Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies

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Purpose of review
The effects of dietary sugar on risk factors and the processes associated with metabolic disease remain a controversial topic, with recent reviews of the available evidence arriving at widely discrepant conclusions.

Recent findings
There are many recently published epidemiological studies that provide evidence that sugar consumption is associated with metabolic disease. Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high-fructose corn syrup along with *ad libitum* diets, provide evidence that consumption of these sugars increase the risk factors for cardiovascular disease and metabolic syndrome. Mechanistic studies suggest that these effects result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for *de novo* lipogenesis and leads to increased uric acid levels. Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for noncalorically sweetened beverages, provide evidence that such strategies have beneficial effects on risk factors for metabolic disease or on BMI in children.

Summary
The accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, cardiovascular disease, and type 2 diabetes.

Keywords
fructose, high-fructose corn syrup, metabolic disease, sucrose, sugar

INTRODUCTION

In August 2009, the American Heart Association Nutrition Committee recommended that women consume no more than 100 kcal/day and men consume no more than 150 kcal/day of added sugar [1]. In June 2010, the Report of the Dietary Guidelines Advisory Committee (DGAC) on the Dietary Guidelines for Americans 2010 suggested a maximal intake level of 25% or less of total energy from added sugars [2]. Although this latter guideline is not recommending people consume 25% of their energy as added sugar, it does imply that after due consideration of the evidence DGAC concluded that consumption of added sugar at this level is not associated with any adverse metabolic effects. The difference in these two guidelines, equivalent to almost three 12-ounce servings of soda for the average woman and more than 3.5 for the average man, illustrates the state of controversy that existed concerning the effects of sugar consumption on the development of metabolic disease in 2010.

Are we any nearer a consensus now, 3 years later? The discrepant conclusions summarized below from review articles evaluating the available data to 2012 suggest we are not.

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KEY POINTS

- Recently published epidemiological studies provide evidence that sugar consumption is associated with metabolic disease.
- Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high-fructose corn syrup along with *ad libitum* diets, provide evidence that consumption of these sugars increase risk factors for cardiovascular disease and metabolic syndrome.
- Mechanistic studies suggest that the adverse effects of sugar consumption result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for *de novo* lipogenesis and leads to increased uric acid levels.
- Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for noncalorically sweetened beverages, provide evidence that such strategies have beneficial effects on the risk factors for metabolic disease or on BMI in children.

(1) Data from prospective and intervention studies clearly point to high fructose consumption, mainly in the form of sugar-sweetened beverages (SSBs) as risk factor for metabolic diseases in humans [3].
(2) Although some studies hint toward some potential adverse effects of excessive fructose consumption especially when combined with excess energy intake, the results from clinical trials do not support a significant detrimental effect of fructose on metabolic health when consumed as part of a weight-maintaining diet in amounts consistent with the average-estimated fructose consumption in Western countries [4].
(3) Intake of free sugar or SSBs is a determinant of body weight [5].
(4) Randomized controlled trials at levels even exceeding normal human consumption have been inconclusive, related to SSBs and obesity [6].

This review will present the recent epidemiological, clinical, and mechanistic studies pertaining to the effects of dietary sugar on the risk factors and processes associated with metabolic disease, and provide the perspective of researchers directly involved in the clinical investigations of this topic.

EPIDEMIOLOGICAL STUDIES

Recent studies add to the already considerable epidemiological evidence that sugar consumption is associated with metabolic disease.

(1) Men from the Health Professionals Follow-Up Study in the top quartile of SSB intake had a 20% higher relative risk of coronary heart disease than those in the bottom quartile [7▪].
(2) In Hispanic adults, plasma triglyceride, metabolic syndrome, and waist circumference were associated with consumption of instant SSB and regular soda [8▪].
(3) In the Nurses' Health Study II, one serving per day of SSB was associated with increased risk for type 2 diabetes mellitus (T2DM) [9▪].
(4) In participants from the Nurses' Health Study, Nurses' Health Study II, and the Health Professionals Follow-Up Study, SSB consumption was associated with a higher risk of T2DM; coffee intake was associated with a lower risk, irrespective of the caffeine content [10].
(5) In an analysis across 94 countries, every additional percentage point of calories from sugar/sweeteners was associated with 5% higher prevalence of diabetes [11▪].
(6) An increased consumption of 100 ml/day of SSB was associated with increased insulin resistance by homeostasis model assessment and systolic blood pressure among children at 85 or above percentile for BMI in the Quebec Adiposity and Lifestyle Investigation in Youth Study, and with increased systolic blood pressure and waist circumference in children with impaired glucose tolerance [12].
(7) In healthy adults in Scotland, uric acid levels were positively associated with SSB consumption [13▪].
(8) SSB consumption was positively associated with serum uric acid concentrations in adolescents in Taiwan, as was BMI, body fat, and systolic blood pressure. A total of 25% of the 2727 individuals consumed more than 500 ml of SSB per day [14▪].
(9) Among participants of the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-Up Study, substitution of water, coffee, tea, diet beverages, or low-fat milk for one serving of SSB was associated with weight loss, with the greatest effect occurring with water [15]. The genetic association with BMI was stronger among participants with higher intake of SSB than those with lower intake [16▪].
(10) In adults, frequency of SSB, but not diet beverage, intake was positively associated with

proportion of visceral (VAT) to subcutaneous abdominal adipose tissue (SAT) [17▪].

(11) In teenagers, fructose intake was associated with VAT, but not SAT [18▪].

In contrast to the above reports, an analysis of the National Health And Nutrition Examination Survey 1999–2006 indicated that fructose and non-fructose sugar consumptions at levels representative of the American diet were not associated with indicators of the metabolic syndrome [19].

CLINICAL STUDIES: INTERVENTIONS WITH INCREASED SUGAR INTAKE

Recent clinical studies have investigated the effects of fructose or sugar consumption by providing individuals with SSB or control beverages that were consumed along with *ad libitum* quantities of the individuals' usual diets. The longest of these studies was conducted in Denmark where individuals consumed 1 l/day of sucrose-sweetened cola (~20% energy requirements), isocaloric amounts of low-fat milk, 1 l/day aspartame-sweetened beverages, or 1 l/day water for 6 months. Body weight at the end of the intervention period was not significantly different from baseline in any group. Individuals consuming sucrose exhibited increased VAT, liver and muscle triglyceride, and fasting triglyceride and cholesterol levels, whereas the other three groups did not. The sucrose-induced increase of liver triglyceride was significantly larger compared with all three of the other groups, and the increase in visceral fat was significantly greater compared with the individuals who consumed low-fat milk and who exhibited a comparable change in body weight (sucrose: +1.3%; milk: +1.4%) [20▪▪].

Aeberli *et al.* have published two recent reports in which young men participating in six-arm [21▪▪] or four-arm crossover trials [22▪▪] consumed low (40 g/day, ~6.5% energy requirements) or moderate (80 g/day, ~13% energy requirements) amounts of fructose, glucose, or sucrose as beverages along with *ad libitum* diets for 3 weeks. In the six-arm crossover, LDL particle size was reduced compared with baseline during consumption of moderate fructose or sucrose, and redistribution to a more atherogenic LDL subclass distribution was observed after these interventions plus the low fructose intervention. These three interventions also increased waist : hip ratio, even though low glucose was the only intervention that resulted in significant weight gain compared with baseline [21▪▪]. In the four-arm crossover study, total and LDL-cholesterol were increased after moderate fructose or sucrose compared with moderate glucose consumption. Hepatic insulin sensitivity, indexed by endogenous glucose production during euglycemic–hyperinsulinemic clamps, was decreased during moderate fructose compared with moderate glucose consumption, whereas whole-body insulin sensitivity was not different [22▪▪].

Our group demonstrated that young, healthy individuals consuming 25% energy requirements as high-fructose corn syrup (HFCS)-sweetened beverages for 2 weeks exhibited significant increases of fasting LDL, non-HDL-cholesterol, and apolipoprotein B (apoB); postprandial triglyceride, remnant-cholesterol, and remnant-triglyceride; and small dense LDL (sdLDL), which were comparable to the individuals consuming fructose and greater than those consuming glucose [23▪▪]. In contrast, Silbernagel *et al.* [24] reported that when individuals consumed 150 g/day of fructose or glucose, the only significant difference between the groups was an increase of fasting triglyceride concentrations in the fructose group. They did not measure postprandial triglyceride, fasting apoB, or sdLDL. Given the similarities between this study [24] and our group's study [23▪▪] (both parallel arm, individuals of comparable age and BMI, and similar amounts of sugar consumed), it is interesting to consider why there were numerous differential effects between glucose and fructose on lipids in our study, and only one in this study. A potential reason for the lack of group differences in the study by Silbernagel *et al.* [24] was the highly significant weight gain that occurred in individuals consuming glucose ($+1.7 \pm 0.4$ kg, $P = 0.001$ vs. baseline, $P = 0.056$ vs. fructose), but not in individuals consuming fructose ($+0.2 \pm 0.6$ kg). This difference may possibly be because of fructose malabsorption [25], which they did not assess. As shown in Fig. 1, subdivision of the 48 individuals who participated in our study [23▪▪] into groups that gained or did not gain body weight illustrates that weight gain has a marked effect on the sugar-induced increases of fasting cholesterol, LDL, and apoB concentrations.

The studies by Maersk *et al.* [20▪▪], Aeberli *et al.* [21▪▪,22▪▪] and Stanhope *et al.* [23▪▪] provide direct evidence that consumption of sugar can increase the risk factors for metabolic disease. These results are relevant to public health in that the sugars investigated included the commonly consumed sugars (sucrose and HFCS as opposed to pure fructose) and in quantities comparable to that consumed by a significant number of people [21▪▪,22▪▪], and within the maximal intake level of 25% suggested by DGAC [2]. Obtaining stronger evidence will require clinical trials in which all study food is formulated and provided throughout the investigation to ensure that there are no diet variations between the

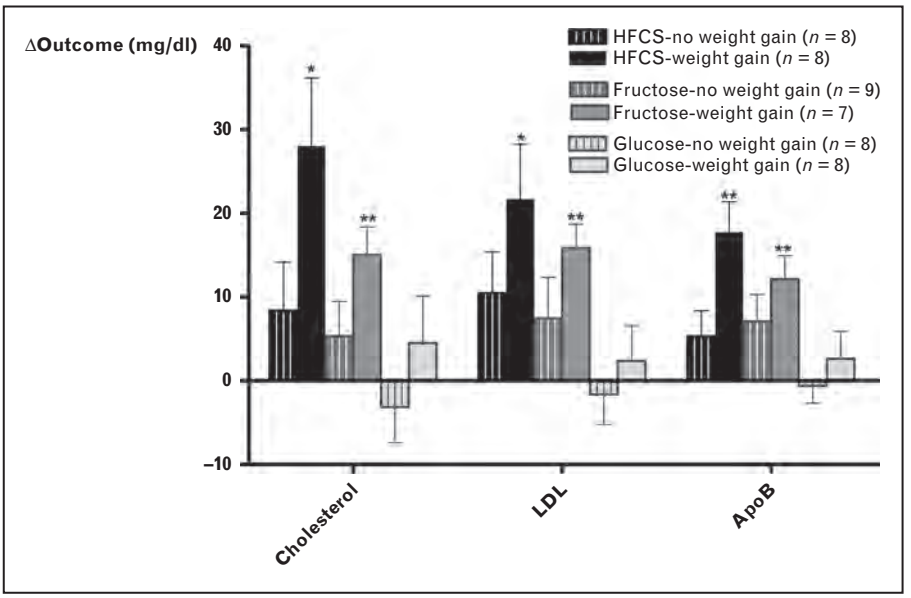

FIGURE 1. Effect of body weight gain on the changes of fasting cholesterol, LDL and apoB in individuals consuming sugar. Changes in fasting lipid outcomes in individuals who gained and did not gain body weight while consuming 25% HFCS-sweetened, fructose-sweetened, or glucose-sweetened beverages for 2 weeks with *ad libitum* diets ($^{*}P<0.05$, $^{**}P<0.01$; 2 weeks vs. baseline). HFCS, high-fructose corn syrup.

experimental groups or interventions that may confound results.

CLINICAL STUDIES PROVIDING MECHANISTIC INSIGHTS

Other recent clinical studies investigating the effects of hyperenergetic feeding protocols and pure fructose have provided mechanistic insights. In an overfeeding study in which diets were supplemented with 1000 kcal/day as candy/SSB, within 3 weeks the individuals exhibited increased body weight (+2%), liver fat (+27%), and increased *de novo* lipogenesis (DNL). The increase of DNL was proportional to the increase in liver fat [26]. Although the lack of a control group prevents differentiating the effects of sugar from those of overfeeding, these results suggest that DNL is involved in the process by which surplus sugar in the context of positive energy balance increases liver fat. Importantly, our group has previously reported that DNL was increased in individuals consuming fructose with energy-balanced, steady-state meals, but not in individuals consuming glucose [27].

However, a recent review of fructose metabolism and isotopic tracer studies concluded that a small percentage of ingested fructose (<1%) appears to be directly converted to plasma triglyceride [28]. This figure is clearly an underestimation, based on acute feeding studies that do not take into account that DNL-derived lipid can spend from 24 to over 72 h in the liver prior to being packaged into very low-density lipoprotein (VLDL) and secreted into the circulation [29,30]. The actual percentage of fructose converted to fat is difficult to quantify, especially under physiologically relevant meal-fed conditions, and has yet to be determined. Accurate estimations will require assessments of DNL and VLDL production, secretion, and clearance using nonsteady state tracer kinetic models. However, the above studies and others demonstrate that DNL is upregulated concurrently with fructose-induced postprandial hypertriglyceridemia [27,31, 32] and liver fat accumulation [26]. The seminal study from Donnelly *et al.* [29] shows that in patients with nonalcoholic fatty liver disease (NAFLD), 26% of both intrahepatic fat and VLDL-triglyceride are made *de novo* [29]. Furthermore, when hepatic DNL is induced, not only are new lipids synthesized and nonesterified fatty acids re-esterified, but also hepatic lipid oxidation is downregulated. Our group has recently reported that the individuals who exhibited increased DNL during fructose consumption also exhibited inhibition of postmeal lipid oxidation [33▪▪]. These combined events create an imbalance between hepatic lipid 'input' and 'export', leading to net intrahepatic fat accumulation. Although we did not measure hepatic lipid in these individuals, the 17% decrease in insulin sensitivity [27] supports the concept that hepatic DNL is a mechanism leading to increased hepatic lipid production, hepatic lipid

accumulation, and thereby to hepatic insulin resistance [34].

Bortolotti *et al.* [35] invetigated the hypothesis that high dietary protein content would reverse the inhibition of lipid oxidation and the increase in postprandial triglyceride levels caused by fructose consumption. The concurrent feeding of fructose and protein did not increase lipid oxidation, and in opposition to the hypothesis, it increased postprandial triglyceride levels. The authors suggest that the supplemental protein may have enhanced hepatic VLDL synthesis, assembly, and secretion.

Our group has also recently reported that 10 weeks' consumption of fructose, but not glucose, led to significantly increased 24-h uric acid profiles [36▪], which suggests that the epidemiological associations [13▪,14▪,37–39] between sugar consumption and uric acid levels are causal. Fasting concentrations of markers of inflammation; monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and E-selectin; as well as retinol binding protein-4 and the liver enzyme, gamma glutamyl transferase; were also increased in these same individuals consuming fructose [36▪,40▪].

Our recent report of the postprandial glucose and insulin responses in the individuals consuming glucose or fructose for 10 weeks [41▪▪] has clinically relevant implications to the potential role of the glycemic index in metabolic disease risk. The adverse metabolic effects of dietary sugars have been attributed by some to glycemic index [42,43]. The glycemic index of fructose is 23 compared with 100 for glucose. The calculated relative glycemic index of the baseline high complex carbohydrate diet, the high glucose intervention diet, and the high fructose intervention diet, consumed during the 24-h blood collections in our studies, were 64, 83, and 38, respectively. As expected, for this study [27] and our more recent 2-week study [23▪▪], the glucose and insulin excursions of the diets paralleled the glycemic index, with exposure being highest on the glucose diet, intermediate on the complex carbohydrate baseline diet, and lowest on the fructose diet. However, it was individuals consuming the high-fructose diets with the lowest glycemic index and glycemic exposure, who exhibited increased VAT and decreased insulin sensitivity [27] and increases of LDL, apoB, and postprandial triglyceride [23▪▪,27]. In contrast, when individuals consumed high-glucose diets, postprandial plasma glucose and insulin excursions increased substantially [23▪▪,27]; however, insulin sensitivity [27] and postprandial triglyceride exposure, LDL, and apoB remained unchanged [23▪▪,27]. Thus, these results do not support the hypothesis that elevated postprandial glucose and insulin excursions contribute to dyslipidemia and insulin resistance. They also demonstrate that studies investigating the relationship of dietary carbohydrates to risk factors for metabolic diseases should accurately determine the glucose and fructose contents of the diets. Dietary fructose may be an important contributor to the inconsistent reported effects of dietary glycemic index on metabolic disease risk. It is likely that other differences between high and low glycemic index diets, with alterations in dietary fiber content being the most likely confounder, underlie these inconsistencies. Nonetheless, the available evidence indicates that it is the fructose and not the glucose component of sucrose and HFCS that is primarily responsible for their adverse metabolic effects.

As the prevalence of pediatric obesity and metabolic syndrome increase, investigations of the effects of sugar consumption in children are needed. The 24-h triglyceride profile was measured in children, with or without NAFLD, during consumption of fructose and glucose in crossover feeding trials [44▪]. As previously shown in adults [45,46], postprandial triglyceride levels were higher during fructose compared with glucose consumption in all children. Importantly, the fructose-induced increases in triglyceride were higher in children with NAFLD than those without NAFLD [44▪].

CLINICAL STUDIES: INTERVENTIONS TO REDUCE SUGAR INTAKE

Several recent clinical studies have demonstrated beneficial effects on metabolic parameters by providing individuals with educational programs aimed at reducing sugar/fructose consumption. Obese African-American and Latino adolescents participated in a 16-week nutrition education intervention focused on decreasing added sugar intake to 10% or less of daily calories and increasing fiber intake. Despite unchanged BMI, individuals exhibited improved insulin sensitivity compared with the control group [47▪]. Goran *et al.* [48] have recently reviewed the interrelationship between genetic factors, liver fat, and sugar consumption, which appear to make Latino children [49] and adults [50] particularly vulnerable to the adverse effects of sugar.

In another study, patients with chronic kidney disease followed dietary instructions and lowered fructose consumption to 12 g/day. After 6 weeks, they exhibited significant decreases in fasting insulin, high sensitivity C-reactive protein and soluble intercellular adhesion molecule, and nonsignificant ($P < 0.1$) decreases in blood pressure and uric acid levels [51].

Three recent studies provide evidence that dietary education programs designed to reduce

sugar and fructose consumption [52], or blinded [53▪▪] or unblinded [54▪] replacement of SSB with noncaloric-sweetened beverages have beneficial effects on BMI in children. Previous studies suggest that consumption of noncaloric sweeteners compared with sucrose or HFCS also has beneficial effects on BMI in adults [55–57]. The explanation for these results could be as simple as people tend to overeat sugar because they like the sweet taste. However, recent studies on the central effects of sugars in the brain [58▪,59▪▪,60], made possible by functional MRI technology, suggest the answer could be more complicated. The most recent of these studies reports that consumption of a fructose-sweetened beverage resulted in greater hypothalamic activation, which would be associated with less appetite suppression, than consumption of a glucose-sweetened beverage in young healthy adults [59▪▪]. Corroborating these results, the individuals recorded significantly higher ratings of fullness and satiety after the glucose, but not fructose, drink [59▪▪].

These data provide a plausible link for the associations between the consumption of SSBs and body weight gain [16▪,61–63]. Confirming this link will be important not only for combating the obesity epidemic, but also the obesity-related increases of metabolic syndrome, cardiovascular disease (CVD), and T2DM. Recent research [20▪▪–23▪▪,27] and older research [64–69] demonstrate that consumption of fructose and fructose-containing sugars has adverse effects on risk factors for metabolic disease that are independent of body weight gain. These results, the results in Fig. 1, and the potential link between sugar consumption and body weight gain suggest that sugar promotes the development of metabolic disease through two mechanisms: directly via the adverse effects of fructose on lipid and carbohydrate metabolism, and indirectly by promoting body weight gain (see Fig. 2).

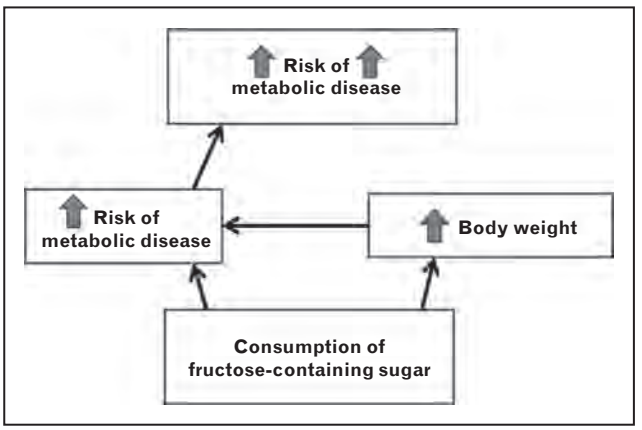

FIGURE 2. Two mechanisms by which sugar increases metabolic risk. Consumption of sugar increases the risk for metabolic disease via the direct effects of fructose on lipid and carbohydrate metabolism. Consumption of sugar may also promote body weight gain. The increased body weight/adiposity further increases the risk for metabolic disease. Thus, consumption of sugar increases the risk for metabolic disease both directly and indirectly.

ANIMAL AND IN-VITRO STUDIES INVESTIGATING MECHANISMS OF THE METABOLIC EFFECTS OF FRUCTOSE

Numerous recent studies, more than can be discussed in this review, have investigated the links between dietary fructose and adverse metabolic effects in animal models or in-vitro systems. We have included a few studies that provide insight into the underlying mechanisms by which fructose induces lipid dysregulation.

The initial phosphorylation of dietary fructose is largely catalyzed by fructokinase, which is not regulated by hepatic energy status. This results in high levels of fructose uptake by the liver with little of the ingested fructose reaching the systemic circulation. Ishimoto *et al.* [70▪▪] have provided compelling evidence concerning the importance of fructokinase in mediating the adverse effects of fructose. They report that fructokinase exists as two isoforms: fructokinase A which is widely distributed and has low affinity for fructose; and fructokinase C, which is expressed primarily in liver, intestine, and kidney and has high affinity for fructose. They demonstrated that fructose-induced metabolic syndrome is prevented in the knockout mice lacking both isoforms, but is exacerbated in fructokinase A knockout mice compared with wildtype mice [70▪▪]. These results demonstrate that fructokinase C is the key driver of the adverse effects induced by fructose. They also suggest that fructokinase A offers some protection against the adverse effects of fructose by allowing for some fructose metabolism in peripheral tissues.

Recent studies have investigated the regulation and effects of fructose-induced DNL. Erion *et al.* [71▪] compared the effect of treatment with carbohydrate response element-binding protein (ChREBP) and control antisense oligonucleotides (ASO) in rats fed high-fructose or high-fat diets. Treatment with ChREBP ASO decreased plasma triglyceride concentrations compared with control ASO in both diet groups, but hepatic lipid content and insulin sensitivity were unaffected. The reduction in plasma triglyceride was more pronounced in the fructose-fed group and attributed to measured decreases of hepatic expression of fructokinase, lipogenic genes, and microsomal

triglyceride transfer protein, and decreased hepatic triglyceride secretion [71▪].

Ren *et al.* [72▪] compared mice fed high-fat diet or high-fructose diets. Liver lipid levels increased within 3 days and indicators of impaired glucose tolerance and insulin signaling were exhibited within 1 week in both groups. As expected, DNL and lipogenic gene expression were increased in fructose-fed mice and decreased in fat-fed mice. Interestingly, fructose feeding activated two endoplasmic reticulum stress pathways, but high-fat feeding did not. The authors suggest that endoplasmic reticulum stress is involved in DNL *per se* rather than resulting from hepatic steatosis or insulin resistance.

Extensive recent work by Johnson and coworkers suggests that fructose-induced increases of uric acid may contribute to the adverse effects of fructose. They report that in fructose-exposed human hepatocytes, uric acid upregulates fructokinase expression [73] and inhibits AMP-activated kinase activity [74], thus amplifying the lipogenic effects of fructose. A series of experiments involving hepatocytes, allopurinol-treated mice, and hyperuricemic patients with low BMI provides evidence that the lipogenic effects of fructose may be partially mediated through direct effects of uric acid to stimulate hepatic fat accumulation [75▪]. Most recently, Tapia *et al.* [76▪] studied three groups of rats receiving uricase inhibitor treatment, SSB, and uricase inhibitor plus SSB. Uricase inhibitor induced glomerular hypertension and SSB induced insulin resistance. In combination, they produced both effects, plus synergistic effects on systemic and glomerular pressure, plasma glucose, hepatic triglyceride, and oxidative stress.

CONCLUSION

The extent to which the adverse metabolic effects of dietary sugar consumption result from direct effects of fructose on lipid and carbohydrate metabolism, to indirect effects resulting from increased body weight and adiposity, or to direct metabolic actions that are exacerbated by weight gain, has not been determined. However, the accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, CVD, and T2DM.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 267–268).

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7. ▪ De Koning L, Malik VS, Kellogg MD, *et al.* Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation 2012; 125:1735–1741; S1..

In addition to reporting a positive association between consumption of SSB consumption and coronary heart disease and intermediate biomarkers, this study also reports that consumption of artificially sweetened beverage was not associated with any of these outcomes.

8. ▪ Mattei J, Malik V, Hu FB, Campos H. Substituting homemade fruit juice for sugar-sweetened beverages is associated with lower odds of metabolic syndrome among Hispanic adults. J Nutr 2012; 142:1081–1087.

This study reports that substituting one serving of homemade fruit juice for instant SSB or regular soda was associated with approximately 30% lower odds of metabolic syndrome, a finding that warrants further investigation.

9. ▪ Pan A, Malik VS, Schulze MB, *et al.* Plain-water intake and risk of type 2 diabetes in young and middle-aged women. Am J Clin Nutr 2012; 95:1454–1460.

In contrast to the finding from the study above, this study reported that consumption of fruit juice, as well as SSB, was associated with increased risk for T2DM.

10. Bhupathiraju SN, Pan A, Malik VS, *et al.* Caffeinated and caffeine-free beverages and risk of type 2 diabetes. Am J Clin Nutr 2013; 97:155–166.

11. ▪ Siegel KR, Echouffo-Tcheugui JB, Ali MK, *et al.* Societal correlates of diabetes prevalence: an analysis across 94 countries. Diabetes Res Clin Pract 2012; 96:76–83.

In addition to the association between SSB and increased incidence of diabetes, this study also reported that each additional unit of fruit and vegetable availability was associated with 3% lower incidence of diabetes.

12. Wang JW, Mark S, Henderson M, *et al.* Adiposity and glucose intolerance exacerbate components of metabolic syndrome in children consuming sugar-sweetened beverages: QUALITY cohort study. Pediatr Obes 2012 [Epub ahead of print]. doi: 10.1111/j.2047-6310.2012.00108.x.

13. ▪ Zgaga L, Theodoratou E, Kyle J, *et al.* The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. PLoS ONE 2012; 7:e38123.

In addition to the positive association between SSB and uric acid, other findings of interest from this study were that consumption of purine-rich vegetables were not associated with uric acid levels and that dairy consumption was negatively associated with uric acid levels.

14. ▪ Lin WT, Huang HL, Huang MC, *et al.* Effects on uric acid, body mass index and blood pressure in adolescents of consuming beverages sweetened with high-fructose corn syrup. Int J Obes (Lond) 2012 [Epub ahead of print]. doi: 10.1038/ijo.2012.121.

This study reports a positive association between SSB and uric acid, and also reports that the presence of obesity exacerbated the SSB-induced increases in uric acid. Johnson and colleagues (Johnson, Seminars in nephrology, 2011) suggest a reverse of this relationship, that SSB-induced increases of uric acid may exacerbate obesity.

15. Pan A, Malik VS, Hao T, *et al.* Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. Int J Obes (Lond) 2013 [Epub ahead of print]. doi: 10.1038/ijo.2012.225.

16. ▪ Qi Q, Chu AY, Kang JH, *et al.* Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012; 367:1387–1396.

The findings of this study suggest that persons with genetic predisposition to obesity are especially vulnerable to the effects of SSB to promote body weight gain.

17. ▪ Odegaard AO, Choh AC, Czerwinski SA, *et al.* Sugar-sweetened and diet beverages in relation to visceral adipose tissue. Obesity (Silver Spring) 2012; 20:689–691.

This study provides support for our group's seminal finding that consumption of fructose can promote VAT accumulation [27].

18. ▪ Pollock NK, Bundy V, Kanto W, *et al.* Greater fructose consumption is associated with cardiometabolic risk markers and visceral adiposity in adolescents. J Nutr 2012; 142:251–257.

This study suggests that our finding that consumption of fructose promoted VAT accumulation in older, overweight/obese adults [27] is relevant to adolescents.

19. Sun SZ, Anderson GH, Flickinger BD, *et al.* Fructose and nonfructose sugar intakes in the US population and their associations with indicators of metabolic syndrome. Food Chem Toxicol 2011; 49:2875–2882.

20. ▪▪ Maersk M, Belza A, Stodkilde-Jorgensen H, *et al.* 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; 95:283–289.

This study reports the first direct experimental evidence that consuming excess sugar with an *ad libitum* diet increases the liver triglyceride content, as previous evidence came from an overfeeding study in which subjects were instructed to consume energy-balanced diets plus excess sugar (Le, Am J Clin Nutr, 2009). It also provides direct experimental evidence that corroborate our previous observation that fructose consumption can increase visceral adiposity [27].

21. ▪▪ Aeberli I, Gerber PA, Hochuli M, *et al.* Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. Am J Clin Nutr 2013; 36:150–156.

This study is important for demonstrating that a moderate dose of sucrose promotes a more adverse lipid profile in as little as 3 weeks.

22. ▪▪ Aeberli I, Hochuli M, Gerber PA, *et al.* Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes Care 2012.

The results of this study are important in that they demonstrate a moderate dose of fructose affects hepatic insulin sensitivity in as little as 3 weeks, and they also corroborate our previous suggestion that fructose induces hepatic insulin resistance prior to whole-body insulin resistance (Stanhope, Curr Opin Lipidol, 2008).

23. ▪▪ Stanhope KL, Bremer AA, Medici V, *et al.* 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–E1605.

This is the first report of the effects of consumption of HFCS-sweetened beverages (>24 h) on metabolic risk factors. Lipid risk factors for CVD (LDL, apoB, and sdLDL) were elevated within 2 weeks of consuming fructose-sweetened or HFCS-sweetened beverages in young (18–40-year-old) men and women. To control for variations in diet and physical activity, the individuals in this study resided at the clinical research center for 48 h prior to the baseline and 2-week intervention blood collections that were analyzed for lipid outcomes.

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33. ▪▪ Cox CL, Stanhope KL, Schwarz JM, *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; 66:201–208.

The results of this study suggest that fructose may promote liver lipid accumulation both directly, via DNL, and indirectly, via DNL-induced inhibition of fatty acid oxidation.

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36. ▪ Cox CL, Stanhope KL, Schwarz JM, *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.

This is the first study to measure and compare the 24-h uric acid profile following sustained consumption of fructose and glucose. The finding suggests that changes of 24-h uric acid exposure, which were markedly increased by only fructose, may be a more sensitive indicator of increased metabolic dysfunction than changes of fasting levels, which were increased by both fructose and glucose. The liver enzyme, gamma glutamyl transferase, and retinol binding protein-4 were also increased during fructose consumption.

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The results from this study suggest the possibility that prolonged consumption of fructose may contribute to the development of metabolic syndrome via induction of specific proinflammatory and prothrombotic mediators.

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This study provides clear evidence that the adverse metabolic effects of fructose compared with glucose consumption are not explained by the glycemic index/glycemic load of the diets, nor mediated through postprandial glucose or insulin exposure.

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The results from this study suggest that children with NAFLD may be more sensitive to the lipogenic effects of fructose consumption than those without NAFLD.

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47. ▪ Hasson RE, Adam TC, Davis JN, *et al.* Randomized controlled trial to improve adiposity, inflammation, and insulin resistance in obese African-American and Latino youth. Obesity (Silver Spring) 2012; 20:811–818.

This study demonstrated that reducing added sugar consumption improved insulin sensitivity in teenagers despite the absence of body weight or fat loss.

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This blinded and randomized 18-month intervention comparing the effects of consuming one daily serving of SSB containing 104 kcal with consuming one serving of noncaloric sweetened beverage in 641 children provides strong evidence that SSB promotes weight gain in children. It also suggests that strategies that target reduction of SSB consumption in children may be effective in lowering the prevalence of pediatric overweight and obesity.

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This study also suggests that strategies that are effective for reducing SSB consumption may lower the prevalence of overweight/obesity in children.

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This study shows that glucose compared with fructose ingestion results in differential brain activation patterns, which may be involved in the effects of SSB to promote body weight gain.

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This study demonstrates that the metabolism of fructose through fructokinase C is necessary to generate adverse metabolic effects. It also demonstrates that when fructose flux through fructokinase C is increased because of knockout of fructokinase A, adverse metabolic effects of fructose are exacerbated.

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This study suggests that ChREBP is involved in the activation of lipogenesis in fructose-fed rats, and that it also has a role in promoting hepatic triglyceride secretion.

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The results of this study suggests that endoplasmic reticulum stress is associated with upregulation of DNL, rather than resulting from hepatic steatosis or insulin resistance. Thus, development of fatty liver because of fructose-induced DNL may be more problematic than fatty liver induced by high-fat diet.

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This study suggests that the lipogenic effects of fructose are exacerbated by high uric acid levels.

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This study provides evidence that SSB and high uric acid levels interact to produce more adverse effects in rats than either SSB or high uric acid levels alone. Although these are important mechanistic results, they have potential clinical implications for hyperuricemic individuals.