Energy Expenditure and Hormone Responses in Humans After Overeating High-Fructose Corn Syrup Versus Whole-Wheat Foods

Mostafa Ibrahim*, Susan Bonfiglio*, Mathias Schlögl1,2, Karyne L. Vinales1, Paolo Piaggi1, Colleen Venti1, Mary Walter3, Jonathan Krakoff1, and Marie S. Thearle1

Objective: This study sought to understand how the dietary source of carbohydrates, either high-fructose corn syrup (HFCS) or complex carbohydrates, affects energy expenditure (EE) measures, appetitive sensations, and hormones during 24 hours of overfeeding.

Methods: Seventeen healthy participants with normal glucose regulation had 24-hour EE measures and fasting blood and 24-hour urine collection during four different 1-day diets, including an energy-balanced diet, fasting, and two 75% carbohydrate diets (5% fat) given at 200% of energy requirements with either HFCS or whole-wheat foods as the carbohydrate source. In eight volunteers, hunger was assessed with visual analog scales the morning after the diets.

Results: Compared with energy balance, 24-hour EE increased 12.8% ± 6.9% with carbohydrate overfeeding (P < 0.0001). No differences in 24-hour EE or macronutrient utilization were observed between the two high-carbohydrate diets; however, sleeping metabolic rate was higher after the HFCS diet (Δ = 35 ± 48 kcal [146 ± 200 kJ]; P = 0.01). Insulin, ghrelin, and triglycerides increased the morning after both overfeeding diets. Urinary cortisol concentrations (82.8 ± 35.9 vs. 107.6 ± 46.9 nmol/24 h; P = 0.01) and morning-after hunger scores (Δ = 2.4 ± 2.0 cm; P = 0.01) were higher with HFCS overfeeding.

Conclusions: The dietary carbohydrate source while overeating did not affect 24-hour EE, but HFCS overconsumption may predispose individuals to further overeating due to increased glucocorticoid release and increased hunger the following morning.

Obesity (2018) 26, 141-149. doi:10.1002/oby.22068

Introduction

Ingestion of added sugars is prevalent in the United States despite nutritional guidelines recommending against this practice (1). Routine carbohydrate overconsumption is likely secondary to the wide availability of easily prepared food products (2,3); however, episodes of massive overeating most likely occur only intermittently and for a single day, such as a holiday or a celebratory event. Associations between the source of carbohydrate consumed and body weight regulation have been hypothesized (4-6). Increasing the proportion of simple or complex carbohydrates in the diet reportedly does not produce significant weight change or alter metabolic risk profiles (5); however, others have reported that a diet with a high proportion of simple sugars causes adverse effects (7-10), while a more recent study showed an improvement in many metabolic parameters with 9-day fructose restriction in children with obesity and metabolic syndrome (11). Whether overconsumption of simple sugars is more detrimental than overeating more complex carbohydrates is unknown.

In the Lifestyle Heart Trial, participants ate a low-fat vegetarian diet high in carbohydrates consisting of primarily vegetables and whole...
grains, and although the experimental group participants reported the same caloric intake as controls, their weight decreased 10 kg (12). Although this effect may be due, in part, to an increase in physical activity, it is possible there is also an effect of diet on energy expenditure (EE). Epidemiologic studies have indicated that an increasing percentage of high-fructose corn syrup (HFCS) in diets correlates with higher energy intake, increased body weight, and increased risk of metabolic and cardiovascular disorders (10). However, fructose is also reported to have a higher obligatory cost of metabolism, acutely increasing diet-induced thermogenesis (DIT) by approximately 2% more than glucose and promoting carbohydrate oxidation and suppressing lipid oxidation to a greater degree than glucose (13). Most of the studies assessing differences between carbohydrate sources on EE have been done over 6 hours, but a longer observation of at least 24 hours may be needed to assess the full effect on EE. It is known that overconsuming carbohydrates, especially fructose, can increase triglycerides and uric acid concentrations (7,8), but acute effects of 1 day of overeating carbohydrates on appetitive and anabolic hormones are not as clear.

Many studies have investigated differences solely between pure fructose and glucose (13-17), but studies with direct comparison of common, readily available, similarly prepared diets, only varying in carbohydrate source, are lacking. In addition, the overall effects of carbohydrate overconsumption for 24 hours have not been well studied. This study investigated whether dietary source of carbohydrates, HFCS versus not, in readily available, easily prepared foods during 24 hours of overeating 200% of energy requirements would differentially impact EE, macronutrient utilization, appetitive and anabolic hormones, or appetite.

**Methods**

**Subjects**
Seventeen healthy adults older than 18 years of age with no evidence of acute or chronic illness, as assessed by history, physical, electrocardiogram, and laboratory measures, participated in this study between 2011 and 2013, which was a smaller study within a larger study designed to examine the effects of overfeeding on EE (NCT00523627), as previously described (18). All subjects provided informed consent; the study protocol was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Each subject completed all procedures while residing in the clinical research unit (CRU) of the NIDDK in Phoenix, Arizona, for approximately 18 days. Normal glucose regulation, as assessed by a 75-g oral glucose tolerance test (19), was an inclusion criterion. Body composition was measured by dual-energy x-ray absorptiometry (Prodigy; GE Lunar Corp., Madison, Wisconsin).

**Diets**
Upon admission, subjects were placed on a weight-maintaining diet (50%, 30%, and 20% of daily energy provided as carbohydrate, fat, and protein, respectively) using unit-specific equations as previously described (20). All subjects underwent five separate 24-hour EE measurements while residing in a whole-room indirect calorimeter (see “EE”) with four distinct diets: twice with a eucaloric diet to increase measurement precision (21) plus three intervention diets. Energy needs for the first eucaloric measurement were calculated as 80% of the weight-maintaining diet to account for restricted activity

| TABLE 1 Characteristics of the two high-carbohydrate (75%) overfeeding diets based on a sample diet of 4,000 kcal (16,736 kJ) |
|---|---|---|---|---|---|
| | HFCS | Whole wheat | | | |
| Breakfast, kcal (kJ) | 851 (3,561) | 672 (2,812) | | | |
| Lunch, kcal (kJ) | 1,161 (4,858) | 1,158 (4,845) | | | |
| Dinner, kcal (kJ) | 809 (3,361) | 1,036 (4,335) | | | |
| Snack, kcal (kJ) | 1,009 (4,222) | 1,009 (4,222) | | | |
| Total weight, g | 3,913 | 4,766 | | | |
| CHO, g | 733 | 4,766 | | | |
| C12:0, g | 976 | 740 | | | |
| Fiber, g | 69 | 72 | | | |
| Energy density, kcal/g (kJ/g) | 1.02 (4.27) | 0.84 (3.51) | | | |
| % of food items containing HFCS | 0.01 | 0.00 | | | |
| % of food served warm | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
| % of protein provided as animal protein | 19.6 | 72 | | | |
| % of protein provided as animal protein | 61.4 | 61.4 | | | |
in the calorimeter; energy intake for the second eucaloric diet was equal to the individual’s 24-hour EE measure from the first assessment. The second eucaloric assessment was the baseline comparator, as subjects were in energy balance (EB). Using a crossover design with intervention diets given in random order, subjects underwent a fasting assessment in which only water was provided and two overfeeding diets consisting of 75% carbohydrates (20% protein, 5% fat) with a caloric content equal to twice EE measured during EB. Subjects were not blinded to the diet received. Each diet was separated by 3 days, during which the subject remained on the CRU. The two high-carbohydrate diets consisted of readily available, easily prepared foods, including rice and beans, and were more likely to be labeled as “natural” or “multigrain.” Foods in the high-carbohydrate diets were matched except for these ingredients, e.g., buttermilk pancakes and white bread versus multigrain waffles and whole-wheat bread. The selection of WW foods was intended to mimic purchasing healthier options. Macronutrient composition of diets was determined using Food Processor Nutrition Analysis software (ESHA Research, Salem, Oregon). All subjects consumed more than 95% of all diets. There was a 3-day washout period between dietary interventions in which subjects consumed the weight-maintaining diet and resided in their room on the CRU. The average coefficient of variation of the subjects’ body weight taken the mornings before beginning dietary interventions was 0.99% ± 0.59%.

Beginning in 2012, subjects completed a visual analog scale (VAS) the morning after each diet to assess hunger-related characteristics by indicating on a Likert scale (0-10 cm) how hungry they felt, their desire to eat, how much food they would like to consume, and how preoccupied they were with thoughts of food (n = 8). No EE, anthropometric, or demographic variables differed between these eight subjects and the larger group.

### EE
During each dietary intervention, 24-hour EE and sleeping measurements were assessed by using whole-room indirect calorimetry, as previously described (21). Ambient temperature averaged 24.6°C ± 1.1°C. Sleeping metabolic rate (SMR), calculated as the average EE between 2330 and 0530 when movement measured by radar sensors was less than 1.5% (< 9 s/min), was extrapolated to an 8-hour time period. DIT was calculated as 24-hour EE during fasting subtracted from 24-hour EE during feeding. The 24-hour EE unadjusted for physical activity is presented because there were no differences in activity, assessed by radar sensors, between dietary assessments (P = 0.15). The RQ was calculated using the nonprotein respiratory quotient (RQ) (i.e., the ratio of carbon dioxide to oxygen consumption) was calculated after subtracting carbon dioxide and oxygen consumption attributable to protein oxidation determined from the 24-hour urinary nitrogen excretion. Carbohydrate and fat oxidation was calculated from the nonprotein RQ as previously described (22).

### Assays
Fasting morning plasma was collected both at entry and exit from the calorimeter and stored for batched assessment of hormone concentrations by the Clinical Core Lab of the NIDDK. In addition, fasting blood was immediately sent for assessment of triglycerides, uric acid, aspartate transaminase, and alanine aminotransferase by using standard clinical assays from the local laboratory, and fasting insulin concentrations were assessed by using an automated immunoenzymometric assay (Tosoh Bioscience Inc., Tewksbury, Belgium). Urine was collected for 24 hours during each dietary intervention.

---

**TABLE 2 Characteristics of the study population, including energy expenditure measures during energy balance**

|                        | Whole population (n = 17) | Men (n = 13) | Women (n = 4) |
|------------------------|--------------------------|-------------|--------------|
| Ethnicity              | 4 Black, 5 White, 8 Native American | 3 Black, 3 White, 7 Native American | 1 Black, 2 White, 1 Native American |
| Age (y)                | 41.2 ± 0.90 (20.9, 54.1) | 42.4 ± 0.84 (20.9, 54.1) | 37.1 ± 0.10 (20.9, 44.3) |
| Weight (kg)            | 77.3 ± 12.3 (51.4, 107.5) | 79.9 ± 19.7 (62.2, 98.3) | 76.5 ± 10.1 (61.4, 107.5) |
| BM (kg/m²)             | 26.3 ± 3.8 (21.1, 39.2) | 25.4 ± 2.1 (21.1, 29.3) | 29.3 ± 6.8 (24.9, 39.2) |
| Body fat (%)*          | 30.4 ± 10.2 (11.9, 50.5) | 25.8 ± 6.2 (11.9, 37.9) | 45.2 ± 4.8 (40.4, 50.5) |
| Fat-free mass (kg)*    | 53.3 ± 8.4 (31.9, 66.3) | 54.6 ± 5.6 (46.9, 66.3) | 33.5 ± 8.8 (31.9, 53.2) |
| Fasting glucose (mmol/L)| 5.3 ± 0.2 (4.8, 5.5) | 5.3 ± 0.1 (5.0, 5.5) | 5.1 ± 0.2 (4.8, 5.4) |
| 2-h glucose (mmol/L)   | 6.0 ± 1.2 (3.2, 7.4) | 6.3 ± 1.1 (3.2, 7.4) | 5.5 ± 1.2 (4.5, 7.2) |
| Fasting insulin (pmol/L)| 54.9 ± 33.3 (22.9, 167.4) | 47.2 ± 16.0 (22.9, 76.4) | 76.4 ± 62.5 (27.8, 167.4) |
| Triglycerides (mmol/L) | 1.3 ± 1.2 (0.3, 4.8) | 1.3 ± 1.3 (0.3, 4.8) | 1.3 ± 1.2 (0.3, 4.8) |
| EE (kcal/24 h) [MJ/24 h]| 1,948 ± 269 (1,383, 2,328) | 1,998 ± 240 (1,607, 2,328) | 1,787 ± 332 (1,383, 2,156) |
| SMR (kcal/8 h) [MJ/8 h]| [8.15 ± 1.13 (5.79, 9.74)] | [8.36 ± 1.00 (6.72, 9.74)] | [7.48 ± 1.39 (5.79, 9.02)] |
| RQ (ratio)             | 0.89 ± 0.03 (0.83, 0.93) | 0.89 ± 0.02 (0.86, 0.93) | 0.88 ± 0.04 (0.83, 0.92) |
| Energy balance (kcal/24 h) [MJ/24 h]| 63 ± 78 (−29, 130) | 63 ± 86 (−29, 130) | 61 ± 54 (3, 125) |

Data presented as mean ± SD (minimum, maximum). *Indicates P < 0.05 for difference between males and females as assessed by Student t test. RQ, respiratory quotient; SMR, sleeping metabolic rate; EE, energy expenditure; MJ, megajoule.
Serum ghrelin, active glucagon-like peptide 1, and insulinlike growth factor 1 (IGF-1) were measured by using enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Minneapolis, Minnesota). Adiponectin, C-reactive protein, fibroblast growth factor 21 (FGF21), leptin, pancreatic polypeptide, and peptide YY were measured by using Luminex assays (R&D Systems; Millipore, Billerica, Massachusetts). Urinary free cortisol (UFC) concentrations were measured by using ELISAs (Cayman Chemical Company, Ann Arbor, Michigan).

### Statistical analysis

Statistical analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina). Alpha was set as 0.05. Assuming an expected increase in 24-hour EE of 288 ± 116 kcal (1,205 ± 485 kJ; 14.4% ± 5.8%) when overfeeding using a diet with 75% carbohydrate (21), a sample size of 17 provides greater than 80% power to detect an absolute difference of 100 kcal (418 kJ; 4%) between the two dietary interventions using a paired t test.

All results are presented as the mean ± SD, except for fasting insulin, which was not normally distributed and is presented as the median and interquartile range. EE changes with overfeeding and fasting are expressed as a percentage of the EE during EB (i.e., EE

| Table 3 Energy expenditure measurements during 200% overfeeding with diets containing either primarily whole wheat or high-fructose corn syrup |
|----------------------------------------------------------|---------|----------------|---------------------------------|-------------------|
| **Intake (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 2,011 ± 252 (1,508, 2,310) | 3,799 ± 472 (2,719, 4,412) | 3,903 ± 561 (2,663, 4,656) | 0.1 |
| 41.9 ± 6.3 (31.6, 9.6) | 15.90 ± 1.91 (11.38, 18.46) | 16.33 ± 2.35 (11.14, 19.49) | |
| **EE (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 1,948 ± 269 (1,383, 2,328) | 2,187 ± 323 (1,388, 2,561) | 2,209 ± 311 (1,383, 2,608) | 0.5 |
| 8.15 ± 1.13 (5.79, 9.74) | 9.15 ± 1.35 (5.81, 10.72) | 9.24 ± 1.30 (5.79, 10.91) | |
| **NPRQ** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 0.92 ± 0.04 (0.84, 0.97) | 1.0 ± 0.06 (0.90, 1.10) | 0.99 ± 0.07 (0.84, 1.09) | 0.2 |
| **SMR (kcal/8 h) [MJ/8 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 517 ± 65 (358, 579) | 560 ± 90 (355, 706) | 595 ± 96 (355, 740) | 0.007 |
| 14.76 ± 2.07 (1.70, 2.42) | 2.34 ± 0.38 (1.49, 2.95) | 2.49 ± 0.40 (1.49, 3.10) | |
| **DIT (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 14.6 ± 77 (2, 306) | 384 ± 146 (134, 567) | 404 ± 145 (129, 680) | 0.5 |
| 0.61 ± 0.32 (0.01, 1.28) | 1.61 ± 0.61 (0.56, 2.37) | 1.70 ± 0.61 (0.54, 2.85) | |
| **Carbohydrate oxidation (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 1,126 ± 240 (721, 1,466) | 1,760 ± 480 (1,050, 2,447) | 1,692 ± 470 (681, 2,311) | 0.4 |
| 4.71 ± 1.00 (3.02, 6.13) | 7.36 ± 2.01 (4.39, 10.24) | 7.04 ± 1.97 (2.85, 9.67) | |
| **Lipid oxidation (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 426 ± 211 (106, 844) | 13 ± 339 (−499, 652) | 79 ± 392 (−460, 856) | 0.2 |
| 1.78 ± 0.88 (0.44, 3.53) | 0.05 ± 1.42 (−2.09, 2.73) | 0.33 ± 1.64 (−1.92, 3.58) | |
| **Protein oxidation (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| 369 ± 94 (42, 441) | 384 ± 143 (61, 674) | 409 ± 101 (229, 598) | 0.5 |
| 1.54 ± 0.38 (0.18, 1.85) | 1.61 ± 0.60 (0.26, 2.82) | 1.71 ± 0.42 (0.96, 2.50) | |
| **Carbohydrate balance (kcal/24 h) [MJ/24 h]** | **WW diet (n = 17)** | **HFCS diet (n = 17)** | **P, ΔHFCS-WW** |
| −119 ± 202 (−423, 285) | 1,029 ± 340 (408, 1,841) | 1,172 ± 371 (521, 1,782) | 0.052 |
| −0.50 ± 0.85 (−1.77, 1.19) | 4.31 ± 1.42 (1.71, 7.70) | 4.90 ± 1.55 (2.18, 7.46) | |

All 17 subjects consumed all diets. Data presented as mean ± SD (minimum, maximum). P value for ΔHFCS-WW determined by using paired t test. *Indicates P < 0.001 for difference between both overfeeding diets and energy balance as assessed by one-way ANOVA followed by Dunnett’s test to control for multiple comparisons.

DIT, diet-induced thermogenesis; EE, energy expenditure; HFCS, high-fructose corn syrup overfeeding diet; NPRQ, nonprotein respiratory quotient; SMR, sleeping metabolic rate; WW, whole-wheat flour overfeeding diet; MJ, megajoule.
Metabolic consequences

There were no increases in uric acid or liver function tests (aspartate transaminase, alanine aminotransferase) the morning after high-carbohydrate overfeeding. However, insulin, ghrelin (Table 4), and triglycerides increased after both overfeeding diets (triglycerides: WW: 1.06 ± 0.85 vs. 1.46 ± 0.88 mmol/L [94 ± 75 vs. 129 ± 78 mg/dL]; P < 0.0001; HFCS: 1.18 ± 0.90 vs. 1.36 ± 0.97 mmol/L [104 ± 80 vs. 120 ± 86 mg/dL]; P = 0.006). The degree of insulin and ghrelin increase did not differ between the two overfeeding diets; however, the increase in triglycerides was greater after the WW diet (Δ = 0.40 ± 0.26 vs. 0.20 ± 0.26 mmol/L [35 ± 23 vs. 18 ± 23 mg/dL]; P = 0.02).

Hormone changes with the dietary interventions are shown in Table 4. No appetite hormones or inflammatory markers differed between the two overfeeding diets. Of all hormones assessed, only the change in IGF-1 and UFC concentrations differed between the two. IGF-1 increased only on the morning after the WW diet (Δ = 0.55 ± 0.26 vs. −0.13 ± 0.26 nmol/L; P = 0.03). This difference between the IGF-1 changes persisted after adjustment for baseline IGF-1, age, sex, and body fat. UFC concentrations were similar among EB, fasting, and overfeeding with the WW diet but were higher during HFCS overfeeding (adjusted ΔHFCs-WW: 32.3 ± 43.9 nmol/24 h; P = 0.01). After adjusting for differences in body fat, no correlations were observed between hormone changes and EE measures with overfeeding. All results were similar if the data set was limited only to men or to those classified as having obesity (23).

VAS data

The morning after the HFCS diet, subjects with VAS data reported greater feelings of hunger (5.2 ± 2.9 vs. 2.7 ± 2.6 cm; P = 0.01) and a stronger desire to eat (5.5 ± 3.2 vs. 3.2 ± 2.4 cm; P = 0.02), and were more preoccupied with thoughts of food (3.9 ± 2.5 vs. 2.0 ± 1.5 cm; P = 0.01) compared with the morning after the WW diet (Figure 2). Although there was no difference in how much food subjects felt they could consume (4.7 ± 2.8 vs. 3.4 ± 2.5 cm; P = 0.1), the overall point estimate was in a direction similar to those of the other hunger variables. In exploratory, bivariate analyses, VAS hunger scores were not correlated with EE, macronutrient oxidation measures, or hormone concentrations, with the exception that both the change in FGF21 and the concurrent (morning after) FGF21 concentrations correlated similarly with all VAS scores (e.g., feelings of hunger: r = 0.6, P = 0.02, Figure 3; r = 0.54, P = 0.03, respectively).

Discussion

The primary purpose of this study was to understand whether choosing foods with whole-grain carbohydrates (i.e., WW) rather than HFCS would differentially impact EE or macronutrient oxidation during 24 hours of overfeeding in subjects with normal glucose regulation. As secondary, exploratory goals, we evaluated the hormone and hunger changes that occur with carbohydrate overfeeding. We found no differences in overall EE, RQ, or DIT between the two overfeeding diets. However, SMR was higher after HFCS consumption. Forty percent of subjects had evidence of net DNL with carbohydrate overconsumption. Insulin, ghrelin, and triglycerides increased with overfeeding regardless of the carbohydrate source; however, the HFCS diet was additionally associated with an increase in UFC and greater hunger ratings the following morning. Although overeating in general should be avoided, if overconsumption does occur, choosing HFCS may lead to increased hunger the following morning, due either to increased sleeping EE, increased cortisol, or an increased sensitivity to ghrelin.

In prior studies, fructose increased EE and carbohydrate oxidation more than glucose but with a smaller insulin increase (13,24). However, these studies only assessed EE for a few hours after a...
## TABLE 4 Hormone and inflammatory marker changes during the dietary interventions

|                       | **HFCS diet (n = 17)** | **WW diet (n = 17)** | **Fasting (n = 17)** |
|-----------------------|------------------------|----------------------|---------------------|
|                       | Before diet  | After diet  | % Change       | Before diet  | After diet  | % Change       | Before diet  | After diet  | % Change       |
| Leptin (pmol/l)       | 469 ± 655    | 457 ± 544    | 6 ± 21%        | 459 ± 612    | 409 ± 439    | 1 ± 15%        | 489 ± 678    | 193 ± 414*   | −75 ± 13%     |
|                       | (87, 2,751)  | (99, 2,162)  | (−33, 50)      | (103, 2,635) | (105, 1,884) | (−28, 30)      | (75, 2,888)  | (7, 1,721)   | (−40, −92)*   |
| Adiponectin (ng/ml)   | 7,144 ± 2,915 | 7,541 ± 2,240 | 13 ± 32%      | 7,653 ± 2,377 | 7,950 ± 2,807 | 4 ± 15%        | 6,976 ± 2,766 | 7,868 ± 2,686 | 17 ± 23%      |
|                       | (2,743, 13,760) | (4,486, 12,322) | (−14, 122)    | (4,615, 13,086) | (4,588, 13,846) | (−36, 26)      | (3,092, 13,080) | (3,769, 14,065) | (−8, 82)*     |
| CRP (nmol/l)          | 21.9 ± 20    | 27.6 ± 30.5  | 16 ± 48%      | 32.4 ± 31.4  | 30.5 ± 26.7  | 16 ± 95%       | 21.0 ± 13.3  | 46.7 ± 53.3*  | 107 ± 106%    |
|                       | (3.8, 130.5) | (−31, 163)   |              | (3.8, 130.5) | (3.8, 114.3) | (−37, 378)     | (2.9, 43.8)  | (2.8, 228.6) | (−33, 420)*   |
| IGF1 (nmol/l)*        | 12.2 ± 3.9   | 12.1 ± 3.5   | −1 ± 6%       | 11.8 ± 3.4   | 12.3 ± 3.5*   | 5 ± 9%         | 12.3 ± 3.4   | 11.4 ± 3.1*   | −7 ± 11%      |
|                       | (7.6, 23.3)  | (7.9, 21.1)  | (−10, 10)     | (8.1, 20.6)  | (8.1, 21.7)   | (−7, 31)*      | (7.6, 22.5)  | (6.9, 18.9)  | (−28, 10)*    |
| FGF21 (pg/ml)         | 335 ± 457    | 372 ± 452    | 15 ± 33%      | 318 ± 441    | 343 ± 495    | 30 ± 124%      | 329 ± 436    | 376 ± 491*    | 14 ± 27%      |
|                       | (78, 1,989)  | (80, 1,940)  | (−33, 128)    | (43, 1,879)  | (56, 2,148)  | (−15, 510)     | (66, 1,868)  | (60, 2,044)  | (−14, 96)*    |
| Insulin (μIU/ml)      | 63*          | 76*          | 27 ± 44%      | 49           | 76*          | 58 ± 71%       | 56           | 35*          | −38 ± 30%     |
|                       | (IQR: 35, 70) | (IQR: 49, 90) | (−24, 133)*   | (IQR: 35, 76) | (IQR: 56, 83) | (−29, 200)*     | (IQR: 35, 90) | (IQR: 21,63) | (−75, 12)*    |
| Ghrelin (pmol/l)      | 6.3 ± 2.2    | 7.1 ± 2.2*   | 15 ± 15%      | 6.5 ± 2.8    | 7.5 ± 2.6*   | 13 ± 34%       | 7.1 ± 3.6    | 6.3 ± 1.3    | −2 ± 19%      |
|                       | (3.8, 12.9)  | (4.8, 13.9)  | (−1, 56)*     | (4.1, 10.4)  | (5.1, 12.5)  | (−57, 107)     | (3.6, 4.4)  | (4.3, 8.9)   | (−60, 33)     |
| GLP-1 (pmol/l)        | 6.5 ± 7.4    | 5.6 ± 5.5    | −3 ± 27%      | 7.2 ± 7.6    | 7.1 ± 7.9    | −2 ± 23%       | 4.3 ± 2.3    | 4.3 ± 2.9    | 1 ± 33%       |
|                       | (1.7, 30.5)  | (2.1, 22.6)  | (−55, 41)     | (1.7, 26.8)  | (1.6, 26.5)  | (−45, 41)      | (1.5, 10.7)  | (2.1, 13.6)  | (−56, 48)     |
| PYY (pmol/l)          | 28.5 ± 16.5  | 28.3 ± 14.0  | 4 ± 36%       | 29.8 ± 10.3  | 30.5 ± 14.8  | 3 ± 45%        | 29.5 ± 13.0  | 20.3 ± 15.5*  | 21 ± 15%      |
|                       | (9.8, 57.0)  | (11.0, 55.8) | (−65, 134)    | (12.0, 47.0) | (7.8, 70.8)  | (−58, 103)     | (14.8, 58.0) | (2.0, 47.3)  | (−98, 147)    |
| PP (pmol/l)           | 10.8 ± 12.2  | 10.8 ± 14.6  | 51 ± 174%     | 9.1 ± 6.9    | 11.0 ± 14.3  | 172 ± 434%     | 7.2 ± 6.5    | 20.6 ± 13.6*  | 434 ± 364%    |
|                       | (1.7, 41.8)  | (1.7, 58.1)  | (−73, 510)    | (1.2, 22.0)  | (6.5, 55.2)  | (−82, 1,558)   | (1.0, 19.4)  | (3.8, 53.1)  | (−80, 1,160)* |

Urinary free cortisol (nmol/24h)*

|                      | Before diet  | After diet  | % Change       |
|----------------------|--------------|-------------|----------------|
|                      | 108.7 ± 47.2 | 41.7, 202.9 | 83.1 ± 35.6    |
|                      | (29.3, 185.5) | (27.6, 142.4) | 86.4 ± 31.5    |

Data presented as mean ± SD (minimum, maximum), except for insulin, which is presented as median (interquartile range [IQR]). Percent change was calculated as: (“After Diet” measure − “Before Diet” measure)/ “Before Diet measure” × 100. Urinary free cortisol was measured from a 24-h urine collection taken during the differing diets. All other concentrations are from fasting blood collections taken the morning before and the morning after the diets.

*Indicates P < 0.05 for change in fasting plasma concentrations before and after the diet as assessed by paired t test and confirmed after adjusting for baseline concentrations in ANCOVA, or that percent change is significantly different than 0%. All significant changes with fasting differed from overfeeding responses with P < 0.001.

Indicates P < 0.05 for differences between hormone response to HFCS and WW diets.

HFCS, high-fructose corn syrup overfeeding diet; WW, whole-wheat flour overfeeding diet; CRP, C-reactive protein; FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide 1; IGF1, insulinlike growth factor 1; PP, pancreatic polypeptide; PYY, peptide YY.
single meal, which may not be sufficient to fully assess the effects of differing diets. Also, many past studies using either pure fructose or glucose (24) or the provided mixed meals (13,25) were not representative of the changes in food preparation that have occurred over past decades. The foods used in our overfeeding diets may be a better indicator of “real-world” differences between choices a consumer might make. In support of our findings, a study assessing the EE effects of overfeeding with a supplemental glucose, sucrose, or fructose drink in women found no differences in carbohydrate oxidation or EE among these three simple sugars (25). Contrary to our findings, a study assessing EE responses to long-term consumption of glucose- versus fructose-sweetened beverages in subjects with overweight found that consuming fructose was associated with reductions in resting EE over a 10-week period (26), so it is possible that longer-term feeding with our diets may result in EE differences. There was no difference in total 24-hour EE, but we did observe a higher SMR after the HFCS diet. DIT was similar during the two diets despite the increased fiber in the WW diet. When subsumed into the total 24-hour EE, the difference in SMR was not enough to
lead to a statistically significant difference in total 24-hour EE in this small group, as the study was only powered to detect 24-hour differences of 100 kcal (418 kJ) or greater. Fructose bypasses the rate-limiting step of glycolysis, allowing for quicker metabolism (27), but synthesis of glycogen from fructose requires more energy than glycogen synthesis from glucose. In our study, the large amount of carbohydrates consumed may still have been undergoing metabolism and storage overnight, such that the increased energy cost of glycogen synthesis from fructose was more evident at that time. The differences in energy content of the final meal may have contributed to the differences in SMR; however, as shown in Figure 1, the separation of EE per minute between the two diets appeared to occur after the DIT of the snack was completed, and that difference was sustained through the night. The positive carbohydrate balance likely resulted in glycogen storage, which ranged from 100 to 460 g/d, consistent with previous literature indicating that the body can accommodate a gain of up to 500 g/d of glycogen during carbohydrate overfeeding (28). The increased SMR was not due to differences in net DNL between diets as the individuals with evidence of net DNL were the same no matter the source of carbohydrates.

For most biomarkers and hormones we assessed, the HFCS and WW overfeeding diets had similar effects. It has been reported that HFCS increases uric acid (29), but in these subjects with normal renal function and normal glucose regulation, we did not observe a change in uric acid the morning after high-carbohydrate overfeeding. However, we did observe the expected (29) increase in triglycerides and insulin concentrations. Surprisingly, the increase in triglycerides was greater after the WW diet. We hypothesize this may indicate that metabolism of the carbohydrates consumed the day before was still ongoing or that the activity of lipoprotein lipase, a key enzyme involved in the removal of triglycerides from plasma (30), was inhibited to a greater degree with the WW diet. As expected, IGF-1 decreased with fasting (31); however, IGF-1 only increased with overfeeding of the WW diet and not with HFCS. The IGF-1 increase was small but may reflect growth hormone responses from the prior day. This would be consistent with a greater inhibition of lipoprotein lipase during the WW diet, as growth hormone inhibits lipoprotein lipase (32). Cortisol has been reported to stimulate lipoprotein lipase activity (33), and UFC was higher with the HFCS diet. Although average UFC was within the physiologic range, this increase may indicate that HFCS induces a small physiologic stress and theoretically may contribute to the development of insulin resistance that has been reported to occur at higher rates in individuals who increase their consumption of sugar-sweetened beverages (34).

Although the sample size was small and the results were primarily hypothesis generating, there was consistently less hunger the morning after the WW diet than on the morning after the HFCS diet. The responses following the HFCS diet were similar to those after EB despite the doubling of energy intake. We hypothesize that the potential reasons for the increased hunger include the increased UFC or the increased SMR with the HFCS diet or differences in sensitivity to ghrelin induced by HFCS. At supraphysiologic doses, corticosteroids increase hunger and food intake (35); however, any relationship between physiologic cortisol and hunger or food intake is unclear. Daily EE correlates with both hunger and subsequent food intake (36,37), and, possibly, increased EE overnight could contribute to increased hunger upon awakening. Despite the large amount of energy intake the day prior, small increases in ghrelin, a “hunger hormone” known to decrease after meals (38), occurred after both overfeeding diets, but the ghrelin increase was not correlated with hunger scores. It is theoretically possible, however, that HFCS increases sensitivity to ghrelin. Individual differences in FGF21 may also contribute to feelings of hunger, as FGF21 was the only hormone that correlated with individual hunger scores. FGF21 increases with fasting and is associated with increased food intake in rodents after fasting or protein restriction (39). Although the physiologic underpinnings of the increased hunger scores after the HFCS diet are unclear, increased hunger, as opposed to an expected compensatory satiety after eating excess energy, may contribute, in part, to the weight gain that has been reported in individuals with a high consumption of sugar-sweetened beverages (34,40).

We had a small sample size and few women were represented, but we utilized a repeated-measures design to increase our power and recruited people representative of most body sizes. Still, with this sample size, our ability to do subgroup analyses was limited. Future studies with diets varying in carbohydrate source are required to confirm that hunger sensations increase after HFCS and, further, that the hunger translates to increased food intake. The recommendation to consume a low-fat, high–complex-carbohydrate diet is based on studies using home-cooked whole grains (12,41). It is possible that we may have observed different results if the WW diet more closely represented these past studies, but the foods in our study may be more representative of the modern-day lifestyle of many who choose convenience foods. The fasting hormone concentrations were measured before and after the diets at the same time each morning; if serum had been collected during the postprandial period, results may have been different.

**Conclusion**

We investigated differences in EE over 24 hours using common, readily available sources of HFCS versus WW. In general, the overall effects of overeating carbohydrates were similar regardless of the
source of the carbohydrates and favored storage of the large majority of excess energy consumed. However, the HFCS diet resulted in a higher SMR, increased UFC, and increased hunger the next day. Our results indicate that HFCS may make it difficult to compensate for overeating on the following day by creating a physiologic milieu that may portend a potential for further excess food intake.

Acknowledgments

The authors thank the clinical research staff of the Obesity and Diabetes Clinical Research Section of the Phoenix Epidemiology and Clinical Research Branch for their excellent care of the participants.

Published 2017. This article is a U.S. Government work and is in the public domain in the USA.

References

1. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a statement from the American Heart Association. Circulation 2009;120:1011-1020.
2. Ha V, Jayalath VH, Corzma AI, Mirrahiami A, de Souza RJ, Sievenpiper JL. Fructose-containing sugars, blood pressure, and cardiometabolic risk: a critical review. Curr Hypertens Rep 2013;15:281-297.
3. Pannacciuelli N, Salbe AD, Ortega E, Venti CA, Bogardus C, Kraulj J. The 24-h carbohydrate oxidation rate in a human respiratory chamber predicts ad libitum food intake. Am J Clin Nutr 2007;86:625-632.
4. Ma Y, Olendzki B, Chiriboga D, et al. Association between dietary carbohydrates and body weight. Am J Epidemiol 2005;161:359-367.
5. Saris WH, Astrup A, Prentice AM, et al. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. The carbohydrate ratio management in European national diets. Int J Obstet Relat Metab Disord 2000;24:1310-1318.
6. Melanson KJ, Angelopoulos TJ, Nguyen Y, Zukley L, Lowndes J, Rippe JM. High-fructose corn syrup, energy intake, and appetite regulation. Am J Clin Nutr 2008;88:1738S-1744S.
7. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr 2004;79:537-543.
8. Couchepin C, Le KA, Bortolotti M, et al. Markedly blunted metabolic effects of fructose in healthy young female subjects compared with male subjects. Diabetes Care 2008;31:1254-1256.
9. Stanhope KL, Grifffen SC, Bair BR, Swarbrick MM, Keim NL, Havel PJ. Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup, sucrose-, fructose-, and glucose-sweetened beverages with meals. Am J Clin Nutr 2008;87:1194-1203.
10. Stanhope KL, Havel PJ. Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup. Am J Clin Nutr 2008;88:1733S-1737S.
11. Lustig RH, Mulligan K, Noworolski SM, et al. Isothermal fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. Obesity (Silver Spring) 2016;24:453-460.
12. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998;280:2001-2007.
13. Schwarz JM, Schutz Y, Froidevaux F, et al. Thermogenesis in men and women induced by fructose vs glucose added to a meal. Am J Clin Nutr 1989;49:667-674.
14. 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 2013;36:150-156.
15. David Wang D, Sievenpiper JL, de Souza RJ, et al. Effect of fructose on postprandial triglycerides: a systematic review and meta-analysis of controlled feeding trials. Atherosclerosis 2014;232:125-133.
16. Lecoultre V, Egli L, Carrel G, et al. Effects of fructose and glucose overfeeding on hepatic insulin sensitivity and intrahepatic lipids in healthy humans. Obesity (Silver Spring) 2013;21:782-785.
17. Luo S, Mon tro se r o JS, Sar pel le h K, Page KA. Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards. Proc Natl Acad Sci U S A 2015;112:6509-6514.
18. Schlegl M, Piaggi P, Pannacciuelli N, Bonfiglio SM, Kraulj J, Thearle MS. Energy expenditure responses to fasting and overfeeding identify phenotypes associated with weight change. Diabetes 2015;64:3680-3689.
19. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36 (Suppl 1):S67-S78.
20. Ferraro R, Boyce VL, Swinburn B, De Gregorio M, Ravussin E. Energy cost of physical activity on a metabolic ward in relationship to obesity. Am J Clin Nutr 1991;53:1368-1371.
21. Thearle MS, Pannacciuelli N, Bonfiglio S, Pacak K, Kraulj J. Extent and determinants of thermogenic responses to 24 hours of fasting, energy balance, and five different overfeeding diets in humans. J Clin Endocrinol Metab 2013;98:2791-2799.
22. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. J Clin Invest 1986;78:1568-1578.
23. World Health Organization. Physical Status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: WHO; 1995.
24. Tappy L, Randin JP, Felber JP, et al. Comparison of thermogenic effect of fructose and glucose in normal humans. Am J Physiol 1986;250:E718-E724.
25. McDevitt RM, Poppi tt SD, M urtagh tood PR, Prentice AM. Macronutrient disposal during controlled overfeeding with glucose, fructose, sucrose, or fat in lean and obese women. Am J Clin Nutr 2000;72:369-377.
26. 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.
27. Henry RR, Cospo PA, Thoburn AW. Current issues in fructose metabolism. Annu Rev Nutr 1991;11:21-39.
28. Acheson KJ, Schutz Y, Bessard T, Anantharaman K, Flatt JP, J equier E. Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. Am J Clin Nutr 1988;48:240-247.
29. Angelopoulos TJ, Lowndes J, Zukley L, et al. The effect of high-fructose corn syrup consumption on triglycerides and uric acid. J Nutr 2009;139:1242S-1245S.
30. Brunzell JD, Hazzard WR, Porte D, Jr., Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J Clin Invest 1973;52:1578-1585.
31. Clemmons DR. Metabolic actions of muscle-like growth factor-I in normal physiology and diabetes. Endocrinol Metab Clin North Am 2012;41:425-443, viii-viii.
32. Ottosson M, Vikman-Adolfsson K, Enerback S, Elander A, Bjorntorp P, Eden S. Growth hormone inhibits lipoprotein lipase activity in human adipose tissue. J Clin Endocrinol Metab 1995;80:936-941.
33. Ottosson M, Vikman-Adolfsson K, Enerback S, Olivelcrona G, Bjorntorp P. The effects of cortisol on the regulation of lipoprotein lipase activity in human adipose tissue. J Clin Endocrinol Metab 1994;79:820-825.
34. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292:927-934.
35. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of gluco corticoids on energy metabolism and food intake in humans. J Am Physiol 1996;271:E317-E325.
36. Caudwell P, Findlayson G, Gibbons C, et al. Resting metabolic rate is associated with hunger, self-determined meal size, and daily energy intake and may represent a marker for appetite. Am J Clin Nutr 2013;97:7-14.
37. Piaggi P, Thearle MS, Kraulj K, Votrubova SB. Higher daily energy expenditure and respiratory quotient, rather than fat-free mass, independently determine greater ad libitum overeating. J Clin Endocrinol Metab 2015;100:3011-3020.
38. Benedict C, Axelsson T, Soderberg S, et al. Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels of the satiety hormone leptin in older adults. Diabetes 2014;63:3955-3963.
39. Lager T, Henagan TM, Albarado DC, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest 2014;124:3913-3922.
40. Bandyck SC, Thearle MS, Venti CA, Kraulj K, Votrubova SB. Soda consumption during ad libitum food intake predicts weight change. J Acad Nutr Diet 2014;114:444-449.
41. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990;336:129-133.