Fructose Not to Blame for Weight Gain?

Sievenpiper JL, de Souza RJ, Mirrahimi A, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Ann Intern Med 2012;156:291–304.

Study Overview

Objective. To examine the effects of fructose consumption on body weight in controlled feeding trials.

Design. Meta-analysis.

Study selection. Controlled feeding trials lasting 7 or more days that compared the effect on body weight of free fructose and nonfructose carbohydrates in diets providing similar calories (isocaloric trials), or diets supplemented with free fuctose to provide excess energy (hypercaloric trials). Exclusion criteria included trials where fructose was delivered only as sucrose or only as high-fructose corn syrup and where the fructose delivery method was intravenous. Trials with fewer than 7 days follow-up, those that lacked a control group, and those that did not provide body weight data were also excluded.

Main outcome measure. Difference in end body weight. The authors chose end body weight due to lack of consistent data across all trials for weight change; some trials reported on end difference and did not include baseline results, while others reported weight change from baseline.

Main results. 41 trials published in 32 reports met the inclusion criteria. 5 of the initial reports included both isocaloric and hypercaloric trials, while 4 of the initial reports contained 2 distinct trials of the same type. 31 of the trials were isocaloric feeding trials, with a total of 637 participants in 3 population subgroups for analysis: diabetic (13 trials), overweight/obese (5 trials), and normal body weight (13 trials). The remaining 10 trials were hypercaloric and comprised a total of 119 participants in 2 population subgroups for analysis: overweight/obese (2 trials) and normal body weight (8 trials).

For the isocaloric trials, the median age was 43 years, the male-to-female ratio was 1.5:1, and the median number of participants was 14. 48% of the isocaloric trials were conducted in Europe, 61% were in an outpatient setting, and the median follow-up was 4 weeks. Overall in the isocaloric trials, fructose did not have a significant effect on body weight (total mean difference, −0.14 kg [95% CI, −0.37 to 0.08 kg]). There was a statistically significant weight loss in the overweight/obese subgroup (mean difference, −0.55

kg [95% CI, –1.09 to –0.02 kg]). However, 3 of the 5 trials in the overweight/obese subgroup tested diets that had an overall negative energy balance. For the hypercaloric trials, the median age was 24.7 years, the male to female ratio was 8:1, and the median number of participants was 12. 80% of the hypercaloric trials were conducted in Europe, 80% were in an outpatient setting, and median follow-up was 1.5 weeks. Overall in the hypercaloric trials, fructose did have a statistically significant body-weight increasing effect (mean difference, 0.53 kg [95% CI 0.26 to 0.79 kg]). However, since these trials supplemented a controlled diet with high doses of fructose, it is difficult to determine whether the fructose itself or the additional calories caused the weight gain.

Conclusion. Fructose is not associated with weight gain when substituted for other carbohydrates in similar-calorie diets. Fructose consumption may cause weight gain when added as excess energy in a hypercaloric diet.

Commentary

An increase in fructose consumption in Western diets, mostly in the form of high-fructose corn syrup (eg, sugar-sweetened beverages) and added sucrose (eg, table sugar), has paralleled increases in overweight, obesity, and diabetes in the United States over the past several decades [1,2]. Many studies have examined the association between fructose consumption and body weight, but results remain inconclusive. Some trials find that fructose increases body weight while others do not. A previous meta-analysis comparing fructose to other carbohydrates in relation to body weight found no effect, but it only examined isocaloric rather than hypercaloric studies [3].

This meta-analysis by Sievenpiper et al adds to the literature by evaluating the association of fructose to body weight in both isocaloric and hypercaloric settings. The meta-analysis used trial-level data from 41 different trials, representing 637 individuals in 31 isocaloric trials and 119 individuals in 10 hypercaloric trials. The authors found different results in the isocaloric and hypercaloric trials. The overall results for the isocaloric trials did not reveal any significant association except for statistically significant (but not clinically significant) weight loss in the overweight/obese subgroup. However, this finding can probably be explained by the fact that 3 of the 5 trials in the overweight/obese subgroup tested diets that had an overall negative energy balance. The results for the hypercaloric trials did indicate that fructose consumed in excess of a controlled diet led to weight gain. However, Sievenpiper et al was not able to rule out confounding from excess energy, and thus the weight gain could not be attributed directly to fructose.

Fructose has been proposed to cause weight gain and negative health effects by various mechanisms. Some studies have suggested that fructose ingestion does not lead to satiety [4] (perhaps by failing to stimulate leptin and inhibit grehlin), and others suggest that fructose may lower the basal metabolic rate [5]. In addition, fructose has been shown to raise uric acid levels, and elevated uric acid levels are independently associated with obesity, hyperinsulinemia, hypertension, and renal disease [6–8]. Fructose has been shown to cause insulin resistance in humans [9,10] and has been associated with increased adiposity and weight gain in mouse models [11]. In light of this evidence, the findings from Sievenpiper et al can be interpreted in various ways. Since the authors only found weight gain in hypercaloric but not isocaloric settings, weight gain from excess fructose may be attributed mostly to excess calories rather than from differences in the mechanism of metabolism of fructose [12] or its impact on basal metabolic rate [5]. This study does not allow us to make conclusions about the impact of fructose on satiety in real-world settings; given the controlled nature of the diets used in the studies included in this meta-analysis, we cannot determine if fructose impacts satiety leading people to eat more and gain weight. As importantly, the authors did not examine intermediate and other health outcomes such as insulin resistance, blood pressure, or adiposity.

The limitations of this meta-analysis are acknowledged by the authors. First, the small number of participants in each trial may not fully represent the general population, and the demographics of the subjects differ by study type. The isocaloric trials enrolled more middle-aged and older men than women, and the hypercaloric trials enrolled more young men than women. It was not possible to analyze gender or age as potential variables. Second, since only 7 of the 31 isocaloric trials and none of the hypercaloric trials lasted 12 or more weeks, we cannot be certain whether any effects will remain in the long-term. Third, the authors only analyzed end weight between the comparator groups rather than changes on body weight pre- and post intervention because of lack of data about baseline weight in some trials, and this may cause a measurement bias. However, when the authors imputed missing data using a standardized formula and analyzed baseline weight subgroups from each trial, they

found no significant differences in outcome. Fourth, over half of the trials eligible for inclusion in the meta-analysis were considered to be of poor quality (Heyland MQS < 8). Due to the limited number and small size of relevant trials, the authors chose to include all of these studies. The authors did analyze by study quality for effect modification to see if stratifying by poor quality studies and high quality studies produced any change in results, but did not find any evidence. Finally, publication bias is a potential limitation, even though the authors attempted to limit this by conducting a thorough search for existing trials, contacting authors for more data, and finding no evidence of asymmetry or small-study effects using the Egger and Begg tests. Still, half of the hypercaloric trials were conducted and published by the same investigators in a homogenous group in Switzerland, indicating potential publication bias.

Applications for Clinical Practice

Fructose consumed as a substitute for other carbohydrates with a net neutral calorie diet does not seem to increase body weight but may lead to short-term excess weight gain in the setting of a hypercaloric diet. Since sugar-sweetened beverages and other forms of fructose often are consumed as added calories, clinicians should continue to counsel patients to limit intake. However, this study does not answer whether fructose itself is worse than other forms of carbohydrates with regards to satiety and overall health. Further studies are necessary to guide clinical practice.

—Joey Nicholson, MLIS, MPH, and Melanie Jay, MD, MS

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