Consumption of Honey, Sucrose, and High-Fructose Corn Syrup Produces Similar Metabolic Effects in Glucose-Tolerant and -Intolerant Individuals[1,2]

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Abstract

Background: Public health recommendations call for a reduction in added sugars; however, controversy exists over whether all nutritive sweeteners produce similar metabolic effects.

Objective: The objective was to compare the effects of the chronic consumption of 3 nutritive sweeteners [honey, sucrose, and high-fructose corn syrup containing 55% fructose (HFCS55)] on circulating glucose, insulin, lipids, and inflammatory markers; body weight; and blood pressure in individuals with normal glucose tolerance (GT) and those with impaired glucose tolerance (IGT).

Methods: In a crossover design, participants consumed daily, in random order, 50 g carbohydrate from assigned sweeteners for 2 wk with a 2- to 4-wk washout period between treatments. Participants included 28 GT and 27 IGT volunteers with a mean age of 38.9 ± 3.6 y and 52.1 ± 2.7 y, respectively, and a body mass index (in kg/m^2) of 26 ± 0.8 and 31.5 ± 1.0, respectively. Body weight, blood pressure (BP), serum inflammatory markers, lipids, fasting glucose and insulin, and oral-glucose-tolerance tests (OGTTs) were completed pre- and post-treatment. The OGTT incremental areas under the curve (iAUCs) for glucose and insulin were determined and homeostasis model assessment of insulin resistance (HOMA-IR) scores were calculated.

Results: Body weight and serum glucose, insulin, inflammatory markers, and total and LDL-cholesterol concentrations were significantly higher in the IGT group than in the GT group at baseline. Glucose, insulin, HOMA-IR, and the OGTT iAUC for glucose or insulin did not differ by treatment, but all responses were significantly higher in the IGT group compared with the GT group. Body weight was unchanged by treatment. Systolic BP was unchanged, whereas diastolic BP was significantly lower in response to sugar intake across all treatments. An increase in high-sensitivity C-reactive protein (hsCRP) was observed in the IGT group in response to all sugars. No treatment effect was observed for interleukin 6. HDL cholesterol did not differ as a result of status or treatment. Triglyceride (TG) concentrations increased significantly from pre- to post-treatment in response to all sugars tested.

Conclusions: Daily intake of 50 g carbohydrate from honey, sucrose, or HFCS55 for 14 d resulted in similar effects on measures of glycemia, lipid metabolism, and inflammation. All 3 increased TG concentrations in both GT and IGT individuals and elevated glycemic and inflammatory responses in the latter. This trial was registered at clinicaltrials.gov as NCT01371266. *J Nutr* 2015;145:2265–72.

Keywords: sucrose, honey, high-fructose corn syrup, glycemia, triglycerides

Introduction

The per capita consumption of added sugars in the United States has increased over the 20th century, although recently, intakes have declined or stabilized (1, 2). There is concern that the elevated consumption of added sugars has led to negative health effects (3). There is speculation that added sugars in general and high-fructose corn syrup (HFCS)[5] in particular contribute, directly or indirectly, to obesity as well as to a variety of other metabolic disorders and disease states. This is supported by research linking sugar intake to excessive body weight, cardiometabolic disease risk, and increased all-cause mortality

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[5] Abbreviations used: BP, blood pressure; GFHNRC, Grand Forks Human Nutrition Research Center; GT, glucose tolerant (or tolerance); HFCS, high-fructose corn syrup; HFCS55, high-fructose corn syrup containing 55% fructose; hsCRP, high-sensitivity C-reactive protein; IGT, impaired glucose tolerance; OGTT, oral-glucose-tolerance test.

(3–7). As a result, numerous public and private health agencies have recommended reductions in added sugar intake. The Institute of Medicine currently recommends that no more than 25% of daily energy should be consumed as added sugars (8), whereas the American Heart Association recommends ≤25 g added sugars/d for women and ≤38 g added sugars/d for men (5.0% and 7.5% of total energy, respectively) for a 2000-kcal daily diet (9). More recently, the 2015 Dietary Guidelines Advisory Committee recommended limiting added sugar intake to a maximum of 10% of total daily energy intake, citing overwhelming evidence linking added sugar intake to chronic disease risk and difficulty in achieving a "healthy food pattern" when added sugar intake exceeds 9% of total energy (10). Current recommendations from the WHO state that the intake of free sugars should be reduced throughout the life course and that in both children and adults it is recommended to reduce free sugar intake to <10% of total energy (11).

Of particular concern are the hypothesized effects of added sugars on glucose control and diabetes risk. After a thorough review of the scientific literature, the 2015 Dietary Guidelines Advisory Committee concluded that there is strong evidence showing that "higher consumption of added sugars, especially sugar-sweetened beverages, increases the risk of type 2 diabetes among adults and this relationship is not fully explained by body weight" (10). Thus, individuals with impaired glucose control may be particularly susceptible to the negative metabolic effects of added sugars. Additional concerns include the effect of added sugar intakes on cardiovascular disease risk factors related to serum lipids, blood pressure, and inflammation. Elevated fasting TGs are associated with a high intake of sucrose, glucose, and fructose (12, 13). Although there is some evidence linking sugar intake to blood pressure and systemic inflammation, the clinical evidence is inconclusive (9).

The increase in added sugar consumption is attributed to a greater use of HFCS, which appeared on the market in the early 1970s (14, 15). It is important to note that, although the consumption of added sugars remains relatively high, the amount of intake has stabilized or declined recently (1, 2). Of the currently available nutritive sweeteners, HFCS is thought to be uniquely detrimental to human health (16). In part, this is due to early research demonstrating that the consumption of large amounts of isolated fructose resulted in adverse metabolic effects (7, 8, 11–13). A significant body of evidence in both human and animal models suggests that large, supranutritional doses of isolated fructose elevate glycemia and serum TG concentrations and that this may increase the risk of chronic disease (17, 18). Sucrose, like HFCS, is also composed of approximately equal proportions of glucose and fructose. Honey is another nutritive sweetener with a chemical and compositional make-up similar to both HFCS and sucrose (i.e., an approximately equal amount of glucose and fructose). Whereas sucrose and HFCS are often viewed as detrimental to health, honey has been traditionally viewed as a "natural" sweetener believed to have health benefits not derived from other sugars, perhaps due to its content of other phytochemicals (19). The reported health benefits of honey consumption include antioxidant, antimutagenic, anti-inflammatory, and antibacterial properties, perhaps as a result of non-sweetener-based bioactive compounds (19, 20). However, no controlled human trials have been performed that directly compare honey, sucrose, and HFCS. Thus, the purpose of this study was to determine the metabolic and health effects of the chronic consumption of HFCS, sucrose, and honey in individuals with normal glucose tolerance (GT) as well as those with impaired glucose tolerance (IGT). We hypothesized that honey would result in improved glycemia and insulin sensitivity compared with sucrose and HFCS.

Methods

Study design and intervention. This study was a single-center, randomized crossover trial to determine the effect of a daily intake of 3 different nutritive sweeteners—sucrose, HFCS containing 55% fructose (HFCS55), and honey—on glycemic responses, markers of inflammation, serum lipids, and blood pressure (BP) in men and women with GT and IGT. The sugars were provided for 2 wk with a washout period of 2–4 wk between treatments. Throughout the trial participants consumed their habitual diets with the exclusion of added nutritive sweeteners at the table or as sugar-sweetened beverages except for those provided. All study visits were at the USDA Agricultural Research Service, Grand Forks Human Nutrition Research Center (GFHNRC), Grand Forks, North Dakota. The study was carried out between June 2011 and October 2014. All endpoint measurements were obtained by qualified technical staff at the GFHNRC.

The University of North Dakota Institutional Review Board approved the protocol for implementation. All participants were informed verbally and in writing of the study requirements and gave written informed consent before enrollment. Participants received a $200 stipend upon completion of the trial. The study was registered at clinicaltrials.gov as NCT01371266.

Participants. Volunteers were recruited from Greater Grand Forks Area, Grand Forks, North Dakota, for participation in this trial. Recruited participants were men and women between 20 and 80 y of age who were of normal weight to obese [BMI (kg/m^2) = 18–39.9]. Sixty participants were sought for inclusion, with a goal of half with GT and half with IGT. The exclusion criteria included the presence of diabetes or other known metabolic disease; the use of medications known to affect glucose metabolism, pregnancy, or lactation; or any history of eating disorders. Recruitment was performed through advertisements in local newspapers and fliers and via e-mailed notifications.

Initial screening was performed with an online application that screened out participants who exceeded the age or weight requirements. Those who were eligible after this process were asked to present to the GFHNRC for additional screening. Height (model 214; SECA) and weight with a calibrated digital scale (model 50735; Fairbanks) were obtained with subjects wearing light clothing and no shoes. Blood pressure was measured 3 times with a BP TRU monitor (model BPM-300; BP Medical Devices) after participants had been seated quietly for 5 min, and the mean of these measures was calculated. Fasting finger-stick blood glucose concentrations (Accu-Check Aviva; Roche Diagnostics) were used to determine eligibility and to classify participants as GT (glucose <100 mg/dL) or IGT (glucose = 100–125 mg/dL). A medical history screening questionnaire was used to exclude participants with known disease and those taking medications prohibited by the study protocol. Recruited participants completed the Web-based Diet History Questionnaire FFQ for the determination of usual macronutrient and sugar intake at baseline (21).

Dietary treatments. Participants were provided daily with a 50-g portion of carbohydrate from honey (Dutch Gold Honey), HFCS55 (CornSweet 55; Archer Daniels Midland), or sucrose (C&H Sugar; Domino Foods). The honey chosen for use in this study is a product formed from a blend of honeys of different floral sources, color, and geographic origin, which is the most commonly used type of honey in the United States. Table 1 shows the nutrient content of the nutritive sweeteners that were tested. In addition to the primary mono- and disaccharides, honey contains very small amounts of tri-saccharides, protein, and certain vitamins and minerals (19). All nutritive sweeteners were provided for daily intake as beverages prepared with fruit drink flavoring powder. All drinks were prepared in the metabolic kitchen of the GFHNRC. The nutritive sweetener and flavoring were placed into large plastic beverage containers for distribution to the participants with instructions to add water and mix well before consumption. During the intervention periods, study participants picked up the packaged sweeteners once per week. The 3 test sugars were provided with the assignment order blocked to ensure counterbalanced randomization. Participants consumed each beverage for 14 d with a 2- to 4-wk washout period between treatments. Participants were counseled by a registered dietitian to not

TABLE 1 Nutrient content of test nutritive sweeteners: honey, sugar, and high-fructose corn syrup

	Honey,[1] g/100 g	Sugar,[1] g/100 g	HFCS55,[2,3] g/100 g
Carbohydrate	82.4	99.9	77.0
Sucrose	0.9	99.8	0
Glucose	35.8	0	55
Fructose	40.9	0	41
Other saccharides	1.4	0	4
Galactose	0	0	0
Protein	0.3	0	0
Fat	0	0	0

[1] Data from reference 22.
[2] HFCS55, high-fructose corn syrup containing 55% fructose.
[3] CornSweet 55 (Archer Daniels Midland).

consume any additional added sugars at the table or in the form of sugar-sweetened beverages during the intervention. Compliance was determined by a questionnaire on which participants recorded the percentage of each treatment consumed and their compliance with restriction of other added sugars and sugar-sweetened beverages.

Data collection. Blood was drawn from participants on days 0 and 15 of each experimental period after an overnight fast of ≥10 h. Fasting blood samples were used to determine serum glucose, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, TG, IL-6, and high-sensitivity C-reactive protein (hsCRP) concentrations. Immediately after the time 0 blood draw, participants consumed a 50-g portion of glucose (SUN-DEX; Fisherbrand) for an oral-glucose-tolerance test (OGTT). Additional blood draws for glucose and insulin were obtained at 15, 30, 60, 90, and 120 min. Whole-blood samples were centrifuged at 3000 g for 10 min at 4°C to obtain serum; samples were placed into aliquots and stored at −80°C until analysis. Body weight was measured before each blood draw.

Biochemical analysis. Serum concentrations of glucose, TGs, and total and HDL cholesterol were measured by COBAS Integra 400 Plus (Roche Diagnostics) with corresponding test kits. The glucose kit (04404483) has an analytical range of 2.16–720 mg /dL, a within-run CV ≤2.43%, and a total CV ≤3.26%; the TG kit (20767107) has an analytical range of 0.00–8750 mg/dL, a within-run CV ≤0.85%, and a total CV ≤1.06%; the cholesterol kit (0303977) has an analytical range of 3.87–800 mg/dL, a within-run CV ≤0.85%, and a total CV ≤1.06%; and the HDL kit (03038637) has an analytical range of 0.00–120 mg/dL, a within-run CV ≤1.60%, and a total CV ≤3.50%. Analytical sensitivities for glucose, TGs, total cholesterol, and HDL cholesterol are 2 ulU/mL (within-run CV ≤6.4%, total CV ≤8.0%) and 0.1 mg/L (within-run CV ≤6.0%, total CV ≤10.0%). Serum insulin and hsCRP concentrations were determined by the Immulite 1000 System (Siemens Healthcare) with insulin and hsCRP kits (LKIN1 and LKCRP1, respectively; Llaberis). Tests were conducted following the manufacturer's instructions. Analytical sensitivities for insulin and CRP are 2 μU/mL (within-run CV ≤6.4%, total CV ≤8.0%) and 0.1 mg/L (within-run CV ≤6.0%, total CV ≤10.0%). IL-6 was determined with a Quantikine HS ELISA kit (HS600B; R&D Systems). The limit of detection for IL-6 was 0.016 pg/mL (within-run CV ≤6.9%, total CV≤9.6%). LDL-cholesterol concentrations were calculated with the Friedewald formula (23) and the HOMA-IR score was calculated with the formula of Matthews et al. (24).

Statistical analysis. Data are reported as means ± SEs of the mean (SEMs). Baseline characteristics and reported dietary intakes of the GT and IGT groups were compared by using Student's t tests. Primary analysis was conducted to determine the differences on GT as assessed by OGTT before and after the daily consumption of honey, sucrose, and HFCS55. The incremental AUCs under the 120-min glucose and insulin curves were determined for each participant by calculating the AUC between consecutive measurements by using the formula for the area of a trapezoid. The 5 areas were added and corrected for baseline glucose or insulin concentrations, respectively. For each study outcome, data were analyzed by using 3-factor

repeated-measures ANOVA, in which status (GT or IGT), sweetener (honey, sucrose, or HFCS55), and phase (pre- or post-treatment) were main effects and all possible interactions between these 3 factors were included. For all variables, the P values for the interactions: status × phase, sweetener × phase, and status × sweetener × phase were >0.05 and thus are not shown. Tukey's contrasts were used for post hoc comparisons. TGs, hsCRP, and IL-6 were not normally distributed, so values were log-transformed before analysis. An insulin value of 158 μU/mL was observed at time 0 in the post HCFS55 treatment OGTT for 1 IGT participant. Because this participant had a lower insulin value at 15 min (39.8 μU/mL), we assume the tubes were mislabeled but we cannot verify this. Therefore, the fasting insulin value was omitted from the statistical analysis because it was deemed to be an outlier. One GT participant had an extremely high fasting TG concentration (1640 mg/dL) after the sucrose treatment, so we were unable to calculate this individual's LDL concentration. All analyses were conducted by using SAS, version 9.4; P values <0.05 were considered to be significant.

Results

Characteristics of participants. Study participants included a total of 55 volunteers (n = 39 women and 16 men). Baseline characteristics of participants are shown in **Table 2**. The flow of participants through the trial is shown in **Figure 1**. Initial screening was performed on 177 volunteers; 88 were ineligible for participation, resulting in 89 being assigned to treatment with 52 GT and 37 IGT individuals. Dropouts from each group (n = 24 GT; n = 10 IGT) resulted in a total of 55 participants (n = 28 GT and 27 IGT) who completed all aspects of the study.

TABLE 2 Baseline characteristics of individuals with normal and impaired glucose tolerance who consumed 50 g carbohydrate/d from HFCS55, sucrose, or honey for 2 wk in a crossover randomized trial[1]

	Glucose tolerant (n = 28)	Impaired glucose tolerance (n = 27)	P
Age, y	38.9 ± 3.6	52.1 ± 2.7	<0.01
Weight, kg	75.9 ± 3.4	85.9 ± 2.9	0.03
BMI, kg/m²	26.0 ± 0.8	31.5 ± 1.0	<0.001
Serum glucose, mg/dL	90 ± 2	104 ± 2	<0.001
Serum insulin, μU/mL	8.6 ± 1.2	15.7 ± 2.3	<0.01
HOMA-IR score	1.9 ± 0.3	4.11 ± 0.6	<0.01
Blood pressure			
Systolic, mm Hg	122 ± 3	124 ± 3	0.69
Diastolic, mm Hg	74 ± 2	77 ± 2	0.28
Serum hsCRP, mg/L	2.2 ± 0.5	4.6 ± 0.8	<0.01
Serum IL-6, pg/mL	1.6 ± 0.2	2.6 ± 0.5	0.03
Serum total cholesterol, mg/dL	171 ± 7	197 ± 8	0.02
Serum LDL cholesterol, mg/dL	94 ± 7	117 ± 7	0.03
Serum HDL cholesterol, mg/dL	54 ± 2	54 ± 3	0.97
Serum TGs, mg/dL	114 ± 18	130 ± 17	0.30
Reported baseline diet			
Energy, kcal/d	2107 ± 175	1786 ± 161	0.18
Fat, g/d	82 ± 8	68 ± 7	0.16
Protein, g/d	84 ± 8	78 ± 9	0.65
Carbohydrate, g/d	253 ± 19	217 ± 19	0.19
Total sugars, g/d	122 ± 11	106 ± 12	0.33
Sucrose, g/d	39 ± 4	34 ± 3	0.20
Fructose, g/d	27 ± 5	22 ± 3	0.40
Added sugars, g/d	15 ± 2	12 ± 1	0.33

[1] Values are means ± SEMs of observed findings. HFCS55, high-fructose corn syrup containing 55% fructose; hsCRP, high-sensitivity C-reactive protein.

Screened n = 177

Ineligible n = 88

Did not qualify = 58
Declined = 4
Did not sign consent = 8
No show = 3
No longer interested = 5
No reason = 1
No response = 7
Personal = 2

Eligible n = 89

Glucose Tolerant
Randomly assigned to
Treatment
n = 52

Glucose Intolerant
Randomly assigned to
treatment
n = 37

Dropouts n = 24

No response = 2
Unable to draw blood = 5
Conflict with schedule = 6
Declined = 4
Medical reasons = 1
Missed appointments = 3
Personal = 1
Started exercising = 1
Unable to tolerate
  blood draws = 1

Dropouts n = 10

Personal choice = 2
Unable to reach = 1
Conflict with schedule = 1
Declined = 4
No longer interested = 2

Completed all aspects
of the trial
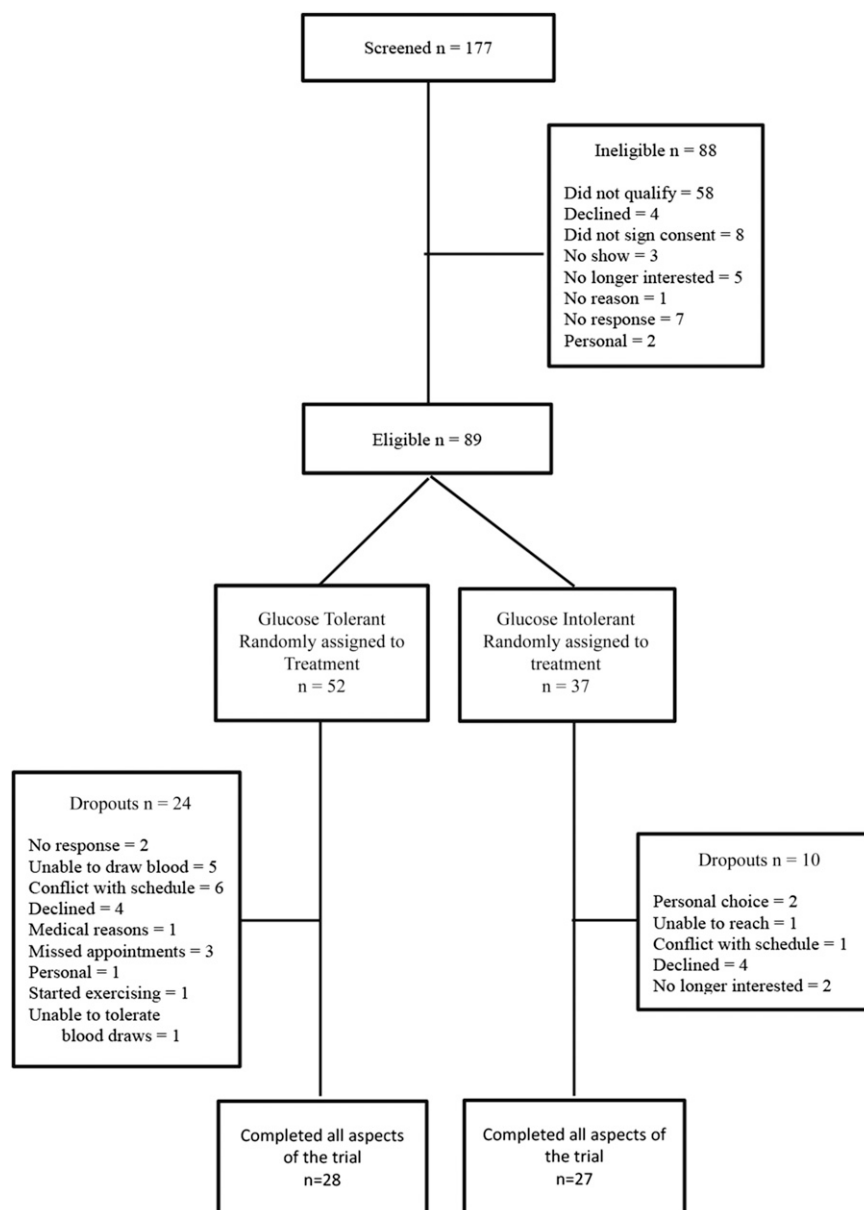n=28

Completed all aspects of
the trial
n=27

FIGURE 1 CONSORT diagram of participant flow through the study. CONSORT, Consolidated Standards of Reporting Trials.

The GT individuals (17 women, 11 men) were 38.9 ± 3.6 y of age with a BMI of 26 ± 0.8; IGT individuals (22 women, 5 men) were 52.1 ± 2.7 y of age with a BMI of 31.5 ± 1.0. Baseline levels were significantly higher in the IGT group for age ($P <$ 0.01), body weight ($P = 0.03$), BMI ($P < 0.001$), fasting serum glucose ($P < 0.001$) and insulin ($P < 0.01$), HOMA-IR ($P < 0.01$), hsCRP ($P < 0.01$), IL-6 ($P = 0.03$), total cholesterol ($P = 0.02$), and LDL cholesterol ($P = 0.03$) compared with the GT group. Baseline dietary intake assessed by the Diet History Questionnaire, which calculates nutrients from all reported food sources, was similar between groups, with no significant differences observed in energy, macronutrients, total sugar, fructose, or sucrose intakes at baseline. Reported intakes for total sugars, sucrose, and fructose for GT and IGT participants are shown in Table 2. Reported "added sugars" intakes were lower than the reported intake in the United States, which is 18.2 g/d in all individuals aged ≥20 y (25).

The quantity of sucrose and fructose provided by our test sugars was similar to the reported intake of participants at baseline. However, it exceeded the reported intake of "added

sugars" by ~35 and ~38 g/d for GT and IGT groups, respectively, and the recommended intake amounts of the Institute of Medicine (8) and the American Heart Association (9). Study treatments were well tolerated by the participants, and reported deviation from the assigned nutritive sweetener intake estimated from compliance questionnaires was <2% (>98% compliance) for all treatments in both GT and IGT participants.

Outcome data. Study results are shown in **Table 3**. No changes were observed in body weight throughout the trial in any treatment group, although there was a significant difference in weight by GT status (weight and BMI: $P = 0.03$ and <0.001 for GT and IGT groups, respectively) by study design.

Throughout testing, the IGT participants had higher fasting serum glucose ($P < 0.001$) and insulin ($P < 0.03$) concentrations and HOMA-IR scores ($P < 0.01$) than did those in the GT group. **Figures 2** and **3** show the pre- and post-treatment 2-h OGTT glucose and insulin responses for GT and IGT groups, respectively. The glycemic response to sugar consumption was unaffected by source. However, regardless of source, insulin incremental AUC

TABLE 3 Pre- and post-treatment outcomes in individuals with normal and impaired glucose tolerance who consumed 50 g carbohydrate/d from HFCS55, sucrose, or honey for 2 wk in a crossover randomized trial[1]

	Honey		Sucrose		HFCS55		P (ANOVA)			
	GT (n = 28)	IGT (n = 27)	GT (n = 28)	IGT (n = 27)	GT (n = 28)	IGT (n = 27)	Phase	Status	Sweetener	Status × sweetener
Weight, kg							0.14	0.04	0.21	0.08
Pre	76.6 ± 3.5	86.0 ± 2.8	76.2 ± 3.4	85.9 ± 3.0	76.5 ± 3.4	86.5 ± 3.0				
Post	76.7 ± 3.5	86.3 ± 2.9	76.9 ± 3.4	86.0 ± 2.9	76.9 ± 3.6	86.4 ± 3.0				
BMI, kg/m^2							0.17	<0.001	0.26	0.07
Pre	26.3 ± 0.8	31.6 ± 1.0	26.1 ± 0.8	31.6 ± 1.0	26.2 ± 0.8	31.8 ± 1.0				
Post	26.3 ± 0.8	31.8 ± 1.0	26.4 ± 0.8	31.6 ± 1.0	26.3 ± 0.8	31.7 ± 1.0				
Serum glucose, mg/dL							0.60	<0.001	0.80	0.64
Pre	90 ± 2	103 ± 2	91 ± 2	103 ± 2	90 ± 1	103 ± 2				
Post	89 ± 2	104 ± 2	90 ± 1	104 ± 2	90 ± 1	102 ± 2				
Serum insulin, μU/mL							0.44	0.03	0.74	0.58
Pre	12.3 ± 4.5	15.5 ± 1.9	9.0 ± 1.3	16.5 ± 2.3	10.2 ± 2.1	15.5 ± 2.2				
Post	8.8 ± 1.4	16.2 ± 1.9	9.0 ± 1.3	15.8 ± 2.1	10.1 ± 1.8	15.0 ± 1.6				
HOMA-IR score							0.93	<0.01	0.76	0.54
Pre	3.0 ± 1.3	4.0 ± 0.5	2.0 ± 0.3	4.3 ± 0.6	2.3 ± 0.5	4.1 ± 0.7				
Post	2.0 ± 0.3	4.2 ± 0.5	2.0 ± 0.3	4.1 ± 0.6	2.3 ± 0.4	3.8 ± 0.4				
Serum glucose iAUC, mg/dL · min							0.35	0.13	0.92	0.98
Pre	3240 ± 458	4030 ± 508	3300 ± 577	4190 ± 499	3270 ± 472	4440 ± 504				
Post	3350 ± 460	4430 ± 504	3410 ± 417	4230 ± 450	3530 ± 475	4120 ± 478				
Serum insulin iAUC, μU/mL · min							<0.001	0.21	0.97	0.80
Pre	5160 ± 734	7260 ± 1080	6040 ± 918	7190 ± 1110	5650 ± 840	7170 ± 921				
Post	5860 ± 813	8560 ± 1280	6320 ± 1010	7570 ± 1160	6120 ± 787	7540 ± 1010				
Blood pressure, mm Hg										
Systolic							0.18	0.07	0.47	0.81
Pre	119 ± 2	122 ± 2	121 ± 3	127 ± 2	121 ± 2	127 ± 3				
Post	119 ± 3	124 ± 2	119 ± 2	124 ± 3	119 ± 2	124 ± 2				
Diastolic							0.05	0.07	0.16	0.51
Pre	71 ± 1	75 ± 2	74 ± 2	77 ± 2	74 ± 1	77 ± 2				
Post	71 ± 1	75 ± 2	73 ± 2	75 ± 2	71 ± 1	76 ± 2				
hsCRP, mg/L							0.14	<0.01	0.48	0.03
Pre	2.3 ± 0.7	5.1 ± 1.1	2.5 ± 0.6	3.8 ± 0.7	2.0 ± 0.7	4.4 ± 0.8				
Post	2.5 ± 0.9	7.2 ± 2.8	2.0 ± 0.4	4.4 ± 0.8	1.9 ± 0.5	5.7 ± 1.3				
IL-6, pg/mL							0.44	<0.001	0.67	0.94
Pre	1.3 ± 0.2	3.1 ± 0.5	1.8 ± 0.3	2.9 ± 0.5	1.3 ± 0.1	3.0 ± 0.5				
Post	1.6 ± 0.3	3.7 ± 0.7	1.4 ± 0.3	3.0 ± 0.4	1.4 ± 0.2	3.2 ± 0.5				
Serum total cholesterol, mg/dL							0.08	0.06	0.05	0.64
Pre	174 ± 8	189 ± 7	174 ± 7	198 ± 8	174 ± 8	193 ± 8				
Post	176 ± 8	196 ± 7	183 ± 7	197 ± 9	173 ± 8	195 ± 7				
Serum LDL cholesterol, mg/dL							0.64	0.05	0.27	0.64
Pre	96 ± 7	110 ± 6	95 ± 7	117 ± 6	94 ± 7	114 ± 6				
Post	96 ± 7	114 ± 6	101 ± 6	114 ± 7	94 ± 7	112 ± 6				
Serum HDL cholesterol, mg/dL							0.57	0.28	0.29	0.61
Pre	56 ± 3	52 ± 3	57 ± 3	53 ± 3	56 ± 2	52 ± 3				
Post	56 ± 3	53 ± 3	58 ± 3	53 ± 3	56 ± 2	52 ± 3				
Serum TGs, mg/dL							0.01	0.18	0.90	0.81
Pre	114 ± 17	133 ± 16	107 ± 18	146 ± 20	120 ± 19	134 ± 15				
Post	120 ± 18	147 ± 21	164 ± 55	147 ± 21	114 ± 16	156 ± 30				

[1] Values are means ± SEMs of observed data. GT, glucose tolerant; HFCS55, high-fructose corn syrup containing 55% fructose; hsCRP, high-sensitivity C-reactive protein; iAUC, incremental AUC; IGT, impaired glucose tolerance.

increased significantly (P < 0.001 for phase) after the 2-wk consumption of the sweeteners in both GT and IGT groups. Glucose and insulin concentrations were higher in the IGT group, but no difference in response by treatment was observed in either group.

Systolic and diastolic BP was within normal limits in both the GT and IGT groups. Systolic BP was unchanged by any treatment in either group. Diastolic BP was significantly reduced from pre- to post-treatment by the sugar treatments (P = 0.05 for phase) regardless of glycemic status. Concentrations of the
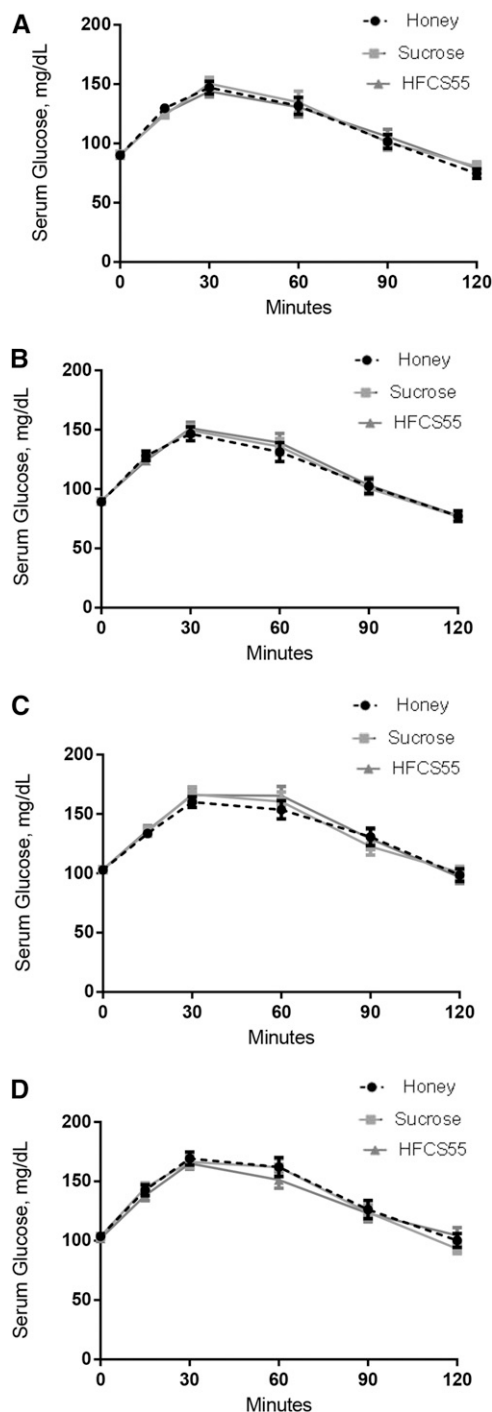
FIGURE 2 Pre- and post-OGTT glycemic responses in participants with normal (A and B, respectively) or impaired (C and D, respectively) glucose tolerance who daily consumed 50 g carbohydrate from HFCS55, sucrose, or honey for 2 wk in a crossover randomized trial. Values are means ± SEMs; $n = 28$ (A, B) or 27 (C, D). HFCS55, high-fructose corn syrup containing 55% fructose; OGTT, oral glucose tolerance test.

Serum total cholesterol concentrations were not significantly different between the IGT and the GT groups. Although ANOVA showed a significant main effect of sweetener on cholesterol ($P = 0.05$), none of the Tukey's contrasts comparing the 3 sweeteners were significant. LDL-cholesterol concentrations were higher in the IGT vs. GT groups at both pre- and post-treatment ($P = 0.05$ for status), but no differences were found by
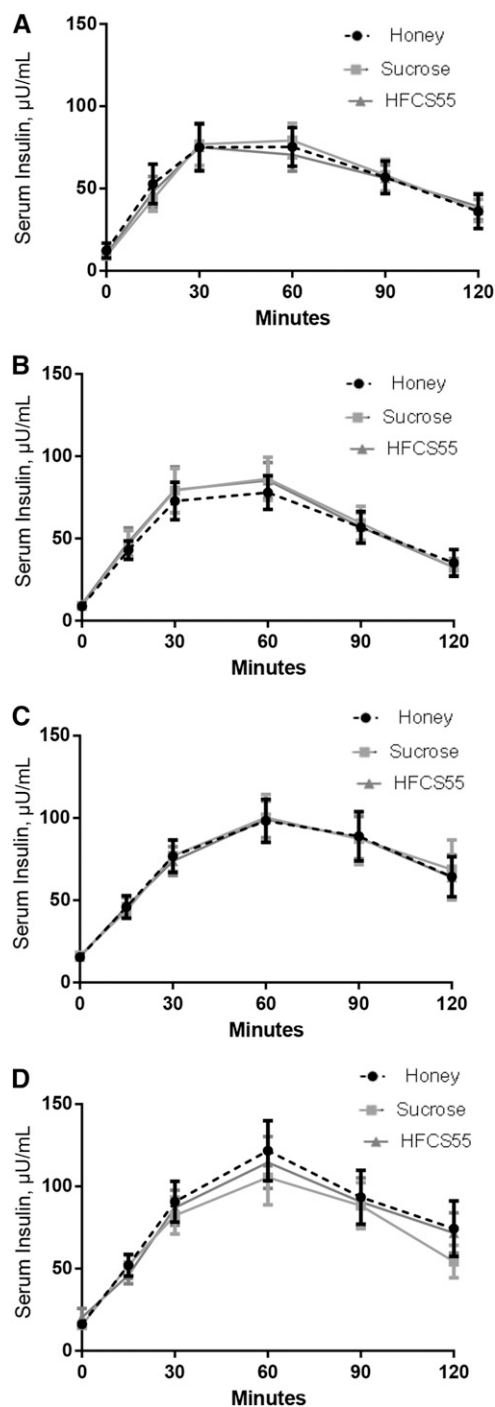

FIGURE 3 Pre- and post-treatment OGTT insulin responses of participants with normal (A and B, respectively) or impaired (C and D, respectively) glucose tolerance who daily consumed 50 g carbohydrate from HFCS55, sucrose, or honey for 2 wk in a crossover randomized trial. Values are means ± SEMs; $n = 28$ (A, B) or 27 (C, D). HFCS55, high-fructose corn syrup containing 55% fructose; OGTT, oral glucose tolerance test.

inflammatory markers hsCRP and IL-6 were higher in the IGT group at both pre- and post-treatment ($P < 0.01$ for status for both markers). An interaction effect (status × sweetener) was observed for hsCRP ($P = 0.03$), which was largely driven by elevated concentrations in the IGT group by all treatments. No treatment effect was observed for IL-6 in response to dietary sugar intake.

treatment. HDL-cholesterol concentrations were not different between IGT and GT groups and did not change in response to treatment. TG concentrations increased significantly from pre- to post-treatment by all of the sugar treatments ($P = 0.01$ for phase).

Discussion

In our randomized crossover trial, we compared 2 wk of a daily intake of beverages sweetened with 50 g carbohydrate from honey, sucrose, and HFCS55 in GT and IGT individuals to test the hypothesis that honey would result in improved glycemia and insulin sensitivity compared with sucrose and HFCS. We measured glycemic, inflammatory, and lipid biomarkers pre- and postintervention and observed no differences in glycemic responses to sugar source. Although IGT participants had higher basal and outcome concentrations of serum glucose and insulin and calculated HOMA-IR score, there was no difference in the response to individual sugars. The findings do not support our hypothesis that honey would result in improved glycemia and insulin sensitivity compared with sucrose and HFCS in either GT or IGT individuals. Moreover, we demonstrate that metabolic, serum lipid, and inflammatory marker responses to honey, sucrose, and HFCS55 were similar within GT and IGT groups, likely due to the fact that the test nutritive sweeteners have similar sugar content.

Body weight was significantly higher in the IGT group at baseline. No changes were observed in body weight in either the GT or IGT groups throughout the trial. This suggests that participants consumed balanced amounts of energy even with the daily addition of 50 g carbohydrate from the sugar treatments. The role of sweetened beverage intake in weight gain remains unresolved. In a systematic literature review, Malik and Hu (26) found a strong positive association between sugar-sweetened beverage consumption, long-term weight gain, and the development of related metabolic conditions. Other studies, however, do not demonstrate a clear causal relation between sugar-sweetened beverage intake and weight gain, particularly when considering total energy intake (27, 28). Because our treatment was administered for only 14 d, it is not possible to determine what effect a longer intervention period would have on body weight. Evidence of a strong relation between nutritive sweetener intake and metabolic disease risk within the context of an energy-balanced diet is not robust; detrimental effects seem to be linked to excessive total energy intake (29). The participants in our study maintained stable body weights throughout the trial, suggesting that they were consuming energy-balanced diets, which may have contributed to the lack of untoward effects on the metabolic markers under investigation.

Systolic BP was unaffected by the daily intake of sucrose, honey, or HFCS55. Our sugar treatments resulted in a small reduction in diastolic BP. Epidemiologic data have shown an association between sugar intake in the form of sweetened beverages and BP. Brown et al. (30) found that a reduction of 1 serving of sugar-sweetened beverages/d [~38 g sugar in a 12-ounce beverage (22)] was associated with a 1.8-mm Hg (95% CI: 1.2, 2.4 mm Hg) reduction in systolic BP and a 1.1-mm Hg (95% CI: 0.7, 1.4 mm Hg) reduction in diastolic BP over 18 mo in a model controlled for potential confounders. Chen et al. (31) demonstrated in a prospective analysis that reducing intake by 1 sugar-sweetened beverage daily was associated with reductions in systolic and diastolic BP (both $P < 0.05$). A meta-analysis performed by Ha et al. (32) found that fructose intake was related to decreases in diastolic BP but no change in systolic or

mean arterial BP. Although the intake of isolated fructose has been shown to have effects on BP (33), we were unable to locate any other clinical trial data suggesting that honey, sucrose, or HFCS have detrimental effects on BP.

The IGT group had serum hsCRP concentrations of >3 mg/L at all time points, which are lower than the values seen in acute inflammation but which may indicate increased risk of cardiometabolic disease in this group (29). Concentrations of hsCRP observed in the GT group were within the normal range (<3.0 mg/L). Although there was a significant status × treatment interaction ($P = 0.03$), the increases observed were not clinically important. Aeberli et al. (34) reported elevations in hsCRP after consumption of isolated fructose, glucose, or sucrose in young men. It is important to note that the dose of sucrose was higher than ours (80 vs. 50 g/d) and the intervention period was longer (2 vs. 3 wk) and that the fructose and glucose were provided in isolated form.

Total and LDL-cholesterol concentrations were consistently higher in the IGT group (P for status = 0.06 and 0.05, respectively). However, total, LDL-, and HDL-cholesterol concentrations were unchanged by intakes of any of the sugars in both the GT and IGT groups. Although the intake of isolated fructose elevates TG concentrations in both healthy and diabetic subjects (18, 35), Angelopoulos et al. (36) reported that there is no evidence that HFCS has the same effect. Diets containing high amounts of sucrose, glucose, and fructose cause elevations in fasting plasma TG concentrations, principally as VLDL cholesterol (12, 13). In our study, TG concentrations were increased by all sugar treatments in both the GT and IGT participants. It is well established that replacing dietary fats with carbohydrates results in elevated plasma TG concentrations (37). We did not assess the dietary intake of our participants during the treatment phases of the trial and are therefore unable to determine the change in macronutrient composition of diets consumed. It is possible that the added sweetened beverage intake resulted in an increase in total carbohydrate. Whether this TG response is attributable to an increase in total carbohydrate or in the individual sugar sources is unknown.

Strengths. The well-controlled nature of the study is its primary strength. The production of the test products was well controlled and participant compliance with the 2-wk treatments was well monitored. The sample size was relatively small, but our use of a crossover design increases the statistical power for outcome determination. Furthermore, it can be argued that the addition of the nutritive sweeteners to the participants' self-selected diets provides a better estimation of "real world" effects than a totally controlled feeding trial would.

Limitations. Specific limitations of our trial should be taken into account. First, we implemented this trial as an outpatient supplementation study and relied on reported compliance to assigned sugar intakes. Participants were asked to restrict the consumption of other added nutritive sweeteners and were queried about this. However, the only variable we used was the intake of the assigned sweetener. Second, our intervention did not include a control test beverage without a nutritive sweetener. Last, the sample size was relatively small and the intervention period of 14 d was short. Although this period is long enough to alter glycemic responses, it did not allow us to evaluate the effect of the treatments on body weight regulation over time.

Conclusions. Our data demonstrate that 2 wk of daily consumption of 50 g carbohydrate from sucrose, honey, and HFCS55 exerted similar effects on measures of glycemia, inflammation,

and lipid status in GT and IGT individuals. Our data do not support the contention that the consumption of honey vs. HFCS or sucrose provides an added health benefit for maintenance of glucose homeostasis and other cardiometabolic outcomes because all 3 sugars evaluated exerted similar metabolic effects.

Acknowledgments

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