High-fructose corn syrup and sucrose have equivalent effects on energy-regulating hormones at normal human consumption levels

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ARTICLE INFO

ABSTRACT

Intake of high-fructose corn syrup (HFCS) has been suggested to contribute to the increased prevalence of obesity, whereas a number of studies and organizations have reported metabolic equivalence between HFCS and sucrose. We hypothesized that HFCS and sucrose would have similar effects on energy-regulating hormones and metabolic substrates at normal levels of human consumption and that these values would not change over a 10-week, free-living period at these consumption levels. This was a randomized, prospective, double-blind, parallel group study in which 138 adult men and women consumed 10 weeks of low-fat milk sweetened with either HFCS or sucrose at levels of the 25th, 50th, and 90th percentile population consumption of fructose (the equivalent of 40, 90, or 150 g of sugar per day in a 2000-kcal diet). Before and after the 10-week intervention, 24-hour blood samples were collected. The area under the curve (AUC) for glucose, insulin, leptin, active ghrelin, triglyceride, and uric acid was measured. There were no group differences at baseline or posttesting for all outcomes (interaction, $P > .05$). The AUC response of glucose, active ghrelin, and uric acid did not change between baseline and posttesting ($P > .05$), whereas the AUC response of insulin ($P < .05$), leptin ($P < .001$), and triglyceride ($P < .01$) increased over the course of the intervention when the 6 groups were averaged.

We conclude that there are no differences in the metabolic effects of HFCS and sucrose when compared at low, medium, and high levels of consumption.

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1. Introduction

Intake of added sugars along with many other nutrients has increased significantly in the United States in the last 40 years—for the 35-year period between 1970 and 2005, Americans' average daily intake of sugar increased from 400 to 476 calories, a 19% increase [1]. During the same period, there has also been a dramatic increase in obesity in the United States and many other countries [2].

Concerned over the potential that added sugars might be a contributing factor to obesity, a number of organizations have recommended a decrease in added sugar consumption. Recommended upper limits of consumption of added sugars from the American Heart Association (AHA) [3] are much more restrictive than those of the Institute of Medicine [4] upon which the Dietary Guidelines for Americans are based [5].

It has also been argued that high-fructose corn syrup (HFCS), in particular, may be uniquely related to the increased

prevalence of obesity because of the temporal relationship between the appearance of HFCS in the American diet as a significant component of added sugars and the rise in obesity [6]. Numerous studies, however, have demonstrated the metabolic equivalence of HFCS and sucrose [7-9] either in acute experiments or in short-term studies where either HFCS or sucrose was consumed at levels up to 25% of calories (90th percentile population consumption level of fructose) as part of mixed nutrient diets. Both the American Medical Association [10] and the Academy of Nutrition and Dietetics [11] have issued statements supporting the metabolic equivalence of HFCS and sucrose. Several studies have implicated a role for sucrose, particularly when consumed in sugar-sweetened beverages in promoting obesity [12].

The debate on added sugars and their relationship to obesity and other potential metabolic problems has been further fueled by research studies comparing pure fructose vs pure glucose [13,14], although neither pure fructose nor pure glucose is consumed to any appreciable degree in the human diet. Fructose and glucose are virtually always consumed together, most commonly as components of sucrose or HFCS [15]. It has also been argued that the fructose moiety in sweetened beverages interacts differently with energy-regulating hormones such as insulin, leptin, and ghrelin, promoting a situation where excess calories may be consumed without appropriate satiety signals, thereby increasing the likelihood of weight gain and obesity [6,12,16]. It has also been argued that the 10% difference in fructose found in HFCS-55 (the most common form of HFCS used in beverages), when compared with sucrose, might further create metabolic abnormalities because of the well-known difference in metabolism between fructose and glucose in the liver [17,18].

In addition, it has been argued that excessive consumption of fructose from sugar-sweetened beverages may result in an increased triglyceride production [19-24]. In particular, it has been argued that postprandial triglycerides may be particularly elevated after large doses of fructose-containing sugars through the process of de novo lipogenesis in the liver [13,25,26].

There is a debate that HFCS may behave differently from sucrose because HFCS has free fructose and glucose, whereas sucrose has fructose and glucose bound as a disaccharide. Several issues are important to note about this debate. First, the bond between fructose and glucose is immediately broken in the small intestine by the enzyme sucrase. Therefore, it is absorbed as free fructose and free glucose. Second, slightly acidic environments or warmth cause this bond to be broken (the process of inversion). Thus, in carbonated soft drinks, which are mildly acidic, if sucrose were used as a sweetener, it would be highly likely that a high percentage of it had already been inverted to glucose and fructose. Furthermore, in our research laboratory, we have shown in acute experiments that HFCS and sucrose behave virtually identically. Nonetheless, because this remains controversial, we felt that it was important to conduct a longer-term study comparing HFCS with sucrose and with both at various doses within the range of human consumption.

The purpose of the current study was to extend previous observations related to acute responses of glucose, energy-regulating hormones, and metabolic substrates by exploring 3 different levels of added sweetener consumption from either HFCS or sucrose (25th, 50th, and 90th percentile population consumption levels of fructose [27] in a randomized, prospective, double-blind, parallel group study. We hypothesized that there would be no differences in the concentration of metabolic substrates or energy-regulating hormones at any level of added sugar consumption within the normal human range when comparing HFCS and sucrose and that the acute metabolic effects of HFCS and sucrose would not change as a result of a 10-week intervention of daily exposure to these sugars.

2. Methods and materials

2.1. Design and participants

This study was a randomized, prospective, double-blind, parallel group study comparing the effects of 3 different doses of HFCS-55 (55% fructose) with comparable doses of sucrose (50% fructose) on circulating concentrations of hormones regulating body weight and appetite (insulin, leptin, and active ghrelin). Participants were randomly assigned to 1 of 6 groups by following an order dictated by a random sequence generated from a free Web site (random.org). Participants consumed 8%, 18%, or 30% of calories in low-fat (1% fat) milk (Tetra Pak, Denton, TX, USA) sweetened with either HFCS-55 or sucrose (representing the 25th, 50th, and 90th percentile population consumption levels of fructose). This corresponds to 40, 90, or 150 g of added sugar per day in a 2000-kcal diet. Low-fat milk was used to enhance participant compliance over the 10-week study. Furthermore, previous investigations that used carbonated soft drinks suffered from the confounding problem of significant inversion of sucrose into its components of fructose and glucose because of the mildly acidic environment of these beverages. We believed that this would not occur with low-fat milk. The stability of the sugars used was confirmed by outside, blinded analysis conducted by Archer Daniels Midland (Argenta, IL, USA). Participants participated in an initial 24-hour stay in our metabolic unit, followed by 10 weeks of free-living consumption of these levels of added sugar, followed by another 24-hour acute stay in our metabolic unit. The experimental protocol was approved by the Western Institutional Review Board.

The study population included men and women between the ages of 20 and 60 years, with a body mass index (BMI) between 21 and 35 kg/m^2. Participants were recruited from newspaper advertisements, postings on the Internet, and a database of individuals who had participated in previous studies in our research laboratory who had indicated a desire to participate in further research trials. All participants were weight stable (no change in weight >3% in the past month, no actions taken in 3 months to lose weight), nonsmokers (not been a regular smoker for at least 12 months and no social smoking for at least 3 months), and normoglycemic (fasting after a 2-hour oral glucose challenge). Participants were excluded if they had uncontrolled blood pressure, a history of thyroid disease, cancer, gastrointestinal disorders, cardiac problems, or eating disorders; if they had ever had a surgical procedure for weight loss; if they had undergone any major

surgical procedure in the previous 3 months; if they started a new medication within the past 3 months (including a change in dose of an existing medication); if they were pregnant or lactating; if they consumed more than 3 alcoholic drinks per week; or if they had any significant food allergy. In addition, participants were not allowed to enroll if they had participated in any other clinical trial within the previous 30 days. All participants provided signed informed consent. All procedures of this study and the informed consent were approved by the Western Institutional Review Board.

Participants were randomly assigned to 1 of 6 groups:

- Groups 1 and 2: energy balanced containing 8% calories from HFCS or sucrose
- Groups 3 and 4: energy balanced containing 18% calories from HFCS or sucrose
- Groups 5 and 6: energy balanced containing 30% calories from HFCS or sucrose

The sugar was supplied via premixed, sugar-sweetened, low-fat milk supplied to them in 8-oz, unlabeled, sealed cartons. The milk was supplied in cartons containing either 15 g of added sugar per 8-oz ounce carton or 30 g of sugar per 8-oz carton to provide the same volume of milk for each participant and, hence, the same volume of naturally occurring sugars from the milk. Compliance to milk consumption was measured with daily dietary logs, which were handed in on a weekly basis when participants returned to our clinic facility to receive the weekly supply of milk. A weight maintenance caloric intake level was calculated using the Mifflin St Jeor prediction equation [28] (and appropriate activity factor based on self-reported levels of habitual physical activity), and milk was then prescribed in an amount necessary to meet the desired % HFCS or sucrose content of the diet. Participants had unlimited flexibility in the makeup of the remainder of their diet but were instructed on the need to account for the calories from the milk if they wanted to maintain their initial body mass. Participants were instructed to eat to the same level of "fullness."

2.2. Metabolic unit procedures

Participants performed 2 overnight stays in the metabolic unit, one after completion of screening and one after 10 weeks of intervention, as described by Melanson et al [7]. In summary, a fasting blood sample was obtained at 8:00 AM via an intravenous catheter. A standardized breakfast was provided at 9:00 AM, after which blood samples were obtained every 30 minutes until midnight and hourly thereafter until 8:00 AM on day 2 of the visit. Additional standardized meals were provided for lunch and dinner. Each meal was accompanied by the test beverage of the group to which they were assigned. All meals were standardized for energy and macronutrient content and consumed within 15 minutes of being served to ensure standardization of nutrient appearance in the blood stream.

2.3. Anthropometric measurements

Anthropometric measurements were taken before the study in all participants. Body composition in the beginning

and the end of study was determined by iDXA (GE Medical Systems, Madison, WI, USA). Fasting-state, multiple measures were taken, and percent body fat and lean body mass were obtained.

2.4. Blood serum measurements

Blood samples obtained in the metabolic unit were used to measure glucose, insulin, leptin, active ghrelin, and triglycerides. Blood was collected in BD (Becton Dickinson, Franklin Lakes, NJ, USA) vacutainers containing ethylenediaminetetraacetic acid for the preparation of plasma. Immediately after collecting blood samples, serine protease inhibitor (Pefabloc SC [AEBSF], 1 mg/mL sample; Roche Diagnostic Cooperation, Indianapolis, IN, USA) were added to prevent the degradation of active ghrelin molecule. Aliquots from collected samples were stored at –80 C until tested. Bloods for insulin, leptin, and active ghrelin were tested in batches once an adequate number of pretesting and posttesting samples had been obtained. Plasma glucose was measured using the YSI 2300 analyzer (YSI Life Sciences, Yellow Springs, OH, USA). Plasma insulin, leptin, and active ghrelin were assayed simultaneously using MILLIPLEX MAP Human Metabolic Hormone Panel (EMD Millipore, St Charles, MO, USA). Assays were run on Luminex 200 (Luminex Corporation, Austin, TX, USA) with xPONENT software. Additional blood was obtained in a standard Serum Separator BD vacutainer and allowed to clot, and then the serum was obtained and stored as described for plasma. These serum samples were used for the measurement of triglycerides and uric acid by CPL Laboratories (Orlando, FL, USA) using standard techniques.

2.5. Statistical analyses

All data are presented as means ± SD and analyzed using SPSS-PASW Statistics (version 19; SPSS, Chicago, IL, USA). Twenty-four-hour area under the curve (AUC) was measured for all analytes measured in the metabolic unit using the trapezoidal method and was not calculated for participants with more than 3 consecutive missing values or for those without a baseline or final (8:00 AM) value. Outcome measures were analyzed via a 2-way analysis of variance with repeated measures (6 groups × 2 time points). Significant differences among groups at different dosages were assessed using preplanned LS means comparisons. Statistical significance was defined by $P < .05$.

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3. Results

3.1. Demographic information

A total of 465 participants who enrolled met the qualifying criteria, completed fasting baseline testing, and began the intervention. A subset of 141 participants were enrolled in the substudy requiring the overnight visit, with 138 participants (male, 79; female, 59), finishing the intervention, and performing the second overnight visit. Baseline descriptive data on these 138 are shown in Table 1. Baseline dietary intake for all groups is presented in Table 2.

Participants dropped out of the protocol for a variety of reasons including noncompliance with milk consumption, dissatisfaction with time commitment, new job, or other personal commitments. No participant reported any adverse effects from the interventions.

3.2. Body mass and body composition

There were overall increases in all measures of adiposity for the entire cohort—body mass (76.9 ± 13.9 kg vs 78.0 ± 14.5 kg, $P <$ .001), BMI (27.0 ± 3.6 kg/m^2 vs 27.4 ± 3.7 kg/m^2, $P <$ .001), waist circumference (84.7 ± 9.8 cm vs 85.0 ± 10 cm, $P <$ .05), body fat percentage (33.6% ± 8.8% vs 34.1% ± 8.7%, $P <$ .001), fat mass (25.3 ± 10.9 kg vs 26.1 ± 8.9 kg, $P <$ .001), and fat-free mass (52.3 ± 10.9 kg vs 52.7 ±11.0 kg, $P <$ .001). However, in all cases, there were no differences among the groups in the change from pretesting to posttesting (time × group interaction, $P >$ .05).

3.3. Metabolic unit data

Fasting values of glucose, insulin, leptin, ghrelin, triglycerides, and uric acid were not different among the groups at baseline or week 10 ($P >$ .05). After 10 weeks, whole-day AUC was increased in the entire cohort for insulin (5848 ± 2655 vs 6271 ± 3372, $P <$ .05), leptin (347 ± 305 h * µg/L vs 386 ± 325 h * µg/L, $P <$ .001), and triglycerides (29.5 ± 17.0 mmol/L vs 32.3 ± 16.4 mmol/L, $P <$ .001), but were unchanged for glucose, ghrelin, and uric acid ($P >$ .05). In all cases, there were no differences in the response to the 6 different interventions at baseline or posttesting (interaction, $P >$ .05; Table 2). Daily fluctuations in insulin (Fig. 1), leptin (Fig. 2), ghrelin (Fig. 3), and triglycerides (Fig. 4) are shown in Figs. 1–4.

There were no differences among the groups in dietary intake at baseline. Study participants failed to completely accommodate the calories from the low-fat, sugar-sweetened milk as evidenced by an overall increase in energy intake over the course of 10 weeks, as shown in Table 3. This increase was larger in sucrose 30% than in HFCS 8% and larger in HFCS 30% than in both 8% groups. There was also a greater increase in the proportion of calories that came from carbohydrates in both 30% groups compared with sucrose 8%, but not when compared with HFCS 8%. The sucrose 8% group also showed a smaller decrease in the proportion of calories from fat compared with both the sucrose 18% and HFCS 30% groups.

4. Discussion

This study compared the metabolic effects of 3 different levels of sucrose and HFCS-55 under randomized, controlled, blinded conditions in men and women between the ages of 20 and 60 years. The two, 1-day experimental visits to our metabolic units were separated by 10 weeks of free living where individuals consumed 8%, 18%, or 30% of calories in a eucaloric, mixed nutrient diet. This study confirmed our hypothesis that there would be no difference between HFCS and sucrose with regard to effects on energy-regulating hormones and that these values would not change over a 10-week free-living period at these consumption levels. These findings provide further validation of the acute findings that our research team published related to the equivalence of HFCS and sucrose when delivered at average population levels for a 24-hour period [7]. These findings also provide further information concerning the difference between results when comparing the commonly consumed sugars of HFCS and sucrose as compared with the more artificial condition of pure fructose vs pure glucose where differences in energy-regulating hormones have been demonstrated. In addition, these findings provide evidence contrary to what Maersk et al [29], Ventura et al [17], and Goran et al [18] have speculated that the additional 10% of fructose in HFCS-55 might make metabolic differences when compared with sucrose.

It has been argued that HFCS and sucrose may behave differently in metabolism and physiology. There are 2 components of this argument. First, people argue that the bond between glucose and fructose in sucrose may make it behave differently when it is compared with HFCS where fructose and glucose are not bonded together. However, White and others [15] have argued that the bond between fructose and glucose in sucrose is rapidly broken by the sucrase enzyme in the small intestine, and thus, HFCS and sucrose are both absorbed in an identical fashion as fructose and glucose. Second, it has been argued by Goran and others [18] that the 10% difference in fructose may be caused by differences in metabolism between HFCS and sucrose. Our data do not support this speculation.

The 24-hour postprandial hormone profiles (insulin, leptin, ghrelin) and metabolic substrates (glucose, triglyceride, uric acid) were not significantly different between HFCS- and sucrose-sweetened milk at 3 different consumption levels

Table 1 – Participant characteristics						
	Entire cohort (n = 138)	HFCS 8% (n = 20) [a]	Sucrose 8% (n = 25)	HFCS 18% (n = 26)	Sucrose 18% (n = 23)	HFCS 30% (n = 23)	Sucrose 30% (n = 21)
Age (y)	38.3 ± 11.3	39.1 ± 11.8	32.8 ± 10.7	38.7 ± 10.9	40.2 ± 10.4	42.2 ± 11.5	37.2 ± 12.5
Weight (kg)	79.3 ± 13.5	79.6 ± 13.8	82.2 ± 15.0	78.6 ± 12.8	80.1 ± 14.0	77.5 ± 12.3	75.5 ± 12.6
BMI (kg/m^2)	27.4 ± 3.5	28.2 ± 3.9	28.2 ± 3.9	27.7 ± 3.4	26.6 ± 3.3	27.8 ± 3.5	25.9 ± 3.5
Systolic blood pressure (mm Hg)	110.1 ± 9.3	106.6 ± 8.9	111.3 ± 8.7	110.4 ± 7.7	108.6 ± 8.8	113.4 ± 10.0	109.2 ± 9.9
Diastolic blood pressure (mm Hg)	72.9 ± 7.4	70.2 ± 6.9	72.2 ± 7.3	73.4 ±7.7	83.2 ± 6.2	75.0 ± 9.0	72.1 ± 6.3
Glucose (mmol/L)	4.9 ± 0.4	4.9 ± 0.3	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.3	4.9 ± 0.3

Values are means ± SD.

[a] Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% of calories, respectively.

| Table 2 – Baseline dietary intake before beginning 10 weeks of daily consumption of sugar-sweetened, low-fat milk [a]						
	Entire cohort (n = 138)	HFCS 8% (n = 20)	Sucrose 8% (n = 25)	HFCS 18% (n = 26)	Sucrose 18% (n = 23)	HFCS 30% (n = 23)	Sucrose 30% (n = 21)
Energy intake (kcal)	2102.3 ± 689.0	2142.9 ± 738.5	2245.9 ± 605.3	2066.0 ± 591.6	2079 ± 642.8	1838.5 ± 581.8	2292.5 ± 957.5
% Energy from fat	32.4 ± 7.0	30.7 ± 5.8	30.2 ± 6.5	33.3 ± 6.8	35.2 ± 6.8	34.4 ± 7.0	30.3 ± 8.3
% Energy from carbohydrate	48.0 ± 8.0	48.2 ± 7.1	48.6 ± 7.8	46.2 ± 8.2	47.7 ± 7.1	48.1 ± 8.6	50.0 ± 9.4
% Energy from protein	18.3 ± 5.1	19.1 ± 5.2	19.7 ± 6.5	19.4 ± 5.1	15.8 ± 2.5	16.7 ± 4.6	18.7 ± 5.2
Saturated fat (g)	25.8 ± 12.3	24.6 ± 10.3	26.2 ± 11.2	26.5 ± 12.9	29.1 ± 16.5	24.0 ± 10.5	24.5 ± 13.0
Total fiber (g)	18.9 ± 8.9	18.9 ± 7.3	18.7 ± 5.8	16.8 ± 9.0	17.9 ± 6.5	17.5 ± 11.2	24.4 ± 11.2

Values are means ± SD.

[a] Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% of calories respectively.

after 10 weeks. This finding is consistent with the previous research published by our group, in which the acute metabolic effects of sucrose and HFCS consumption at 30% of energy on circulating glucose, insulin, leptin, and ghrelin were compared in normal-weight women [7] and found to be virtually identical. In another study, 24-hour AUC response of glucose, leptin, and ghrelin during the consumption of HFCS-sweetened beverages were not significantly different from those when sucrose-sweetened beverages were consumed and when participants have included overweight and obese population and men [9]. The current study provided evidence for the equivalent metabolic response between HFCS and sucrose

after long-term (10-week) consumption of HFCS- and sucrose-sweetened beverages at 3 different dosage levels within the reference range of human consumption for added fructose.

Fructose's metabolism through energy regulatory hormones has been proposed as a possible mechanism to explain trends in HFCS consumption and obesity. Fructose does not stimulate insulin secretion from pancreatic islets [30]. Of particular importance, insulin may play a pivotal role in the sequence of events that lead to increased satiety with the ingestion of most carbohydrates [31]. As such, elevated blood glucose and, subsequently, increased circulating insulin can amplify satiety through actions in the central nervous system
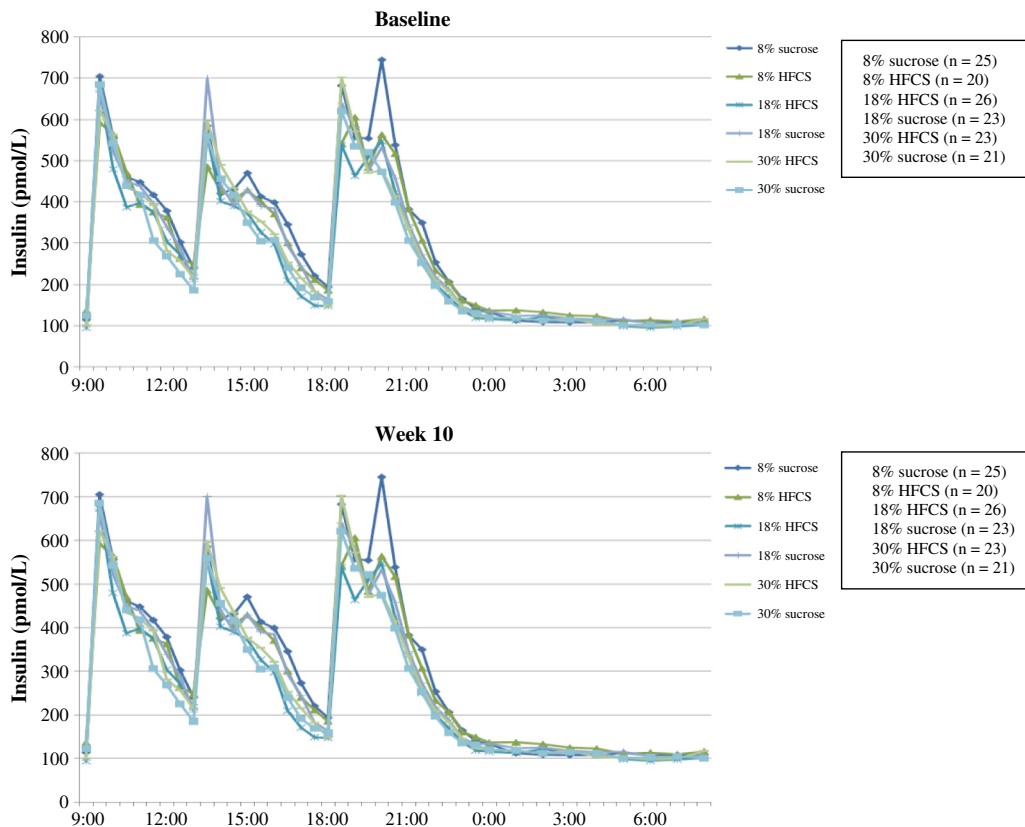
Fig. 1 – Fluctuation of insulin throughout the day before and after the study. There were no differences among 6 different intervention groups at baseline or posttesting (interaction, $P > .05$). In the entire cohort, AUC insulin increased over the course of the intervention ($P < .05$), but there was no difference among the groups (interaction, $P > .05$). All measurements represent averages at each time point for all participants in each condition. Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% calories, respectively.
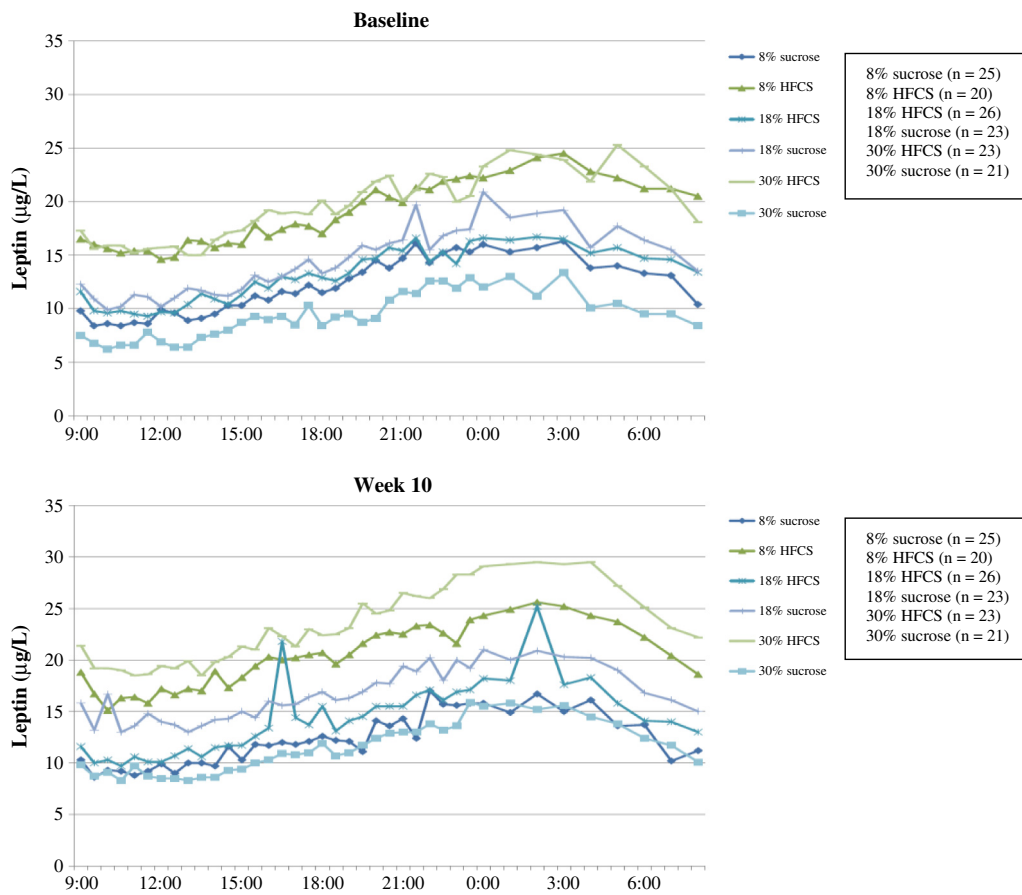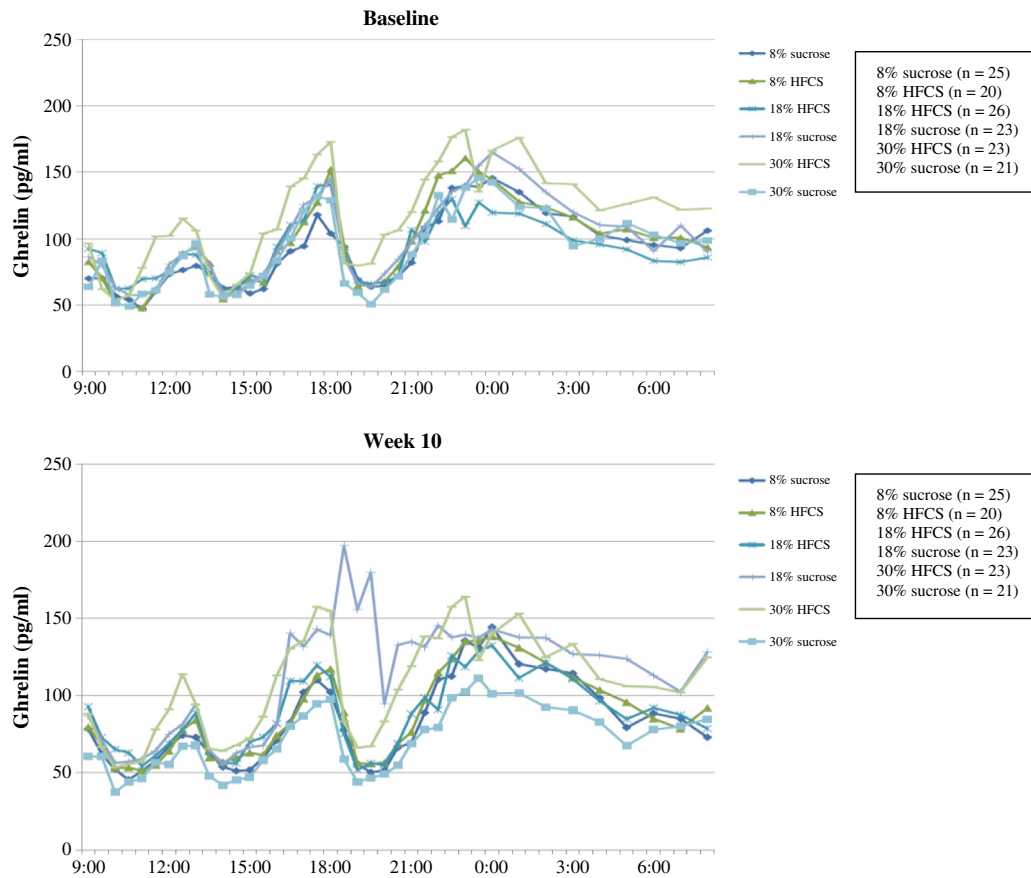
Fig. 2 – Fluctuation of leptin throughout the day before and after the study. There were no differences among 6 different intervention groups at baseline or posttesting (interaction, P > .05). In the entire cohort, AUC leptin increased over the course of the intervention (P < .001), but there was no difference among the groups (interaction, P > .05). All measurements represent averages at each time point for all participants in each condition. Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% calories, respectively.

[32,33], or by stimulating leptin synthesis and secretion [34]. The lack of differences in leptin response among groups observed in this study is not surprising because of similar responses in plasma glucose in the postprandial state.

A number of epidemiologic studies have reported an association between sugar-sweetened beverage consumption and increased energy intake and obesity in children and adults [35-37]. One recent meta-analysis evaluated 88 cross-sectional and prospective studies and that higher intake of sugar-sweetened beverages was associated with greater body weight, greater energy intake, and lower intake of other nutrients [38]. Because weight gain, overweight, and obesity represent complicated metabolic conditions, however, it would appear unlikely that a single food or food group is primarily causal [39,40]. In contrast, several meta-analyses and literature reviews have reviewed clinical trials and concluded that fructose intake, even up to the 95th percentile population consumption level of fructose, was not associated with increased likelihood of obesity [41,42]. A recent systematic review and meta-analysis by Sievenpiper and colleagues [43] suggested that fructose did not seem to cause weight gain when it was substituted for other carbohydrates in diets providing similar calories. In contrast, when

fructose was supplied at high doses providing excess calories, a modest increase in the body weight occurred. These investigators speculated that this effect may be caused by the added extra calories rather than the fructose per se [43]. The current study appears to add additional credence to the concept that isocaloric substitution of fructose-containing sugars in up to the 90th percentile of consumption levels for fructose does not create a hormonal environment that would promote the likelihood of obesity.

In the current study, there were no differences in glucose, insulin, leptin, or ghrelin when consumed at 8%, 18%, or 30% of calories in a mixed nutrient diet. Furthermore, there were no differences in any of these parameters when comparing acute measurements at the beginning or the trial and after the 10 weeks of free living where individuals consumed these various levels of sugars. To put this in perspective, the 8% consumption of calories from added sugars (40 g of added sugar in a 2000-kcal diet) represents the 25th percentile population consumption level for fructose and is approximately the upper level amount of calories from added sugars recommended by the AHA not to be exceeded by adult men (the recommendation for adult women is even lower). The 18%
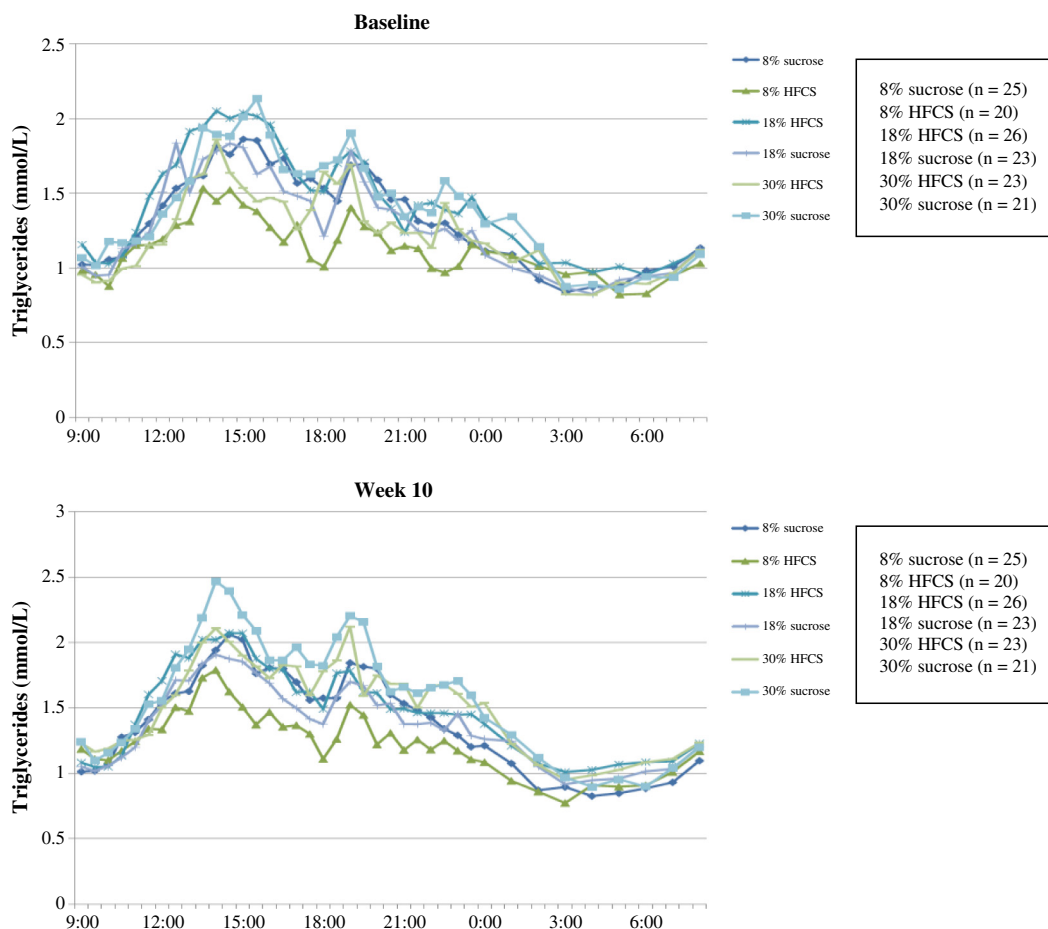
Fig. 3 – Fluctuation of active ghrelin throughout the day before and after the study. There were no differences among 6 different intervention groups at baseline or posttesting (interaction, P > .05). There was no change in AUC active ghrelin in the entire cohort (P > .05), and there was no difference among the groups (interaction, P > .05). All measurements represent averages at each time point for all participants in each condition. Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% calories, respectively.

consumption of calories from added sugars (90 g of added sugar in a 2000-kcal diet) in the current study represents 2 to 3 times the upper limit recommended by the AHA, whereas the 30% consumption of calories from added sugars (150 g of added sugar in a 2000-kcal diet) in the current study represents approximately 4 times the upper limits recommended by the AHA [3] and is similar to the upper limit of 25% established by the Institute of Medicine in the Dietary Reference Intakes for carbohydrates [4]. It should also be noted that there were no differences between HFCS and sucrose in any parameter at any dosage level. Our data are consistent with the systematic review and meta-analysis of controlled feeding trials published by Cozma et al [44], which concluded that isocaloric exchange of fructose for other carbohydrates improved long-term glycemic control without effecting insulin in people with diabetes.

Diabetes Associations have typically taken the approach of setting an upper threshold of the intake of fructose or fructose-containing sugars based on potential adverse effects on serum lipids. The American Diabetes Association [45] guidelines acknowledge that fructose produces a lower glycemic response in individuals with diabetes and replaces sucrose and starch in the diet. However, it does not provide

specific recommendations about sugar consumption other than to state that the "mix of carbohydrate, protein and fat may be adjusted to meet the metabolic goals and individual preferences of the person with diabetes." The British Diabetes Association [46], European Association for the Study of Diabetes [47], and Canadian Diabetes Association [48] all have various recommendations for optimal diet in people with type 2 diabetes. However, these recommendations focus on the percentage of calories from carbohydrates, protein, and fat without specific recommendations for dietary sugars.

It has been postulated that excessive consumption of fructose can result in increased blood pressure through the metabolism of adenosine triphosphate to adenosine monophosphate and, ultimately, to uric acid [16]. Uric acid is postulated to contribute to endothelial dysfunction, which could ultimately result in increased blood pressure [16]. In the current study, there were no differences in uric acid in response to any of the conditions or either of the added sugars. Most of the previous research done in this area has explored fructose delivered in boluses by itself, in large quantities, or in animal models. Our data would suggest that increases in uric acid do not occur when fructose and glucose are consumed together at normal population consumption levels. Our data are also

Fig. 4 – Fluctuation of triglyceride throughout the day before and after the study. There were no differences among 6 different intervention groups at baseline or posttesting (interaction, P > .05). In the entire cohort, AUC triglyceride increased over the course of the intervention (P < .01), but there was no difference among the groups (interaction, P > .05). All measurements represent averages at each time point for all participants in each condition. Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% calories, respectively.

consistent with the systematic review and meta-analysis of controlled feeding trials published by Wang et al [49], which did not find support for uric acid increasing the effects of isocaloric dose intake in nondiabetic or diabetic participants.

It has also been argued that fructose consumption can result in an increased triglyceride production through the process of de novo lipogenesis [13]. It has been further argued

that this process may be exacerbated when fructose and glucose are consumed together because glucose enters the glycogenetic pathway, leaving fructose only the de novo lipogenesis pathway [29,30]. Although these qualitative differences may occur, it is not clear whether the quantity of lipids produced through de novo lipogenesis is meaningful in the overall energy economy. In the current study, there were no

	Entire cohort (n = 138)	HFCS 8% (n = 20)	Sucrose 8% (n = 25)	HFCS 18% (n = 26)	Sucrose 18% (n = 23)	HFCS 30% (n = 23)	Sucrose 30% (n = 21)
Energy intake (kcal)	333.1 ± 662.8 ***	−67.0 ± 520.8	55.2 ± 785.0	416.9 ± 542.9 **	280.3 ± 566.5	716.6 ± 566.5 ***	552.9 ±661.7 **
% Energy from fat	−8.0 ± 8.3 ***	−5.1 ± 5.2 **	−2.9 ± 6.8	−7.5 ± 9.9 **	−11.5 ± 7.9 ***	−11.6 ± 8.1 ***	−9.7 ± 7.3 ***
% Energy from carbohydrate	2.4 ± 7.1 ***	5.3 ± 7.6 **	2.4 ± 7.1	9.7 ± 12.0 **	10.2 ± 9.7 ***	10.9 ± 9.5 ***	11.6 ± 9.6 ***
% Energy from protein	0.8 ± 4.7 *	1.2 ± 6.0	2.0 ± 4.6	−1.2 ± 4.9	2.4 ± 2.4	1.6 ± 4.8	−0.8 ± 4.2

Table 3 – Changes in energy and macronutrient intake (before-after) over the course of 10 weeks of daily consumption of sugar-sweetened, low-fat milk [a]

Values are means ± SD.
[a] Beverages included HFCS- or sucrose-sweetened low-fat milk supplying 8%, 18%, or 30% of calories, respectively.
  * Significant change from baseline, P < .05.
 ** Significant change from baseline, P < .01.
*** Significant change from baseline, P < .001.

differences between any dosage of either HFCS of sucrose with regard to postprandial triglycerides. The expected increase in triglycerides occurred after every eating occasion, but no differences were found among 3 different levels of added sugars. The slight rise in fasting triglycerides has been observed after higher carbohydrate diets, particularly with simple sugars, and merits further investigation [19]. It should be noted that added sugars were provided in low-fat milk in the current study. Thus, the effects of the supplemental proteins in the milk might have interfered with the effects of the sugar and reduced triglyceride excursions. It has been reported that patients on protein supplement can decrease intrahepatic lipids and alter lipoprotein kinetics [50-52]. The use of low-fat milk as a delivery vehicle for the various sweeteners represents an additional limitation because providing groups with different amounts of vitamin D may have impacted on results.

Strengths of the current study include the relatively large sample size and the tight control over both acute and free-living diet consumptions. Weaknesses include the high dropout rate and perhaps the decision not to include adolescents, which is the highest sugar-sweetened beverage consumption group in the United States. It should also be noted that this study was conducted for a 10-week period. It is possible that a longer exposure to these levels of sugars might impact on the results. Furthermore, fructose could not be directly measured, which should be taken into consideration in interpreting these results.

The finding that HFCS and sucrose at 3 different levels of normal human consumption up to the 90th percentile consumption of fructose behave similarly with regard to energy-regulating hormones and that there are no differences between the 3 different doses and no changes over 10-weeks provides evidence that speculation that there may be differences between HFCS and sucrose does not appear to apply to normal human consumption levels. This isocaloric trial provides further evidence that fructose and glucose supplied together do not create a hormonal environment that would promote obesity. This finding is consistent with systematic analyses and meta-analyses published by Sievenpiper and colleagues [43]. These findings provide further evidence that calories consumed appear to be more important in promoting obesity than any particular kind of carbohydrate consumed.

The current study suggests that the strategy of significantly restricting sugar-sweetened beverages as a component of an overall strategy to combat obesity may not rest on any solid research basis. Furthermore, longer-term trials to resolve this issue appear warranted.

Acknowledgment

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