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REVIEW TOPIC OF THE WEEK

Fructose and Cardiometabolic Health

What the Evidence From Sugar-Sweetened Beverages Tells Us

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ABSTRACT

Recent attention has focused on fructose as having a unique role in the pathogenesis of cardiometabolic diseases. However, because we rarely consume fructose in isolation, the major source of fructose in the diet comes from fructose-containing sugars, sucrose and high fructose corn syrup, in sugar-sweetened beverages and foods. Intake of sugar-sweetened beverages has been consistently linked to increased risk of obesity, type 2 diabetes, and cardiovascular disease in various populations. Putative underlying mechanisms include incomplete compensation for liquid calories, adverse glycemic effects, and increased hepatic metabolism of fructose leading to *de novo* lipogenesis, production of uric acid, and accumulation of visceral and ectopic fat. In this review we summarize the epidemiological and clinical trial evidence evaluating added sugars, especially sugar-sweetened beverages, and the risk of obesity, diabetes, and cardiovascular disease and address potential biological mechanisms with an emphasis on fructose physiology. We also discuss strategies to reduce intake of fructose-containing beverages. (J Am Coll Cardiol 2015;66:1615–24) © 2015 by the American College of Cardiology Foundation.

The adverse health effects of sugar have long been a matter of much public and scientific interest. For decades, it has been thought that a high intake of sugar is associated with the development of obesity, type 2 diabetes, and cardiovascular disease (CVD). Given the distinct metabolic fates that differentiate fructose from glucose, recent attention has focused on fructose as having a unique role in the etiology of these conditions. Fructose is found in sucrose or common table sugar, which is a disaccharide composed of 1 glucose molecule and 1 fructose molecule linked via an α1-4 glycoside bond, and is obtained from either sugar cane or beets. Fructose and glucose are also both found as naturally occurring monosaccharides that exist in fruit, honey, and some vegetables. Sweeteners such as high fructose corn syrup (HFCS), which is produced from corn starch through industrial processing, contain free fructose and free glucose in relatively equal proportions and have progressively replaced the use of sugar in the United States since their appearance in the market in the late 1960s primarily due to their low cost. The most common forms of HFCS contain either 42% (HFCS-42) or 55% (HFCS-55) fructose, along with glucose and water. HFCS-55 has the sweetness equivalent of sucrose and is widely used to flavor carbonated soft drinks. HFCS-42 is somewhat less sweet and is mainly used in processed foods including canned foods (e.g., soups and fruits), cereals, baked goods, desserts, sweetened dairy products, condiments, fruit-flavored noncarbonated beverages, candies, and many fast food items.

On the basis of national survey data from the United States, mean intake of total fructose as a percentage of total energy increased from 8.1% in 1978 to 9.1% in 2004, with greater increases observed in adolescents and young adults (1). It is important to note that this increase was due to increases in fructose from sugars and sweeteners and not from naturally occurring

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

GL = glycemic load

HFCS = high fructose corn syrup

RCT = randomized controlled trial

SSB = sugar-sweetened beverage

fructose in fruit. With the exception of children 1 to 3 years of age, the estimated intake of naturally occurring fructose decreased from 11 to 16 g/day in 1978 to 7 to 9 g/day in 2004 for all age groups, representing an overall decrease of 3 to 7 g/day (1).

Because we rarely consume fructose in isolation, the major source of fructose in the diet comes from fructose-containing sugars (sucrose and HFCS) largely in the form of added sugar (i.e., those sugars that are added to foods and beverages during processing and preparation). As a result, glucose intake tends to covary with fructose intake, and epidemiological studies cannot completely differentiate between the effects of fructose *per se* and those specifically attributable to glucose.

Time-trend data over the past 3 to 4 decades have shown a close parallel between the rise in added sugar intake and the obesity and diabetes epidemics in the United States (2). Largely driving these trends has been the dramatic increase in the consumption of sugar-sweetened beverages (SSBs), which are the single greatest source of calories and added sugars in the U.S. diet, accounting for nearly one-half of all added sugar intake (3) (**Table 1**). One 360-ml can of regular soda contains about 35 g of sugar (140 calories) or 7% of total calories (on the basis of 2,000 kcal/day) (4). In the United States, SSBs are primarily sweetened with HFCS, whereas in Europe sucrose is the predominant sweetener.

Consumption of SSBs thus accounts for the majority of total fructose intake in the diet, either from sucrose or HFCS, and in this regard, relations between SSB and cardiometabolic diseases reflect potential effects of fructose and glucose or unique metabolic effects of fructose alone in epidemiologic studies (**Table 2**).

Although consumption of SSBs and added sugar appear to have decreased modestly in the past decade (4), data from NHANES (National Health and Nutrition Examination Survey) show that one-half of the U.S. population consumes SSBs on a given day, with 1 in 4 obtaining at least 200 calories from these beverages and 5% obtaining at least 567 calories—equivalent to 4 cans of soda (5). These values exceed American Heart Association recommendations for no more than 100 to 150 kcal/day from all added sugar for most adults as well as recommendations from the World Health Organization and the 2015 Dietary Guidelines Advisory Committee to limit intake of added sugars to no more than 10% of energy.

Over the past decade, a large body of evidence has accumulated that shows a strong association between SSBs and obesity and related chronic diseases (6–8). For this reason and because they provide "empty" calories and almost no nutritional value, SSBs have been identified as a suitable target for public health interventions. However, controversy remains over whether the associations are causal, if glucose or fructose moieties of sugars differentially affect cardiometabolic risk, and what type of public action should be taken on the basis of existing evidence. In this review, we provide a brief overview of fructose metabolism and summarize the epidemiological evidence evaluating the relationship among fructose, obesity, diabetes, and cardiovascular risk in adults, focusing on fructose-containing beverages or SSBs, because they are the most abundant and well-characterized source of fructose in the diet. We also discuss biological mechanisms underlying these associations with an emphasis on the role of fructose. Finally, we discuss healthier alternatives to SSBs and strategies to reduce SSB intake.

TABLE 1 Mean Intake of Added Sugars and Percentage Contribution of Various Foods Among the U.S. Population by Age, National Health and Nutrition Examination Survey 2005–2006

	All Persons (n = 8,272)	2 to 18 Years (n = 3,553)	19+ Years (n = 4,719)
Mean intake of added sugars, tsp	21	23	20
Food Group by Rank*			
1. Soda/energy/sports drinks	35.7	31.8	37.1
2. Grain-based desserts	12.9	10.9	13.7
3. Fruit drinks	10.5	15.0	8.9
4. Dairy desserts	6.6	7.9	6.1
5. Candy	6.1	6.8	5.8
6. Ready-to-eat cereals	3.8	6.4	2.9
7. Sugars/honey	3.5	1.4	4.2
8. Tea	3.5	2.1	4.0
9. Yeast breads	2.1	1.9	2.2
10. Syrups/toppings	1.9	2.8	1.5

*Rank for all persons only. Columns for other age groups are ordered by this ranking. Data from National Cancer Institute. Sources of calories from added sugars among the US population, 2005 to 2006.

FRUCTOSE METABOLISM

Fructose metabolism differs from that of glucose in 2 major ways. First, there is nearly complete hepatic extraction of fructose, and second, as shown in **Figure 1**, there are different enzymatic reactions in the initial steps of the metabolism of fructose and glucose. Fructose is absorbed from the gut into the portal vein and is metabolized in the liver, where it is converted into fructose-1-phosphate by the enzyme fructokinase. Fructose-1-phosphate is then split into 2 3-carbon molecules, namely glyceraldehyde and

TABLE 2 Key Points Regarding Fructose, HFCS, and SSBs

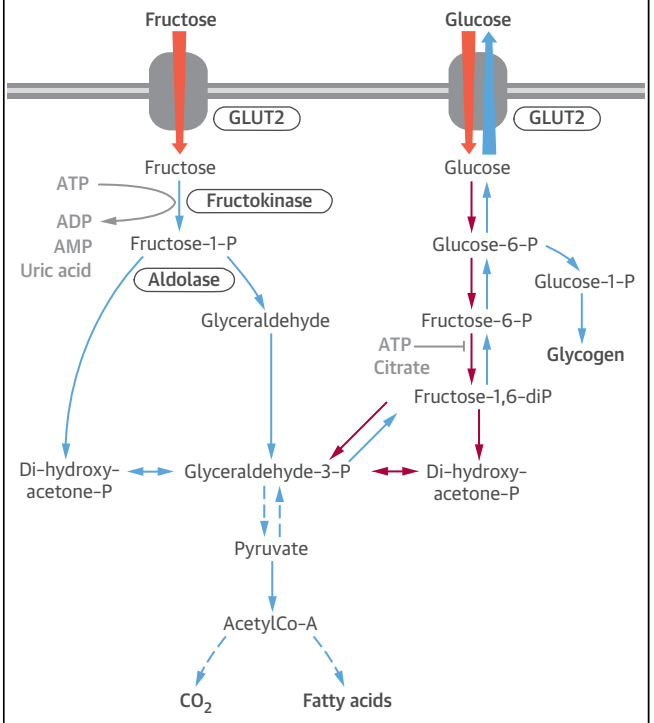
Fructose
- Fructose is found in: sucrose, a disaccharide composed of 1 glucose molecule and 1 fructose molecule; HFCS, containing relatively equal amounts of glucose; and fruit, honey, and some vegetables as a naturally occurring monosaccharide.
- The major source of fructose in the diet comes from fructose-containing sugars (sucrose and HFCS) that are added to foods and beverages and contain relatively equal amounts of glucose.
- Thus, intakes of glucose and fructose covary, and epidemiological studies cannot completely differentiate between their effects.

HFCS
- HFCS is produced from corn starch through industrial processing. The most common forms contain 42% or 55% fructose along with glucose and water.
- Use of HFCS has progressively replaced the use of sugar in the United States due to its low cost.
- HFCS is the primary sweetener used in SSBs in the United States and in many processed foods.

SSBs
- SSBs include soft drinks, fruit drinks, and energy drinks that are sweetened by HFCS or sucrose, which are added to the beverages by manufacturers, establishments, or individuals.
- SSBs are the greatest source of fructose-containing sugars in the diet and thus account for the majority of total fructose intake.
- Relations between SSB and cardiometabolic diseases reflect the potential effects of fructose and glucose or unique metabolic effects of fructose alone in epidemiological studies.

HFCS = high fructose corn syrup; SSB = sugar-sweetened beverage.

FIGURE 1 Fructose Metabolism in Liver Cells



Fructose metabolism **(red arrows)** differs from glucose **(blue arrows)** due to: 1) a nearly complete hepatic extraction; and 2) different enzyme and reactions for its initial metabolic steps. Fructose taken up by the liver can be oxidized to CO_2 and then converted into lactate and glucose; glucose and lactate are subsequently either released into the circulation for extrahepatic metabolism or converted into hepatic glycogen or fat. The massive uptake and phosphorylation of fructose in the liver can lead to a large degradation of adenosine triphosphate to AMP and uric acid. Reprinted with permission from Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 2010;90:23–46. AcetylCo-A = acetyl coenzyme A; ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; diP = diphosphate; P = phosphate.

dihydroxyacetone phosphate, by aldolase. Glyceraldehyde is further converted into glyceraldehyde-3-phosphate, which, along with dihydroxyacetone phosphate, can then enter various metabolic pathways to form "classical" energy substrates such as glucose, glycogen, lactate, and fatty acids. Because these processes are not dependent on insulin, fructose is metabolized without requiring insulin secretion and without increasing plasma glucose.

Of particular note, unlike glucose, fructose can bypass the main rate limiting step of glycolysis at the level of phosphofructokinase, allowing it to act as a substrate for hepatic *de novo* lipogenesis and production of lipids. Thus, intake of fructose in high amounts can promote triglyceride synthesis from unchecked pathways. The actual amount of fructose needed to increase blood triglyceride levels is debated (9). Significant increases in post-prandial triglycerides have been shown in response to consumption of 25% of energy from fructose and HFCS, but not glucose (10). Recent data has also shown that consuming HFCS-sweetened beverages containing 10% to 25% of energy produced significant linear increases in post-prandial triglycerides, suggesting a dose-response relationship between fructose consumption and increases in triglycerides (11). Because added sugar intake in the United States constitutes about 14.9% of energy, with 71% of the population consuming ≥10% energy from added sugar (4), these effects of fructose are relevant to usual consumption patterns.

The massive uptake and phosphorylation of fructose in the liver can also deplete intracellular adenosine triphosphate, leading to an increase in uric acid production, which has been shown to induce metabolic complications. These differences in hepatic metabolism can theoretically lead to a variety of different short- and long-term cardiometabolic effects of fructose compared with glucose.

ADDED SUGARS AND SSBs IN RELATION TO OBESITY, DIABETES, AND CARDIOVASCULAR RISK

SSBs are a major source of added sugars (including both fructose and glucose) in U.S. diets. Numerous epidemiological studies have evaluated the relationship between consumption of SSBs and the

development of obesity and related cardiometabolic conditions in adults. Cross-sectional and ecological studies are not able to establish temporality and infer causality; thus, evidence from these designs are not discussed in this review. Rather, we consider carefully conducted and analyzed prospective cohort studies, which are considered the strongest nonrandomized study design, able to capture long-term diet and disease relationships. All of these studies adjusted their analyses for potential confounding by various diet and lifestyle factors; however, residual confounding by unmeasured or imperfectly measured factors may still exist. Higher SSB or sugar intake could be a marker of a globally unhealthy diet. Therefore, incomplete adjustment for various lifestyle factors could lead to an overestimation of associations. Although randomized controlled trials (RCTs) with hard clinical outcomes are regarded as the highest grade of evidence in epidemiology, they are not the most appropriate or feasible study design to evaluate long-term effects of diet on disease. However, RCTs of intermediate outcomes can provide important mechanistic insight. Most of the studies that we consider defined SSBs to include carbonated and noncarbonated soft drinks and sweetened fruit drinks that contain caloric sweeteners; however, slight differences in definitions are expected due to heterogeneity in assessment methods. Such differences are unlikely to affect levels of fructose consumption.

OBESITY: OBSERVATIONAL STUDIES

The majority of (3,6,7) but not all (12) systematic reviews have reported positive associations between SSB and weight gain or risk of overweight or obesity. We recently conducted a comprehensive systematic review and meta-analysis of cohort studies and RCTs of SSBs and weight gain in children and adults (7). On the basis of 7 cohort studies in adults, with 174,252 participants, a 1-serving/day increase in SSBs was associated with an additional weight gain of 0.12 kg over 1 year. Although this estimate seems modest, adult weight gain in the general population is a gradual process, occurring over decades and averaging about 1 lb/year (0.45 kg/year). Thus, eliminating SSBs from the diet could be an effective way to prevent age-related weight gain.

The association between SSBs and obesity is strengthened by our analysis of gene-SSB interactions, which examined whether consumption of SSBs can modify the genetic risk of obesity, using a genetic predisposition score on the basis of 32 obesity genes identified from genome-wide association studies (13). On the basis of data from 3 large cohorts, we found that individuals who consumed ≥1 SSB serving/day had genetic effects on body mass index (BMI) and obesity risk that were approximately twice as large as those who consumed <1 serving/month. These data suggest that regular consumers of SSBs may be more susceptible to genetic effects on obesity, implying that a genetic predisposition to obesity can be partly offset by healthier beverage choices.

OBESITY: RCTs

Compared with observational studies, evidence from RCTs is limited, and the majority of trials evaluate short-term effects of specific interventions on weight change rather than long-term patterns. In our recent meta-analysis of 5 trials including 292 adults, we found that adding SSBs to the diet significantly increased body weight (7). Similarly, another meta-analysis of 7 RCTs found a significant dose-dependent increase in body weight when SSBs were added to participants' diets (12). However, in their meta-analysis of another 8 trials aiming to reduce SSB consumption (for prevention of weight gain), there was no overall effect on BMI, but a significant benefit was observed among individuals who were initially overweight (12). This meta-analysis included 2 large and rigorously conducted RCTs in children and adolescents (14,15), which have overcome many of the limitations of previous trials such as small sample sizes, short duration, lack of blinding, and poor compliance. Although the trial by Ebbeling et al. (14) found that reducing SSBs had a significant benefit on BMI in the first year of the trial during active intervention, it did not find a significant between-group difference after an additional 1 year of follow-up without active intervention (14). This finding actually supports rather than refutes a benefit of reducing SSB consumption on adolescent obesity, suggesting that to achieve long-term benefits, the intervention needs to be sustained over time. These studies provide strong evidence that decreasing consumption of SSBs significantly reduces weight gain and obesity in this age group.

TYPE 2 DIABETES

A growing body of evidence indicates that SSB consumption is associated with increased risk of diabetes through effects on adiposity and independently through other metabolic effects. Although experimental evidence from RCTs is lacking due to high cost and other feasibility considerations, findings from prospective cohort studies have shown a relatively strong and consistent association in well-powered studies. We conducted a meta-analysis of 8 prospective cohort studies evaluating SSB intake and risk of

diabetes (8). On the basis of 310,819 participants and 15,043 cases, individuals in the highest category of SSB intake (usually 1 to 2 servings/day) had a 26% greater risk of developing diabetes compared with those in the lowest category (none or <1 serving/month). For this analysis, we selected estimates that did not adjust for potential intermediates in the etiologic chain, such as total energy intake and BMI. A similar association was found in a subcohort of 15,374 participants and 11,684 incident cases from the EPIC (European Prospective Investigation into Cancer and Nutrition) study (16), where a 1-serving/day increase in SSBs was associated with a 22% increased risk of diabetes. A recent meta-analysis of 17 cohort studies found that a 1-serving/day increase in SSBs was associated with an 18% increased risk of diabetes. Adjusting for BMI reduced this estimate to 13%. Given the similar estimates from studies in the United States where HFSC is the primary sweetener and in Europe where sucrose is used, there does not appear to be any appreciable difference regarding the effect of sweetener type on risk of diabetes. However, food sources of fructose may make a difference in metabolic effects. Some studies have shown beneficial effects of whole fruit consumption on risk of diabetes, whereas higher consumption of fruit juices was associated with increased risk (17). These results indicate that the liquid versus solid forms of calories from sugars may affect metabolic diseases differently. Fructose in beverages is absorbed more quickly than fructose in whole foods such as fruit and vegetables, which are absorbed more slowly due to their fiber content and slow digestion. The rapid absorption of liquid fructose increases the rate of hepatic extraction of fructose, *de novo* lipogenesis, and production of lipids.

CARDIOVASCULAR RISK

There is increasing evidence that higher SSB consumption increases cardiovascular risk by contributing to the development of hypertension, dyslipidemia, inflammation, coronary heart disease, and stroke. In over 88,000 women in the NHS (Nurses' Health Study) followed for 24 years, we found that those who consumed ≥2 servings/day of SSBs had a 35% greater risk of coronary heart disease (CHD) (nonfatal myocardial infarction or fatal CHD) compared with infrequent consumers (18). Additional adjustment for potential mediating factors (including BMI, total energy intake, and incident diabetes) attenuated the association, but it remained statistically significant, suggesting that the effect of SSBs may not be entirely mediated by these factors. Similar results were found in the HPFS (Health Professionals Study) among 42,883 men (19). In this study, intake of SSBs was also significantly associated with increased plasma concentrations of inflammatory cytokines (19).

Recent evidence has also emerged linking intake of SSBs to increased risk of stroke. Among 84,085 women and 43,371 men in the Harvard cohorts followed for 28 and 22 years, respectively, ≥1 SSB serving/day was associated with a 16% increased risk of total stroke compared with no servings in multivariable-adjusted models including BMI (20). This association was attenuated and no longer statistically significant after adjusting for hypertension and diabetes, suggesting that these factors may be mediators. In the multiethnic cohort of 2,564 residents in Northern Manhattan followed for a mean of 10 years, daily soft drink consumption was associated with an increased risk of vascular events only in participants free of obesity, diabetes, and metabolic syndrome at baseline and adjusted for a number of factors including BMI and hypertension (21). A Japanese cohort of 39,786 men and women followed for 18 years found significant positive associations between SSB intake and total and ischemic stroke in women but not in men in models adjusted for hypertension and diabetes (22). Adjustment for BMI and total energy intake had little effect on estimates, suggesting that these factors are not major mediators.

Intake of both added sugar and SSBs was associated with an increased risk for CVD mortality in an analysis of NHANES III Linked Mortality cohort data (4). After a median of 14.6 years of follow-up, added sugar intake was associated with a 2-fold greater risk of CVD death comparing extreme quintiles of intake. In contrast, an analysis from the National Institutes of Health-AARP Diet and Health Study, a prospective cohort of older U.S. adults, found that intake of total fructose but not of added sugar was associated with a modest increase in risk of all-cause mortality in men and women (23). However, total sugars from beverages including added sugar were positively associated with risk of all-cause, CVD, and other-cause mortality in women, whereas only fructose from beverages was positively associated with risk of all-cause and CVD mortality in men. The authors suggest that the differential associations by sex may be due to hormonal and biological differences or different levels of dietary misreporting, but these results may be also due to chance.

FRUCTOSE, GOUT, AND OTHER METABOLIC CONDITIONS

Regular consumption of SSBs has been associated with hyperuricemia as well as with gout, which is a

common form of inflammatory arthritis arising from deposition of uric acid in articular cartilage, in 2 large cohorts (24,25). In particular, higher consumption of both total and added fructose from SSBs was associated with increased risk of gout in a dose-response manner. Gout and hyperuricemia have been associated with hypertension, diabetes, metabolic syndrome, kidney disease, and CVD (26). Consumption of SSBs has also been associated with development of albuminuria, a marker of early kidney damage; formation of kidney stones; and increased risk of chronic kidney disease (27,28). In the NHS II, sucrose consumption was associated with an increased risk of kidney stones (29). Observational studies have also found that a higher intake of sucrose and fructose is associated with a higher frequency of gallstones (30). Individuals with either kidney disease or gallstones have been shown to have elevated cardiovascular risk (31,32). The studies discussed in this section reported estimates that were adjusted for BMI, suggesting that these associations are not completely dependent on body weight.

RCTs OF FRUCTOSE, SSBs, AND CARDIOVASCULAR RISK MARKERS

Data from short-term trials and experimental studies of intermediate outcomes also provide important evidence linking fructose-containing beverages with diabetes and cardiovascular risk and support findings from observational studies. Recently, Stanhope et al. (11) showed that consuming beverages containing 10%, 17.5%, or 25% of energy requirements from HFCS produced significant linear dose-response increases in post-prandial triglycerides, fasting low-density lipoprotein (LDL) cholesterol, and 24-h mean uric acid concentrations in a 2-week, parallel-arm, nonrandomized, double-blinded intervention study. Raben et al. (33) found that a sucrose-rich diet consumed for 10 weeks resulted in significant elevations of post-prandial glycemia, insulinemia, and lipidemia compared with a diet rich in artificial sweeteners in overweight healthy subjects (33). A randomized crossover trial among normal weight healthy men found that after 3 weeks, SSBs consumed in small to moderate quantities (600 ml SSB/day containing 40 to 80 g of sugar) significantly impaired glucose and lipid metabolism and promoted inflammation (34). Of note, LDL particle size was reduced for high fructose and high sucrose SSBs. A 10-week intervention comparing the effects of sucrose and artificially sweetened food or beverages on markers of inflammation found that serum levels of haptoglobin, transferrin, and C-reactive protein were elevated in the sucrose group compared with the sweetener group (35).

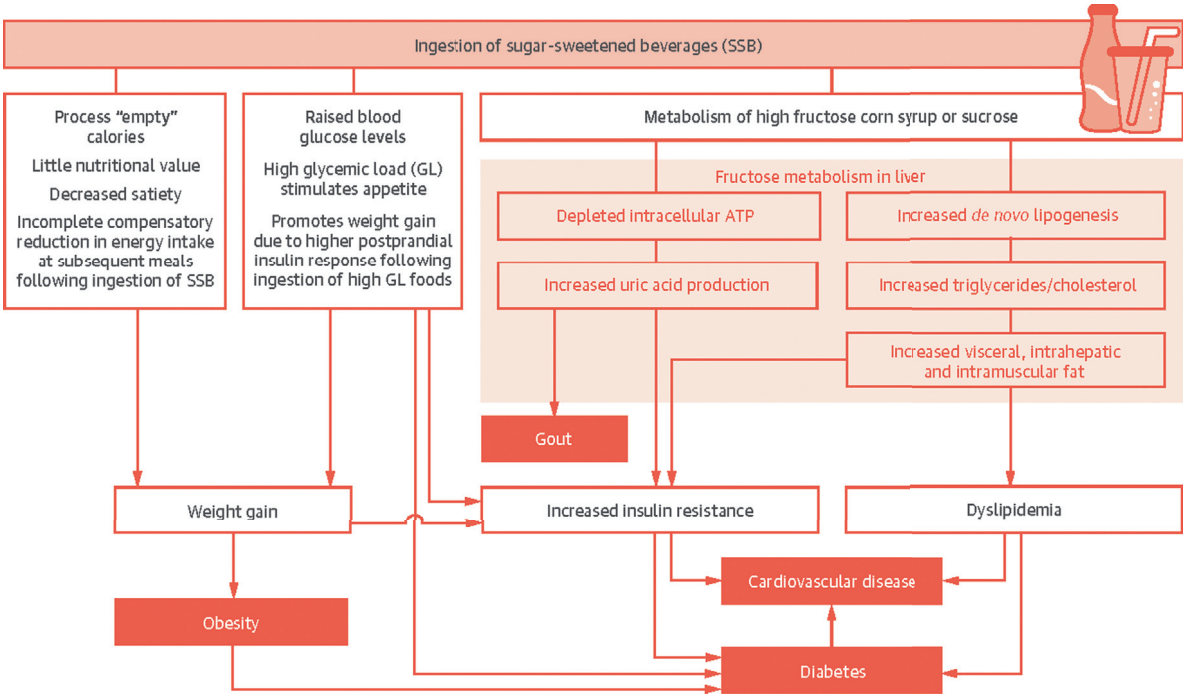
BIOLOGICAL MECHANISMS: LIQUID CALORIES AND UNIQUE METABOLIC EFFECTS OF FRUCTOSE

The prevailing mechanisms linking SSB intake to weight gain are decreased satiety and an incomplete compensatory reduction in energy intake at subsequent meals following ingestion of liquid calories (6). A typical 12 oz (360 ml) serving of soda contains on average 140 to 150 calories and 35 to 37.5 g of sugar. If these calories are added to the typical diet without compensation for the additional calories, 1 can of soda/day could, in theory, lead to a weight gain of 5 lbs in 1 year. Short-term feeding studies comparing SSBs with artificially sweetened beverages in relation to energy intake (36) and weight change (33,36–39) illustrate this point. Some limited evidence supporting incomplete compensation for liquid calories has also been provided by studies showing greater energy intake after isocaloric consumption of beverages compared with solid food (40,41). These studies argue that sugar or HFCS in liquid beverages may not suppress intake of solid foods to the level needed to maintain energy balance; however, the mechanisms responsible for this response are largely unknown.

SSBs may contribute to the development of diabetes and cardiovascular risk in part through caloric effects and the ability to induce weight gain, but also independently through noncalorically-related metabolic effects of constituent sugars (**Central Illustration**). Consumption of SSBs has been shown to induce rapid spikes in blood glucose and insulin levels (33), which in combination with the large volumes consumed, contribute to a high dietary glycemic load (GL). High-GL diets are thought to stimulate appetite and promote weight gain due to the higher post-prandial insulin response following ingestion of a high-GL meal (42) and have been shown to promote hyperinsulinemia and insulin resistance (42). High-GL diets have also been shown to exacerbate inflammatory biomarkers such as C-reactive protein (43) and have been associated with an increased risk of diabetes (44) and CHD (18,19). SSBs may affect risk of CHD through effects on inflammation (45), which influences atherosclerosis, plaque stability, and thrombosis (46). Intake of SSBs could stimulate an inflammatory response through hyperglycemia, which can activate the electron transport chain to produce superoxide radicals (47).

Some evidence suggests that consuming fructose from SSBs as a constituent of sucrose, and HFCS in

CENTRAL ILLUSTRATION **Fructose and Cardiometabolic Health: SSBs**



Malik, V.S. et al. J Am Coll Cardiol. 2015; 66(14):1615–24.

Putative biological mechanisms linking excess sucrose and high fructose corn syrup intake from sugar-sweetened beverages (SSBs) to the development of obesity, gout, diabetes, and cardiovascular disease. Excess calories, incomplete compensation for liquid calories, and high glycemic load (GL) lead to obesity. Increased diabetes and cardiovascular disease risk also occur independently of weight through adverse glycemic effects and increased fructose metabolism in the liver. Excess fructose ingestion promotes hepatic uric acid production, *de novo* lipogenesis, and accumulation of visceral adiposity and ectopic fat, which ultimately increase diabetes and cardiovascular disease risk. ATP = adenosine triphosphate.

slightly higher amounts, and from fruit juices may exert additional adverse cardiometabolic effects. Fructose alone is poorly absorbed but is enhanced by glucose in the gut, thus accounting for the rapid and complete absorption of both fructose and glucose when ingested as sucrose or HFCS. As previously described, fructose is preferentially metabolized to lipid in the liver and can lead to increased hepatic *de novo* lipogenesis, atherogenic dyslipidemia, and insulin resistance. The increase in hepatic lipid content promotes production and secretion of very low-density lipoprotein, leading to increased concentrations of post-prandial triglyceride. Consumption of fructose-containing sugars has been associated with production of small dense LDL cholesterol, which may be due to increased levels of very low-density lipoprotein-induced lipoprotein remodeling, mediated by cholesteryl ester transfer protein and hepatic lipase (9,11).

Fructose has also been shown to promote the accumulation of visceral adipose tissue and the deposition of ectopic fat (48,49). A 10-week study comparing beverages providing 25% of energy from fructose with a beverage providing 25% of energy from glucose showed that fructose-containing beverages increased *de novo* lipogenesis and visceral adiposity, promoted dyslipidemia, and decreased insulin sensitivity compared with the glucose beverage (49). Another study compared daily intakes of 1 l/day of cola, diet cola, milk, or water for 6 months and found that intake of cola increased liver fat, visceral fat, muscle fat, and triglycerides compared with the other beverages (50). Fructose is also the only sugar known to increase serum uric acid levels, which is associated with the development of gout (51). Hepatic uric acid production may also reduce endothelial nitric oxide, which may partly explain the association between SSB and CHD (52). Fructose has also been shown to stimulate transcription of inflammatory factors by activating nuclear factor-kB in mice, further supporting inflammation as a

potential pathway between SSB and CHD (53). A recent meta-analysis found that fructose in isocaloric exchange with glucose increased total cholesterol, uric acid, and post-prandial triglycerides but had no adverse effect on other lipid parameters, insulin, or markers of nonalcoholic fatty liver disease and may be beneficial for body weight, blood pressure, and glycemic control (54). As discussed by the authors, interpretation of these data was limited by the high dose range studied, negative comparators (glucose and starch), short follow-up, and methodological limitations of the available trials (54).

HEALTHY-ALTERNATIVES TO SSBs AND POLICY STRATEGIES

Several beverages have been suggested as alternatives to SSBs, including water, 100% fruit juice, coffee, tea, and artificially sweetened drinks. Unlike SSBs, water does not contain liquid calories, and for most people with access to safe drinking water, water is the optimal calorie-free beverage because it is affordable and accessible. We found that replacement of 1 serving/day of SSBs with water was associated with 0.49 kg less weight gain over each 4-year period (55). In the NHS II, substituting water for SSBs was also associated with a significantly lower risk of diabetes (56).

Because juices contain some vitamins and other nutrients, 100% fruit juice could be perceived as a healthy alternative to SSBs. However, fruit juices also contain a relatively high number of calories from natural sugars, with likely greater amounts of fructose. Previous cohort studies have found positive associations between consumption of fruit juice and greater weight gain (57) and diabetes (58), although some conflicting evidence exists (57,59), suggesting that further research exploring the health effects of juice is warranted. Nonetheless, on the basis of current evidence, it has been recommended that daily intake of fruit juices be limited to 4 to 6 oz.

Numerous prospective cohort studies have shown that regular consumption of coffee (decaffeinated or regular) and tea can have favorable effects on diabetes and CVD risk (60,61), possibly because of their high polyphenol content. Thus, coffee and tea are healthy alternatives to SSBs for individuals without contraindications, provided that caloric sweeteners and creamers are used sparingly. In the NHS II, substituting 1 serving of SSBs with 1 cup of coffee daily was associated with a 17% lower risk of diabetes (62).

Artificially sweetened beverages may be a reasonable alternative to SSBs because they provide few to no calories; however, little is known about the long-term health consequences of consuming artificial sweeteners. Some studies have reported positive associations among diet soda consumption and weight gain, risk of metabolic syndrome, and diabetes (63,64). However, these findings may be due to reverse causation or residual confounding, and short-term trials have reported modest benefits on weight with artificially sweetened beverages as a replacement for SSBs, but long-term data are lacking (7). Yet, some evidence suggests that the intense sweetness of artificial sweeteners may condition toward a greater preference for sweets and enhanced appetite (6). Although consumption of artificially sweetened beverages is preferable to SSBs in the short term, further studies are needed to evaluate their long-term metabolic consequences.

In light of the evidence linking regular consumption of SSBs to obesity and related chronic diseases, national and international organizations have already called for reductions in intake of these beverages to help prevent obesity and improve overall health. The American Heart Association recommends no more than 100 to 150 kcal/day from all added sugar, and both the World Health Organization and 2015 Dietary Guidelines Advisory Committee recommend an upper limit of 10% of total energy from added sugar. Numerous other professional organizations also have specific recommendations for limiting intake of SSBs. In addition to strong and widespread public health recommendations, public policy interventions are needed to change consumption patterns, because they can bring about rapid and effective changes in the food environment. Proposed changes to the nutrition facts label by the U.S. Food and Drug Administration include listing the amounts of added sugar in a product and the percent daily value (%DV)

TABLE 3 Policy Strategies to Reduce Consumption of SSBs

Social marketing and public health campaigns are needed to raise awareness about the health effects of SSBs and added sugar and about healthy alternatives.
Governments should impose financial disincentives, such as taxation of SSBs of at 1east a 10% price increase, and implement limits for use of SNAP benefits for SSBs or subsidize SNAP purchases of healthier foods to encourage healthier beverage choices.
Regulations are needed to reduce exposure to marketing of unhealthy foods and beverages in the media and at sports events or other activities, particularly in relation to children.
Front of package labeling or other nutrition labeling strategies should be implemented to help guide consumers to make healthy food and beverage choices. These changes should be accompanied by concurrent public health awareness campaigns.
Policies should be put in place to reduce the availability of SSBs in the workplace, health care facilities, government institutions, and other public places and ensure access to safe water and healthy alternatives. Restrictions should also be put in place on large portion sizes.
Educational campaigns about the health risks associated with overconsumption of SSBs should be aimed at health care professionals and clinical populations.
National and international campaigns targeting obesity and chronic disease prevention should include the health risks associated with overconsumption of SSBs.
National and international dietary recommendations should include specific guidelines for healthy beverage consumption.

SNAP = Supplemental Nutrition Assistance Program; SSB = sugar-sweetened beverage.

for added sugar. A combination of strategies across multiple levels is thus needed to reduce intake of SSBs, as illustrated in **Table 3**. Implementing and evaluating these types of strategies on changes in consumers' purchasing and eating behaviors as well as health outcomes should be a high priority.

CONCLUSIONS

Intake of added sugar, predominantly sucrose and HFCS from SSBs, has increased markedly in the United States since the late 1960s and constitutes the major source of fructose in the U.S. diet. In this regard, and because we rarely consume fructose in isolation, it is logical to gauge the potential cardiometabolic effects of fructose by evaluating associations with SSBs. Although consumption of SSBs has decreased moderately in recent years, intake levels remain high in the U.S. population and are increasing rapidly in developing countries. On the basis of available evidence from high-quality observational studies and experimental trials of risk markers, we conclude that consumption of SSBs causes excess weight gain and is associated with increased risk of type 2 diabetes and CVD; thus, these beverages are unique dietary contributors to obesity and related chronic diseases. SSBs are thought to promote weight gain in part due to excess calories and incomplete compensation for liquid calories at subsequent meals. These beverages may also increase diabetes and cardiovascular risk independently through an adverse glycemic response and unique metabolic effects of fructose. Short-term mechanistic studies have shown that excess fructose ingestion can result in additional cardiometabolic effects due to increased hepatic *de novo* lipogenesis, accumulation of visceral adiposity, and ectopic fat and production of uric acid.

Several public policy and regulatory strategies to reduce intake of SSBs are already in place or are being considered. Implementing and evaluating such policies are important areas for scientists and policymakers. Key areas that warrant future research include examining the effects of different sugars and sugar moieties on health outcomes over a broad range of doses, investigating the health effects of sugar consumed in solid form in comparison to liquid sugar, and further elucidating the biological mechanism by which intake of liquid calories induces an incomplete compensatory intake of energy at subsequent meals. There is also a need for additional studies to examine the long-term health effects of consuming artificial sweeteners as a substitute for sugar. Lastly, more and higher-quality RCTs are needed to identify effective strategies to reduce SSB consumption at the individual and population level. Although reducing consumption of SSBs or added sugar alone is unlikely to solve the obesity epidemic entirely, limiting intake is 1 simple change that will have a measurable effect on weight control and prevention of cardiometabolic diseases.

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