

The not so toxic truth about sugar

By John L Sievenpiper, MD, PhD.

Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario Canada and Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

Fructose and sugars containing fructose are being blamed for the rise in obesity, diabetes and other non-communicable diseases. There have been dozens of editorials, commentaries, and letters in the scientific literature and numerous pieces in traditional and social media calling for efforts to restrict and regulate their intake¹⁻³. Some have even suggested that sugars are harmful (toxic), requiring public health controls such as taxation¹. Not all levels of evidence, however, are in agreement. High quality evidence, such as that from controlled-feeding trials must be considered when evaluating whether there is valid evidence to support such claims. This article provides a review of such evidence, looking first at fructose and then at all sugars containing fructose.

The role of fructose and sugars containing fructose in the epidemics of obesity, diabetes, and their cardiometabolic^o complications has been the focal point of recent discussions in both the scientific and media arenas. Uncontrolled ecological studies which have linked increasing sugars availability with increasing obesity and diabetes rates^{5,6} as well as animal models testing abnormally high doses of fructose have been used to underpin this debate⁷. Research in this area is being driven by plausible biological mechanisms, whereby glucose requires an active transport mechanism to enter the gut compared to fructose which enters via facilitated transport. It is postulated that fructose, unlike glucose, acts as an unregulated metabolic substrate leading to increases in fat synthesis and uric acid levels as well as impaired satiety signaling through lower insulin and leptin responses and weaker suppression of ghrelin³.

Evaluation of the above hypothesis requires a careful review of the hierarchy of available evidence (Figure 1). The evidence outlined above, i.e. expert

the liver is a minor pathway of fructose metabolism in humans even when fructose is provided at extremely high doses^{8,9}. In contrast to the above, higher quality evidence from prospective cohort studies have failed to show a consistent relation of total sugars, sucrose, or fructose with cardio-metabolic diseases such as diabetes, hypertension, and coronary heart disease across a range of intakes¹⁰⁻¹². In the absence of a clear association, the question becomes whether the adverse effects being ascribed to sugars are driven by the fructose component or the calories they share with all caloric foods. To answer this question, controlled feeding trials provide the best evidence, as they provide the greatest protection against bias.

Hierarchy in Scientific Evidence

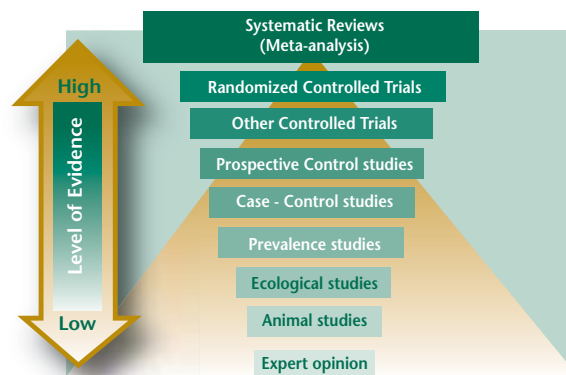


Figure 1. Schematic of the hierarchy of scientific evidence

opinions, ecological studies, and animal models are of lower quality and should be interpreted with caution. For instance, the translatability of animal models has been questioned as mechanisms often do not reflect human metabolism. For example, unlike in rodents, the conversion to fat in

^o Cardiometabolic risk or metabolic syndrome are terms used to describe the collective list of risk factors that are predictive of cardiovascular disease and/or type 2 diabetes⁴

ANALYSIS OF CONTROLLED FEEDING TRIALS OF FRUCTOSE

A series of Canadian Institutes of Health Research (CIHR) funded systematic reviews and meta-analyses of controlled feeding trials were recently conducted^b. Two main trial types were reviewed:

- 1 'isocaloric trials', in which fructose is exchanged for other carbohydrate sources under calorie matched conditions, and
- 2 'hypercaloric trials', in which fructose is added to diets providing excess calories compared with the diets alone.

Analyses of the 'isocaloric trials' failed to show adverse effects even at high doses of fructose

Fructose in isocaloric exchange for other carbohydrates^c was not found to have an adverse effect on cardiometabolic risk factors including body weight, fasting lipids, blood pressure, and glycemic control¹³⁻¹⁸, as well as postprandial triglycerides and markers of non-alcoholic fatty liver disease (unpublished). There were even possible advantages observed; for instance isocaloric exchange of fructose for other carbohydrates resulted in improved glycemic control as well as reduced blood pressure. As long as the comparisons remained calorie matched,

these results held across a large dose range with doses well above the 95th-percentile for intakes in the U.S. (87 g/day or 14% of calories from fructose)¹⁹. In Canada, distribution of fructose intakes are not available for comparison; however, total sugars intakes in Canada are approximately 3% lower on average than US intakes for all age groups^{20,21}.

A lack of effect also persisted under conditions of positive calorie balance. A subset of five of the 'isocaloric trials' provided excess calorie diets (positive calorie balance) in both the fructose and comparator (glucose) arms. This design allowed the effect of fructose to be isolated from that of calories, since for both groups, calories were the same but fed in excess. The effects of diets providing excess calories as fructose were the same when compared to the same diets supplemented with the excess calories as glucose¹⁵.

Effects only observed when fructose is provided as excess calories at extreme doses

Systematic analyses of controlled feeding trials found evidence of adverse cardiometabolic effects only where diets

were supplemented with fructose providing *excess calories* (+18-97% calories) at *extreme doses* (+104-250 g/day) which are well above the 95th-percentile for intake in the population¹⁹. Such abnormal diets were shown to increase body weight and uric acid¹³⁻¹⁸, as well as fasting triglycerides, postprandial triglycerides, markers of non-alcoholic fatty liver disease, glucose, and insulin (unpublished data) compared with the same diets without the *excess calories*.

Summary of analysis of controlled feeding trials of fructose

Taken together, the available evidence from the 'isocaloric trials' does not support any cardiometabolic harm of fructose when it replaces other sources of carbohydrate on a calorie for calorie basis. Only when fructose is added to diets so that it provides excess calories at high doses are metabolic disturbances observed. In the absence of any signal of toxicity in the 'isocaloric trials', the effects seen in the 'hypercaloric trials' appear to be attributable to the excess calories and not to the fructose as a specific source of those calories.

^b ClinicalTrials.gov identifier: NCT01363791

^c Other carbohydrate sources included starch, sugar (sucrose), glucose, maltodextrin, galactose, and high fructose corn syrup

ANALYSIS OF CONTROLLED FEEDING TRIALS OF SUGARS

(SUCROSE AND OTHER FRUCTOSE-CONTAINING SUGARS)

Although controlled trials of fructose have helped to address the role that fructose plays in this debate, one criticism of these trials has been that in free living populations, fructose is rarely if ever consumed in isolation. Fructose is most often co-ingested with glucose in common sweetening agents, such as sugar (sucrose) or high-fructose corn syrup (HFCS) (Figure 2) as well as in fruits and vegetables which contain fructose, glucose and sucrose (Figure 3).

In the above series of systematic reviews and meta-analyses, fructose was not shown to behave differently than sucrose or HFCS, where these sweetening agents were the comparator. However, the question remains whether the evidence for fructose trials holds when fructose is co-ingested with glucose in the form of sucrose or HFCS, the two most commonly used caloric sweeteners.

Three main trial types that allow for the effect of sugars to be isolated from calories were reviewed:

- 1 'isocaloric trials', in which sugars are exchanged for other carbohydrate sources under calorie matched conditions;
- 2 hypercaloric 'addition trials', in which the calories from sugars are added in addition to the normal diet compared with the normal diet alone;
- 3 hypocaloric 'subtraction trials', in which the calories from sugars are subtracted from the diet compared with the normal (sugar-containing) diet.

Sugars Content of Various Sweeteners

Adapted from Canadian Nutrient File and USDA Database

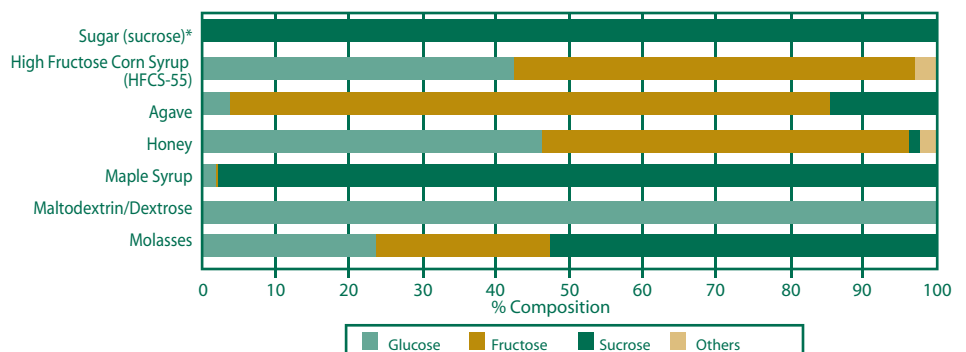


Figure 2. Sugars content of various nutritive sweeteners. *Sucrose is a disaccharide made up of equal parts of the monosaccharides, glucose and fructose which are linked together by a glycosidic bond. Source: Adapted from Canadian Nutrient File and USDA Databases

Sugars Content Fruits and Vegetables

100 grams, edible portion



Figure 3. Sugars content of various fruits and vegetables. Source: Adapted from Canadian Nutrient File and USDA Databases

Analyses of the 'isocaloric trials' of added sugars failed to show adverse effects

The available 'isocaloric trials' of sugars failed to show consistent evidence of adverse health effects. A recent World Health Organization commissioned systematic review and meta-analysis assessed the available evidence for the effect of fructose, sucrose, and HFCS on measures of adiposity in randomized trials²². It showed that sugars (predominantly sucrose) in isocaloric exchange with other sources of carbohydrate do not affect body weight²². Another systematic review of the available trial evidence found a similar lack of effect of sucrose in isocaloric exchange with starch at levels up to 25% of calories on blood lipid, glucose, and insulin control²³. There is insufficient evidence testing doses >25% of calories, and so adverse effects at intakes above this level cannot be ruled out. However, Canadians' intakes of sugars appear to be below this level. According to data from the Canadian Community Health Survey (2004), average *total* sugars intakes among Canadians range from 18.8% to 27.4% of total energy²¹ and it is estimated that approximately half of these sugars are added (i.e. 9% to 14%)²⁷.

There is also insufficient evidence to draw reliable conclusions on the effect of substitution of sucrose for other macronutrients. In this regard, consumption of caloric sweetened beverages (fruit drinks and regular soft drinks) had no effect on body weight or body fat compared to milk in one 4-month

trial in children²⁴; however, long-term effects on growth and lean body mass were not assessed. In another 6-month trial in adults²⁵, results did show that very high intakes of caloric sweetened beverages (1L/day providing 106 g/day sugars) increased ectopic liver and visceral fat in isocaloric comparison with milk²⁵. These preliminary data in adults suggest potential adverse effects under a narrow set of conditions: sugars in liquid form in substitution for milk at very high doses well above population levels of intake. The mean intake of added sugars in the U.S. is 76.7 g/day of which 30.2 g/day is from caloric sweetened beverages²⁶. In Canada, added sugars intake is approximately 52 g/day of which 19.7 g/day is from caloric sweetened beverages^{21,27}, one fifth of the dose used in the above study.

Effects observed in hypercaloric 'addition trials' are linked to excess calories

The hypercaloric 'addition trials' show adverse effects which are predicted by the excess calories provided from the sugars. The World Health Organization commissioned systematic review and meta-analysis²² and another updated systematic review and meta-analysis²⁸ showed that the supplementation of diets with excess calories (+150-530kcal extra calories) from caloric sweetened beverages results in significant weight gain over 3 weeks to 24-months. The weight gain achieved was proportional to the degree of calorie supplementation; in fact, weight gain was less than that predicted by the extra calories provided²⁸.

A similar increasing effect has been seen on triglycerides when calories from caloric sweetened beverages²⁵ or sucrose²³ are fed in addition to the normal diet. However, without a comparator matched for calories in these trials, one cannot conclude that the weight gain would have been different for any other source of excess calories.

Hypocaloric 'subtraction trials' have failed to show consistent effects

Although one would expect weight loss to occur following strategies to reduce sugars in the diet, the hypocaloric 'subtraction trials' have failed to show consistent benefit^{22,28,29}. This is a common result of energy reduced weight-loss diets in general, and likely due to poor adherence and compensation with other sources of calories (i.e. a decrease in calories from one food tends to be replaced with calories from another food)^{30,31}.

Summary of analysis of controlled feeding trials of added sugars containing fructose

Overall, the available trial evidence suggests that sugars are only a determinant of body weight when they add excess calories to the diet. The 'isocaloric trials' demonstrate that added sugars do not appear to behave differently than other forms of carbohydrate up to 25% of calories, which is nearly the 90th percentile for intake in the U.S.³⁰ and more than double estimated average intakes in Canada²⁷. More research is needed to clarify whether sugars behave differently when the calorie matched comparator is another macronutrient.

Nevertheless, there is a lack of trial evidence to inform whether free-living intakes of sugars, more than other sources of calories, result in general overconsumption leading to weight gain and its downstream cardiometabolic complications. To address the role of sugars, in comparison to other calorie sources in the general population, future research should focus on long-term trials under free-living conditions in which sugars are freely replaced with other sources of calories in the diet.

OVERALL CONCLUSIONS

The concerns raised by the ecological and animal studies linking sugars to the development of obesity, diabetes, and other cardiometabolic diseases have not been supported by higher level evidence from controlled feeding trials. The systematic synthesis of data from clinical studies in humans does not support the view that fructose and sugars containing fructose are harmful at typical intakes. Excess calories appear to be the dominant consideration, rather than sugars or the type of sugar, for weight gain and other metabolic disturbances. So how much sugar is safe to consume? The evidence does not indicate harm for added sugars intakes below 25% of total energy. Current estimates of added sugars intakes in Canada are approximately half this level, contributing 9 - 14% of total energy.

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CANADIAN SUGAR INSTITUTE
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10 BAY STREET, SUITE 620
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