sources, its consumption does not result in either increased fasting TGs (63) or postprandial TGs (64). In these meta-analyses, only hypercaloric feeding of fructose resulted in increased TGs. Moreover, in our research laboratory a eucaloric trial involving 65 individuals where no weight gain occurred did not result in increased TGs. However, a larger trial involving 355 men and women between 20 and 60 y of age who consumed either 8%, 18%, or 30% of kcal/d as either sucrose or HFCS as part of a mixed-nutrient diet resulted in a significant 10% increase in TGs (54) (Table 1). This result was driven largely by increases in TGs in the individuals who consumed 30% of kcal/d from added sugars (95th percentile consumption level for fructose). It should be noted that in this latter trial that individuals consumed on average 200 kcal/d more by the end of the study compared with baseline and gained slightly over 2 lbs on average. Thus, it should be viewed as a hypercaloric trial. Moreover, it should be pointed out that even though mean TGs rose by 10% (104 ± 51.8 vs. 114 ± 64.7 mg/dL), both of these concentrations are within the normal population range.

Diets that are high in complex carbohydrates, such as the Dietary Approaches to Stop Hypertension (DASH) diet, which replaces fat with carbohydrates from nonfat and low-fat dairy products, fruits, vegetables, and whole grains, have not been reported to increase TGs, although they may result in modest lowering of HDL cholesterol (65, 66). Thus, it would appear that sugars, in general, and fructose-containing sugars, in particular, when consumed at levels above 20% of kcal, may cause an increase in TGs, particularly when consumed in hypercaloric diets.

The effects of added sugar on total cholesterol and LDL cholesterol have been variable (43, 47, 48, 53, 67, 68). Some investigators have found increases in LDL cholesterol (47, 52, 67, 68). For example, in the study by Stanhope et al. (53), 25% of kcal was given as either pure fructose or pure glucose, which would correspond to 50% of kcal if given as either sucrose or HFCS. These levels are well above the 95th percentile population consumption levels for fructose. The trial by Marckmann et al. (48) provided sucrose at 23% of kcal [516 kcal/(person · d)], whereas the trial by Maersk et al. (47) provided sucrose at 21% of calories [424 kcal/(person · d)], both of which are at approximately the 90th percentile population consumption level for added sugars in the population studied. Other studies have not demonstrated increases in LDL cholesterol even at comparably elevated levels of added sugar consumption (43, 48).

In trials in our laboratory involving various levels of sugar consumption, ranging from the 25th to 95th percentile population consumption level for fructose (160–600 kcal/d), no changes in LDL cholesterol were demonstrated after 10 wk in a free-living environment compared with baseline when consumed as part of a mixed-nutrient diet (54). Thus, the effects of sugar, in general, and fructose-containing sugars, in particular, on LDL cholesterol remain in dispute. Some studies, particularly at levels above the 90th percentile population consumption level of fructose-containing sugars, show an increase in LDL cholesterol, whereas other studies do not. Clearly, more research studies at normally consumed population levels of fructose-containing sugars are warranted.

Blood pressure. Variable effects related to sugar consumption and blood pressure have been reported (69–71). Epidemiologic studies such as the Framingham Heart Study have reported an association between consuming ≥1 SSBs per day and increased odds of developing high blood pressure (21). Johnson et al. (72) have proposed a mechanism by which fructose metabolism may result in increased levels of uric acid, which in turn, according to this theory, may contribute to endothelial dysfunction and thus increase the risk of hypertension. However, studies from our research laboratory and others have not shown increases in blood pressure or uric acid at levels of added sugar consumption up to 30% of kcal/d (the 95th percentile population consumption level of fructose) (73). In another research trial in our laboratory, consumption of fructose-containing sugars (fructose, sucrose, and HFCS) at the 50th percentile population consumption level did not raise mean blood pressure or uric acid when compared with a glucose control (74). Systematic reviews and meta-analyses have reported conflicting

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TABLE 1 Characteristics of trials evaluating added sugar consumption and TGs[1]

Reference	Type of study	Participants	Higher-sugar intervention
Aeberli et al. (40)	Randomized crossover trial	29 healthy normal-weight men aged 20–50 y, living in and around Zurich, Switzerland	High sugars (fructose, glucose, or sucrose), providing 80 g/d; provided daily in 3 200-mL beverages
Antar et al. (41)	Randomized crossover trial with controlled feeding	15 hyperlipoproteinemic patients	High-sucrose diet; 40% of energy from sucrose. 96% of food was given as a formula, and 4% of food was given as supplements of raw fruit and vegetables
Bantle et al. (42)	Randomized crossover trial with controlled feeding	12 men and women with type 2 diabetes	High-fructose, high-carbohydrate diet; 20% of energy from sucrose
Black et al. (43)	Randomized crossover trial with controlled feeding	13 healthy men	25% of total energy (205 g/d) of diet given as sucrose
Cooper et al. (44)	Randomized crossover trial	17 adults with type 2 diabetes and without comorbidities	Usual diet with 28-g sucrose supplement/d
Groen et al. (45)	Crossover trial	15 men and women	Very-high-sucrose diet providing 231 g (46% of energy) monosaccharides and disaccharides/d
Lowndes et al. (46)	Randomized, double-blind, controlled trial	247 healthy overweight and obese adults (162 completers)	Hypoenergetic diet (2500 kcal) providing 20% of energy from HFCS or sucrose
Stanhope et al. (51)	Randomized controlled trial	34 men and women	25% of total energy from HFCS-, sucrose-, fructose-, or glucose-sweetened beverages
Teff et al. (52)	Randomized controlled trial	17 obese men and women	30% of energy from glucose- or sucrose-sweetened beverages
Stanhope et al. (53)	Randomized controlled trial	48 adult men and women	25% of energy from glucose-, fructose-, or HFCS-sweetened beverages
Maersk et al. (47)	Randomized controlled trial	35 healthy adults	Usual diet supplemented with 1-L sugar-sweetened soft drink/d, providing 424-kcal sucrose
Marckmann et al. (48)	Randomized crossover trial	20 postobese adult women; controls matched by age, height, and weight	Ad libitum, high-sucrose diet; 23% of energy (129 g/d) as sucrose
Raben et al. (49) Sørensen et al. (50)	Randomized controlled trial	41 healthy overweight adults (BMI: 25–30 kg/m^2) aged 20–50 y	Ad libitum diet supplemented with sucrose-containing foods and beverages providing 27% (177 g/d) of energy as sucrose
Lowndes et al. (54)	Randomized, double-blind, controlled trial	355 healthy overweight or obese adults	Eucaloric diet with 8%, 18%, or 30% of kcal from added sugars

[1] Adapted with permission from Te Morenga et al. (55). HFCS, high-fructose corn sugar.

results with regard to added sugar consumption and blood pressure. Ha et al. (75) reported a systematic review and meta-analysis involving 18 studies (n = 355) that showed slight decreases in both diastolic and mean blood pressure when fructose was substituted either isocalorically (13 trials) for other carbohydrates or in hypercaloric trials (2 trials).

Te Morenga et al. (55) reported 12 trials (n = 324) with no significant effects of higher sugar intake on systolic blood pressure overall (mean difference: 1.1 mm Hg; 95% CI: −1.0, 3.2 mm Hg; P = 0.32.) Higher sugar intake was associated with significantly greater diastolic blood pressure of 1.4 mm Hg (95% CI: 0.3, 2.5 mm Hg; P = 0.02). Many of the trials reported in the systematic review employed levels of added sugar consumption above the 90th percentile population level.

Thus, the effects on blood pressure of intake of simple sugars at normal population levels remain uncertain.

Sugars, obesity, insulin resistance, diabetes, and MetS. The AHA lists obesity as one of the major lifestyle-related risk factors for heart disease (7). In addition to its direct relation with CVD, obesity is also associated with multiple other risk factors for heart disease including diabetes, dyslipidemias, hypertension, MetS, and an inactive lifestyle. Of particular importance, obesity plays a pivotal role in the development of the insulin-resistance syndrome, which includes hyperinsulinemia, hypertension, hyperlipidemia, type 2 diabetes mellitus, and an increased risk of atherosclerosis. A detailed discussion of the multiple interactions between obesity and the cardiovascular system is beyond the scope of this paper and has been recently reviewed by the authors elsewhere (76).

The relation between sugars and obesity is variable and complicated (77–80). Some epidemiologic studies have reported a positive relation between SSB consumption and obesity (16, 78). Several studies have shown that SSB consumption is associated with increased total energy intake in children, adolescents, and adults (16, 79). Several meta-analyses have reported a positive relation between SSB intake and obesity (16, 79). A meta-analysis by Forshee et al. (80), however, did not find a positive relation between SSB consumption and BMI in children and adolescents. A recent systematic review and meta-analysis by Sievenpiper et al. (81) found that when fructose was substituted isocalorically

for other carbohydrates it did not result in weight gain. In this analysis, hypercaloric feeding trials where fructose was substituted at levels beyond the 95th percentile population consumption level resulted in weight gain. These findings suggest that calories are more important than fructose with regard to weight gain and obesity.

Findings from interventional studies related to SSBs and weight gain have also been variable with several correlating SSB consumption with changes in body weight (49, 68), whereas several others did not (82, 83). Three studies recently published in the New England Journal of Medicine suggested that there may be a link between sugar consumption and obesity in certain populations including obese children and individuals who are genetically predisposed to obesity (84–86). In one randomized controlled trial, a serving of 1 SSB per day was compared with diet beverages and demonstrated that children given the SSB showed more increased weight than children given diet beverages (84). However, this study could not differentiate between whether it was the daily SSB per se or the increased calories given to these children that resulted in the reported difference.

A controversy specifically related to a potential role for HFCS in obesity arose in 2004, when several investigators suggested there might be a unique link between its consumption and obesity (87). However, subsequent research trials in our research laboratory and in others have refuted this argument (51, 88–90). It is also important to note that rates of obesity and diabetes have risen in line with other Western populations in countries where little or no HFCS is available. In addition, obesity and diabetes rates in the United States have continued to climb over the past 15 y (91) despite a decline in added sugar consumption (32).

Several studies have compared large doses (25% of kcal) of pure fructose to pure glucose and reported that energy-regulating hormones including insulin, leptin, and ghrelin were different between the 2 conditions in this model (51, 52). These investigators suggested that these differences could result in overeating. However, when the sugars commonly consumed in the human diet (HFCS and sucrose) were compared head to head in comparable doses in our research laboratory, no differences were found (92).

Given the complexity of obesity it seems unlikely that one component of the diet is a primary cause. An expert panel from the ASN issued a scientific statement reviewing the multiple influences on energy balance and body weight regulation and cautioned against the popular belief that the obesity epidemic is a result of a "few bad foods or one particular component of the diet" (93). Several recent reviews of the literature related to sugars and obesity have also concluded that it is highly unlikely that sugars per se are a major cause of obesity or that reduction in sugar intake would represent a meaningful approach to treating this condition (94, 95).

It would appear that focus only on fructose-containing sugars as the major culprit for the increase in worldwide obesity prevalence avoids clear scientific evidence that the increase in obesity rates results largely from increases in calorie intake over time coupled with increased screen time and presumably sedentary behaviors.

Type 2 diabetes has increased dramatically in the past 20 y and represents a major global health epidemic (96). It has been reported that 6.4% of the world population is currently diabetic. This number is predicted to rise to 7.7% worldwide by the year 2030 (97). It is estimated that the number of people with diabetes rose from 153 million in 1980 to 347 million in 2008 (98). The International Diabetes Federation predicts that the number of people affected by diabetes will grow to 438 million by the year 2030 (99).

Diabetes represents a major risk factor for CVD. Insulin resistance has been clearly linked to diabetes and often precedes diabetes by 10–20 y. Insulin resistance is also thought to be an important mechanism behind MetS. Cross-sectional studies have demonstrated that insulin resistance is a substantial risk factor for ultimately developing diabetes (100–103). The relation of sugar consumption to insulin resistance, MetS, and diabetes has been the subject of numerous research trials (104–108). Results from these trials have been variable.

Fructose was initially thought to be an appropriate substitute for glucose in diabetic patients because the metabolism of fructose compared with glucose led to smaller excursions in both insulin and blood sugar (61, 109). However, research in this area comparing fructose to glucose in diabetic patients reported increased TG production in response to fructose, which could potentially negate any advantages achieved through better glycemic control (61). Indeed, when pure fructose and pure glucose have been compared with each other at 25% of kcal, there is a greater insulin and blood sugar response to glucose than fructose as well as increased TGs (51, 52). These differences, however, disappear when the more commonly consumed sucrose and HFCS are administered at equal levels (92).

The pathophysiology of insulin resistance is not completely understood (110, 111). However, multiple studies have suggested that fatty infiltration of the liver and also ectopic fat deposition in skeletal muscle contribute to insulin resistance. Skeletal muscle is not only the major tissue involved in glucose metabolism, but it has also been observed that ectopic fat deposition in the skeletal muscle accounts for as much as 75% of all insulin resistance (110, 111). Fatty infiltration of the liver may result from excessive deposition of fat in the liver, thereby increasing insulin resistance and dyslipidemia as well as promoting increased hepatic lipogenesis, thus increasing the risk of nonalcoholic fatty liver disease while stimulating atherogenic dyslipidemia (110–120).

Randomized controlled trials have demonstrated conflicting results related to sugar consumption and fatty infiltration of liver and muscle. Several short-term studies have not demonstrated increased deposition of fat in either liver or muscles (121–123). Silbernagel et al. (121) gave 20 healthy individuals 600 kcal/(person · d) of fructose or glucose for 4 wk. Lê et al. (122) gave 16 male offspring of individuals with type 2 diabetes and 8 control subjects a 3.5-g/kg fat-free mass hypercaloric diet for 7 d with 35% increase

energy intake Bravo et al. (123) gave dosages between 160 and 600 kcal/(person · d) to 68 individuals over a 10-wk period. Other studies have suggested that consumption of fructose, particularly at high levels, could lead to ectopic fat deposition in both of these organ systems (47, 124). Both of these studies, however, used high levels of sugars. In the Maersk et al. (47) study, 424 kcal/(person · d) were administered. In the Lê et al. (124) study, 14 kcal/(kg fat-free mass · d) were administered. A research study from our laboratory comparing 3 different levels of fructose-containing sugar consumption (8%, 18%, and 30% of kcal) in 68 healthy men and women aged 20–60 y did not result in increased deposition of fat in the liver or increased ectopic fat deposition in the muscle after a 10-wk free-living research trial (123). Thus, whether there is any unique relation between fructose-containing sugars and insulin resistance remains unresolved.

MetS represents a constellation of findings including dyslipidemia, abnormal glucose handling, high blood pressure, and abdominal obesity. MetS represents a substantial risk factor for CVD. In fact, the National Cholesterol Education Program guidelines recommend that individuals with MetS be treated as though they already have CVD (125). It has been postulated that the consumption of fructose, whether by itself or as a component of HFCS or sucrose, may increase risk factors for MetS (70, 126). The linkage, which has been proposed by Johnson et al. (72), postulates that fructose consumption leads to an increase in uric acid because of degradation of ATP. These increases in uric acid, according to this theory, may contribute to endothelial dysfunction, dyslipidemia, insulin resistance, and high blood pressure, all of which are hallmarks of MetS.

Stanhope et al. (53) reported that obese diabetic individuals who consumed 25% of their energy from fructose compared with individuals who consumed 25% of their energy from glucose developed increased visceral adiposity, which is one of the substantial risk factors for MetS. Other investigators have suggested that fructose consumption may increase inflammatory markers (50). Moreover, the increase in TGs reported in some studies caused by increased fructose consumption may contribute to MetS.

Research in our laboratory, however, has shown that neither fasting glucose nor insulin changed in any group when comparing 8%, 18%, and 30% of kcal/d from either HFCS or sucrose (127). However, fasting insulin did increase in the entire pooled cohort (8 ± 5.4 compared with 10.1 ± 12.8 μIU/mL; $P < 0.01$). Also, TGs in this study rose by 10%, whereas both systolic and diastolic blood pressure did not change. Moreover, recent meta-analyses and systematic reviews of controlled feeding trials did not show increases in blood pressure, fasting or postprandial TGs, or uric acid in both nondiabetic and diabetic patients in isocaloric comparisons of fructose to other carbohydrates (starch, sucrose, galactose, HFCS, and maltose) (81). Furthermore, Sun et al. (128) analyzed NHANES data and did not find increased levels of uric acid related to fructose consumption. A further meta-analysis of NHANES data by the same research group did not show a link between various fructose consumption levels and risk of MetS (38). Research in our laboratory has also demonstrated no increased level of uric acid when consuming fructose-containing sugars up to the 95th percentile population consumption level of fructose (73). Thus, if fructose-containing sugars increase the risk of MetS, the effects appear to be small and mixed, particularly when consumed at normal population levels.

Competing Recommendations for Sugar Intake

Concern over the potential linkage between fructose-containing sugars and various chronic diseases, including CVD, diabetes, obesity, and MetS, has caused a number of scientific and health organizations to issue recommended guidelines for upper levels of consumption of these sugars. Considerable disparity, however, exists among the various recommendations for upper limits that have been issued by various scientific bodies. The AHA has recommended that no more than 150 kcal/d in added sugars should be consumed by the average adult male and no more than 100 kcal/d for the average adult female (14). The WHO has recommended that no more than 10% of calories be consumed from added sugars with the ultimate goal of reducing this to 5% (129). The Scientific Advisory Committee on Nutrition (SACN) in England has issued similar recommendations to the WHO (130). In contrast, the Dietary Guidelines for Americans, 2010 (27) and the Institute of Medicine Carbohydrate Report recommended an upper limit of sugar consumption not to exceed 25% of calories (131). The recently released scientific report of the 2015 Dietary Guidelines for Advisory Committee (DGAC) recommends an upper limit of sugars of no more than 10% of kcal. The committee rated the evidence of sugars and diabetes as "strong" and the evidence from prospective cohort studies related to intake of added sugars and risk of CVD as "moderate" (132).

Research studies in our laboratory have suggested that there are no differences in risk factors for either heart disease or diabetes when comparing 8% of kcal from sugars (roughly the level recommended by the AHA, WHO, SACN, and 2015 DGAC report) to 18% of kcal from added sugars (the 50th percentile level of fructose consumption in the United States) to 30% of kcal from added sugars (the 95th percentile population consumption level and roughly equivalent to the Dietary Guidelines for Americans, 2010 and Institute of Medicine Carbohydrate Report) (28, 131). It is important to note that the duration of our study was 10 wk per subject. Trials of longer duration may yield different results. Although we are not suggesting that individuals consume 30% of kcal from added sugars, these findings suggest that recommending restricting calories at the level recommended by the AHA, WHO, SACN, and 2015 DGAC may be unduly conservative.

Conclusion and Summary

Given the prevalence of CVD throughout the world, studies related to nutritional factors that may increase its risk are of

obvious importance. The relation between fructose, HFCS, sucrose, and CVD remains controversial. Studies to date have yielded mixed results when comparing normally consumed levels of these sugars in the human diet and risk of CVD. However, most of the studies that have suggested increased risk of CVD from added sugars involve administering large doses of fructose-containing sugars (>95th percentile population consumption levels) or consist of animal data, which typically does not transmit well into human nutrition. There does, however, seem to be a marker for increased TGs, which most studies suggest increase when >20% of kcal/d are consumed as added sugars, particularly in hypercaloric trials.

It must be emphasized that numerous risk factors for CVD such as dyslipidemias, hypertension, sedentary lifestyle, diabetes, cigarette smoking, and obesity have all been clearly established. Although it would appear to be prudent to avoid excessive consumption of fructose-containing sugars, levels within the normal range of human consumption at this juncture do not seem to be uniquely related to CVD risk factors.

However, the signal for increased TGs at consumption levels of >20% of kcal suggests that this represents a reasonable and scientifically defensible upper limit for sugar consumption with regard to CVD risk factors. Nonetheless, it would appear more appropriate to focus attention on recommending reduction of established risk factors for heart disease as recommended by the AHA and numerous other scientific organizations rather than focusing undo attention on added sugars.

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