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Effects of high-fructose corn syrup and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects

MyPhuong T. Le[a], Reginald F. Frye[a], Christopher J. Rivard[b], Jing Cheng[c], Kim K. McFann[d], Mark S. Segal[e], Richard J. Johnson[b], Julie A. Johnson[a,*]

[a] Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL 32610, USA
[b] Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Denver, Aurora, CO 80045, USA
[c] Department of Epidemiology and Health Policy Research, University of Florida, Gainesville, FL 32610, USA
[d] Department of Biostatistics and Informatics, University of Colorado Denver, Aurora, CO 80045, USA
[e] Division of Nephrology, Hypertension, and Renal Transplantation, Department of Medicine, University of Florida, Gainesville, FL 32610, USA

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ABSTRACT

It is unclear whether high-fructose corn syrup (HFCS), which contains a higher amount of fructose and provides an immediate source of free fructose, induces greater systemic concentrations of fructose as compared with sucrose. It is also unclear whether exposure to higher levels of fructose leads to increased fructose-induced adverse effects. The objective was to prospectively compare the effects of HFCS- vs sucrose-sweetened soft drinks on acute metabolic and hemodynamic effects. Forty men and women consumed 24 oz of HFCS- or sucrose-sweetened beverages in a randomized crossover design study. Blood and urine samples were collected over 6 hours. Blood pressure, heart rate, fructose, and a variety of other metabolic biomarkers were measured. Fructose area under the curve and maximum concentration, dose-normalized glucose area under the curve and maximum concentration, relative bioavailability of glucose, changes in postprandial concentrations of serum uric acid, and systolic blood pressure maximum levels were higher when HFCS-sweetened beverages were consumed as compared with sucrose-sweetened beverages. Compared with sucrose, HFCS leads to greater fructose systemic exposure and significantly different acute metabolic effects.

1. Introduction

Over the past four decades, the prevalence of health disorders, including hypertension, obesity, metabolic syndrome, diabetes, and kidney disease, has drastically increased. In the United States, one third of the population has hypertension, one third of adults and one sixth of children are obese, 7% have diabetes, and about 20 million have kidney disease [1-5]. In parallel to the dramatic rise in the prevalence of these cardiorenal diseases, a similar increase in the consumption of

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* *Corresponding author*. Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, PO BOX 100486, Gainesville, FL 32610, USA. Tel.: +1 352 273 6007; fax: +1 352 273 6121.
E-mail address: johnson@cop.ufl.edu (J.A. Johnson).

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fructose has occurred. Recent studies have implicated excessive fructose intake as one of the factors driving the increases in these health disorders [3,6-8].

Rapidly metabolized by the body, fructose has been shown to cause a variety of metabolic effects, such as lactic acidosis, lipogenesis, hypertriglyceridemia, liver injury, high blood pressure (BP), insulin resistance, and increased weight gain [7,9-15]. Fructose is also the only natural sugar capable of causing a rise in uric acid levels [16]. Thus, there is a growing concern that fructose may pose a great health risk; and several studies have suggested that the excessive consumption of fructose-containing sweeteners, regardless of its composition, may be a contributing factor in the pathogenesis of cardiorenal diseases [6,12,13,17-23].

Although fructose is a simple sugar that exists naturally in fruits and vegetables, the majority of dietary fructose comes from two sweeteners, sucrose and high-fructose corn syrup (HFCS), which are commonly used in manufactured foods and beverages. Specifically, the increase in fructose consumption is primarily due to the increased use of HFCS in the Western diet. Based upon disappearance data, the annual per capita intake of HFCS from 1967 to 2006 increased from 0.03 to 58.2 lbs, whereas sucrose decreased from 98.5 to 62.3 lbs [6,24].

Sucrose is a disaccharide and consists of 50% fructose and 50% glucose. The HFCS grade used in soft drinks consists of 55% fructose, 42% glucose, and 3% oligosaccharides [25]. Because of the higher fructose dose, soft drinks sweetened with HFCS would provide more fructose into the systemic circulation than soft drinks sweetened with sucrose. Furthermore, HFCS provides an immediate source of free fructose and glucose, whereas sucrose must first be broken down by sucrase. The expression and function of sucrase have been shown to be negatively influenced by such factors as genetic polymorphisms and regulatory inhibition by glucose [26-29].

Because of the potential inefficiency of sucrase, we hypothesized that the amount of fructose available for absorption is reduced, resulting in a lower relative fructose bioavailability from sucrose. Therefore, we speculated that higher fructose systemic concentrations, either through the higher fructose dose or from increased fructose bioavailability from HFCS, would lead to increased fructose-induced adverse metabolic effects. Thus, the aim of the present study was to conduct a prospective randomized crossover study comparing the effects of HFCS- vs sucrose-sweetened beverages on the pharmacokinetics of fructose and acute metabolic and hemodynamic changes.

2. Subjects and methods

2.1. Subjects

Sixty-nine healthy subjects, 18 years or older, of either sex and of any ethnicity were recruited to participate in the study through advertisements or from the study participant database. During a screening visit, a participant's eligibility was ascertained through a health information questionnaire and limited laboratory analyses. Specifically, individuals with a history of hypoglycemia, gout, hepatic or renal disease, or diabetes mellitus, or who had a fasting blood glucose level of at least 126 mg/dL or random blood glucose of at least 200 mg/dL at the screening visit were excluded from the study. Subjects who consumed more than 7 alcoholic drinks per week, who took medication (except for oral contraceptives), who were pregnant or lactating, or who donated blood within 8 weeks before the screening visit were also excluded. Blood glucose levels were determined using the OneTouch Ultra Test Strips and OneTouch Ultra 2 Blood Glucose Meter (LifeScan, Milpitas, CA). The study was approved by the University of Florida Institutional Review Board; and all study participants signed informed, written consent.

2.2. Study designt

The study was a prospective, randomized, single-blinded, crossover trial. Acute changes in metabolic and hemodynamic parameters, such as fructose, glucose, and uric acid concentrations, were measured in participants over a 6-hour period on 2 separate study visits. Qualified participants were randomized in blocks of four, using Proc Plan in SAS (Cary, NC) 9.1.3. Subjects were randomized to 2 different sequences. Subjects randomized to the first sequence received HFCS-sweetened soft drinks at study visit 1 and sucrose-sweetened soft drinks at study visit 2. Subjects randomized to the second sequence received sucrose-sweetened soft drinks at study visit 1 and HFCS-sweetened soft drinks at study visit 2. The two 6-hour study visits were separated by a minimum of 2 days and were conducted at the Clinical Translational Science Institute (CTSI) at the University of Florida, Gainesville, FL. Both the subjects and CTSI nurses were blinded to the sweetener contained in the soft drinks.

2.3. Sugar load from soft drinks

As mentioned, the majority of dietary fructose is currently ingested as HFCS and sucrose. Because soft drinks are a major source of added sugar, we elected to treat our participants with a beverage that was manufactured with either HFCS or sucrose [30,31]. Dr Pepper sweetened with HFCS was purchased locally (Lot# NOV 24 08 12:33 to 12:58RS02218X). Dr Pepper sweetened with cane sugar (sucrose) was purchased from the Dr Pepper Bottling Company (Lot# 800807:11 TBC, http://www.dublindrpepper.com/, Dublin, TX). Except for the sweetener, the compositions of the two Dr Pepper products were similar. Sugar profiles of the 2 types of Dr Pepper were analyzed before and after the end of the study by Silliker (Illinois Laboratory, Chicago Heights, IL). From 24 oz of the soft drinks, the total sugar load was 68.0 g from the HFCS-sweetened beverage and 69.4 g from the sucrose-sweetened beverage (Table 1). The HFCS-sweetened beverage contained 39.2 g of fructose and 28.8 g of glucose. Meanwhile, the sucrose-sweetened beverage contained 34.6 g of fructose and 34.8 g of glucose. Thus, there were about 5 more grams of fructose in the 24 oz of HFCS-sweetened soft drink, resulting in about a 13% higher dose.

2.4. Study protocol

Subjects were instructed to abstain from consuming alcohol for 3 days before each study visit. Following a minimum of an

Table 1 – Carbohydrate amounts in HFCS- and sucrose-sweetened soft drinks

Sweetener	Carbohydrate	Amount (g in 24 oz)	
		Before study	After study
HFCS	Fructose	41.6 ± 0.1	36.8 ± 0.3
	Glucose	30.2 ± 0.2	27.4 ± 0.1
	Sucrose	BLD	BLD
Sucrose	Fructose	27.1 ± 0.4	32.2 ± 0.1
	Glucose	27.4 ± 0.4	32.2 ± 1.9
	Sucrose	20.0 ± 0.3	BLD

For each sugar analysis, three 12-oz cans were used. Data given as mean ± standard deviation. BLD indicates below level of detection.

8-hour overnight fast and no exercising, the participants reported to the CTSI in the morning. They were then assigned to a hospital room and allowed to rest for 15 minutes before measurement of BP and heart rate (HR). Afterwards, an intravenous catheter was inserted by a CTSI nurse. The participants were then randomly challenged with 24 oz of cold, carbonated soft drinks sweetened with either HFCS or sucrose. The soft drinks were poured into 4 cups (~6 oz per cup), and participants were given approximately 5 minutes to consume the sugar load (~75 seconds per cup). Subjects were not given any additional caloric intake during the 6-hour study period.

2.5. Study measurements

Body weight and height were measured at each study visit. Body mass index (BMI) was calculated and averaged. Blood pressure, HR, and blood samples were obtained at the following time points: 0 minute (fasting), 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4.5 hours, and 6 hours. Blood pressure and HR were measured using a Microlife Model #3AC1-AP BP monitor (Microlife USA, Clearwater, FL), which has been approved by the British Society of Hypertension [32]. Plasma from blood collected in BD Vacutainer tubes (BD, Franklin Lakes, NJ) containing sodium heparin were used to quantify fructose. Plasma from blood collected in tubes containing sodium fluoride and potassium oxalate were used to measure glucose and lactate. Serum triglycerides (TG), uric acid, creatinine, and insulin were assayed from blood collected in serum separation tubes. Because the study is similar to a 75-g oral glucose tolerance test, which usually lasts for 2 hours, we measured insulin only at 0, 30 60, and 120 minutes [33]. Samples were immediately centrifuged and separated by CTSI technicians. Urine fructose, uric acid, and creatinine were measured from samples collected before treatment and a 6-hour pooled urine collection after the consumption of the soft drinks. All samples were stored at –80°C until analyses.

2.6. Laboratory analysis

Plasma fructose concentrations were measured by an assay developed on liquid chromatography–tandem mass spectrometry (Le et al, unpublished data, 2009). The fractional excretion of fructose (FE_fructose) was calculated from the following equation:

$$\text{FE\_fructose} = \frac{\text{UFr} \times \text{SCreat}}{\text{SFr} \times \text{UCreat}} \times 100,$$

where SCreat was serum creatinine, SFr was serum fructose, UCreat was urine creatinine, and UFr was urine fructose.

Plasma glucose and lactate concentrations were measured by CTSI with the YSI 2300 STAT Plus analyzer (YSI, Yellow Springs, OH). Triglycerides, uric acid, and creatinine concentrations were analyzed with the VetACE system (Alfa Wassermann, West Caldwell, NJ). Insulin concentrations were measured with an enzyme-linked immunosorbent assay (ALPCO Diagnostics, Salem, NH). Fractional excretion of uric acid (FEUA) was calculated from the following equation:

$$\text{FEUA} = \frac{\text{UUA} \times \text{SCreat}}{\text{SUA} \times \text{UCreat}} \times 100,$$

where SUA was serum uric acid and UUA was urine uric acid [34].

2.7. Statistical analysis

2.7.1. Pharmacokinetic parameters

WinNonlin Professional Edition Version 2.1 (Pharsight, Mountain View, CA) was used to calculate the following pharmacokinetic parameters: area under the curve (AUC) of plasma concentration vs time, maximum observed concentration (Cmax), elimination half-life (HL), mean residence time (MRT), and time of Cmax (Tmax). Because of differences in doses, fructose and glucose AUC/D and Cmax/D were calculated by normalizing by the average doses of the respective sugars from each treatment. Noncompartmental analysis was conducted using linear/log trapezoidal as the calculation method.

Relative fructose bioavailability between sucrose and HFCS was calculated using the following equation (AUC_H = AUC from HFCS, AUC_S = AUC from sucrose, D_H = dose from HFCS, D_S = dose from sucrose, F_H = bioavailability from HFCS, and F_S = bioavailability from sucrose):

$$\text{Relative bioavailability} = \frac{F_H}{F_S} = \frac{D_s \times \text{AUC}_H}{D_H \times \text{AUC}_S}$$

Relative glucose bioavailability was also calculated. Paired t-test was used to compare relative bioavailability.

2.8. Statistical methods

For 40 completed subjects, the study had at least 80% power at $\alpha = .05$ two-sided to detect a paired difference in means of 0.455σ ($\sigma = 1.00$ μmol/L for fructose and $\sigma = 66$ μmol/L for SUA) [35]. Data for nonfasting participants were excluded from analyses for each study visit. Nonfasting state was determined by elevated glucose, insulin, or fructose levels measured at time 0.

Linear mixed effect models for a crossover design were used to compare the effects of HFCS vs sucrose treatments on AUC, Cmax, HL, MRT, and Tmax of the various response parameters [36]. The treatment, sequence, and visit effects were assessed in the models as fixed effects with subjects within sequence as random effect. In addition, fasting values of the metabolic and hemodynamic parameters during study visits 1 and 2 were included in the model as covariates.

Linear mixed effect models were also used to compare the effects of HFCS vs sucrose treatments on the repeated-measures data collected over the 6-hour study period of each

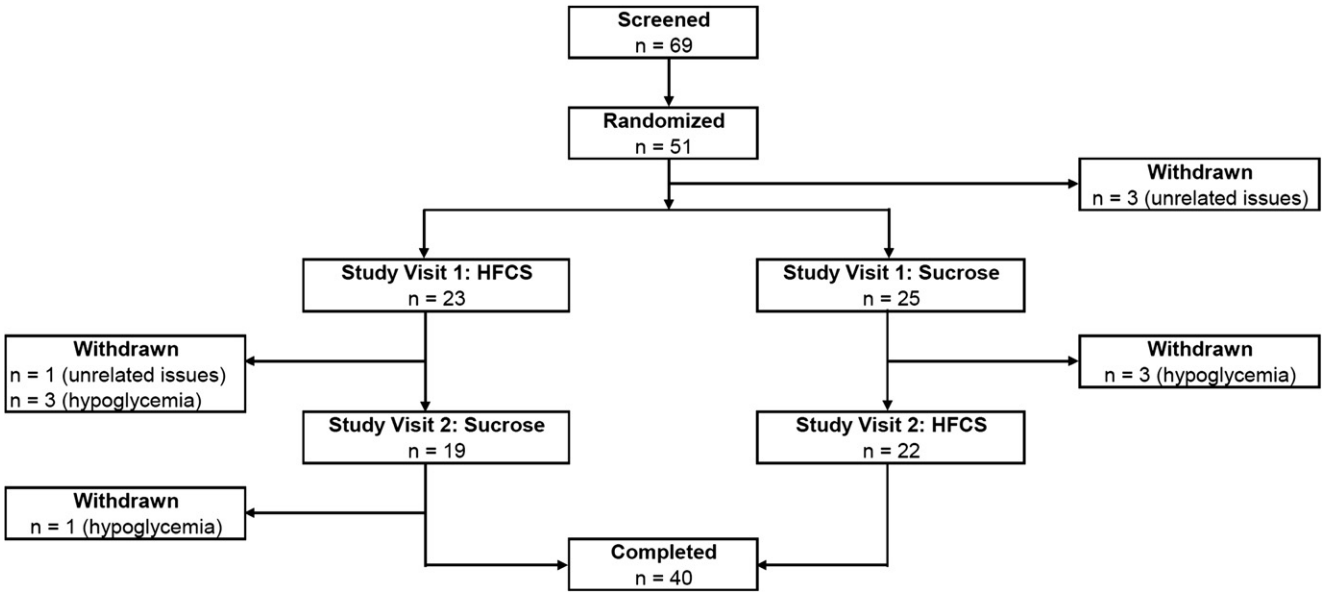

Fig. 1 – Study population. Sixty-nine subjects were recruited. Forty participants completed both treatment arms.

of the response parameters. Treatment, time, interaction of treatment and time, and sequence were included in the models as fixed effects with fasting values as a covariate and subjects within sequence as random effect. Autoregressive (1) covariance structure was used for the repeated measures over time within each treatment, and unstructured covariance structure was used for the repeated measures over 2 treatments within same subjects. Preplanned contrasts were used to compare between the treatments at each time point. Based on the Shapiro-Wilk test, fructose, glucose, insulin, lactate, TG, FE_fructose, and FEUA were not normally distributed. Analyses for these variables were based on $\log_{10}$-transformed data. Results were reported by back transforming the least square means and 95% confidence interval (CI). Fructose and glucose concentrations were also normalized by their respective doses from each treatment. Dose-adjusted concentrations from the 15-minute to 6-hour period were analyzed. All analyses were conducted using SAS 9.2. To adjust for multiple comparisons, statistical significance was defined as $P < .005$.

3. Results

3.1. *Baseline characteristics*

Fifty-one subjects, from ages 18 to 52 years, met the inclusion criteria and were randomized to participate in the study (Fig. 1). Four subjects were withdrawn for reasons unrelated to the study. An additional 7 subjects (3 after consuming HFCS-sweetened soft drinks and 4 from sucrose-sweetened soft drinks) were withdrawn after developing asymptomatic reactive hypoglycemia (mean blood glucose, 52.3 ± 4.0 mg/dL) from the sugar load. *Hypoglycemia* was defined as blood glucose less than or equal to 60 mg/dL that was confirmed by 2 separate measurements. Overall, 40 individuals completed both study visits; and their baseline characteristics are shown in Table 2.

Table 2 – Baseline characteristics of study participants

Variable	Completed subjects (n = 40)
Age	27.1 ± 8.6
Female	24 (60.0)
Race	
White, European American	23 (57.5)
Black, African American	4 (10.0)
Asian	7 (17.5)
Other/multiracial	6 (15.0)
BMI	25.9 ± 4.9
Glucose (mg/dL)	81.0 ± 4.8
Insulin (μIU/mL)	9.8 ± 12.7
TG (mg/dL)	86.5 ± 39.1
SBP (mm Hg)	118.4 ± 9.7
DBP (mm Hg)	75.0 ± 6.4
HR (beat/min)	66.2 ± 8.3
Fructose (μmol/L)	5.4 ± 4.5
FE_fructose (%)	55.0 ± 57.7
SUA (mg/dL)	4.9 ± 1.0
FEUA (%)	5.5 ± 2.0
Lactate (mg/dL)	0.7 ± 0.2

Data given as either mean ± standard deviation or number (percentage). For completed subjects, data for response parameters represent fasting levels at study visit 1. BMI indicates body mass index. DBP, diastolic blood pressure; FE, fructose fractional excretion of fructose; FEUA, fractional excretion of uric acid; HR, heart rate; SBP, systolic blood pressure; SUA, serum uric acid; TG, triglycerides. DBP, diastolic blood pressure; FE, fructose fractional excretion of fructose; FEUA, fractional excretion of uric acid; HR, heart rate; SBP, systolic blood pressure; SUA, serum uric acid; TG, triglycerides.

Table 3 – Fasting levels of response parameters at each study visit of completed subjects

Parameter	Treatment sequence			
	All			
	HFCS → sucrose		Sucrose → HFCS	
	Visit 1	Visit 2	Visit 1	Visit 2
Fructose (μmol/L)	5.4 ± 3.9	4.4 ± 1.4	5.4 ± 5.0	4.6 ± 2.0
FE_fructose (%)	45.9 ± 28.3	42.0 ± 23.2	62.5 ± 73.5	48.0 ± 35.9
SUA (mg/dL)	4.9 ± 0.9	4.8 ± 0.8	4.9 ± 1.0	5.0 ± 1.0
FEUA (%)	5.5 ± 1.5	5.1 ± 2.2	5.5 ± 2.3	5.0 ± 2.1
Glucose (mg/dL)	79.7 ± 5.3	81.4 ± 6.5	82.1 ± 4.1	80.3 ± 6.7
Insulin (μIU/mL)	10.4 ± 15.7	9.0 ± 13.1	9.2 ± 9.8	9.6 ± 10.7
Lactate (mg/dL)	0.6 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	0.7 ± 0.3
TG (mg/dL)	92.2 ± 46.5	79.9 ± 45.7	81.9 ± 32.2	94.6 ± 44.0
SBP (mm Hg)	118.1 ± 9.5	119.8 ± 9.5	118.7 ± 10.1	119.1 ± 10.2
DBP (mm Hg)	74.7 ± 6.2	74.4 ± 8.5	75.3 ± 6.8	74.9 ± 6.8
HR (beat/min)	66.5 ± 7.3	66.4 ± 7.4	65.9 ± 9.2	66.5 ± 9.3

Data given as mean ± standard deviation. DBP, diastolic blood pressure; FE, fructose fractional excretion of fructose; FEUA, fractional excretion of uric acid; HR, heart rate; SBP, systolic blood pressure; SUA, serum uric acid; TG, triglycerides. DBP, diastolic blood pressure; FE, fructose fractional excretion of fructose; FEUA, fractional excretion of uric acid; HR, heart rate; SBP, systolic blood pressure; SUA, serum uric acid; TG, triglycerides.

3.2. *Effects of HFCS vs sucrose on acute metabolic and hemodynamic parameters*

Table 3 lists the fasting levels of the various response parameters measured at the 2 study visits for both of the treatment sequences. The sequence and visit effects were insignificant for all of the response parameters.

3.3. *Fructose, FE_fructose, and relative bioavailability of fructose*

Fructose AUC was about 20% greater and Cmax was about 15% greater from the HFCS-sweetened beverages than from the sucrose-sweetened beverages (Table 4). From the repeated-measures data, there was also a significant treatment effect of HFCS ($P = .0032$) vs sucrose on changes in postprandial fructose concentrations over the 6-hour study period (Fig. 2A). Fructose levels were higher from the HFCS treatment at 30 and 90 minutes.

Although the values were higher from HFCS, treatment effects were no longer significant when normalized for the differences in dose of fructose between HFCS and sucrose (Table 4, Fig. 2B). Thus, a gram of fructose from either HFCS or sucrose is absorbed in a similar manner, which is indicated by a lack of difference in relative fructose bioavailability between the 2 sweeteners (1.07 ± 0.24, $P = .1219$). Although there was a greater FE_fructose from HFCS-sweetened soft drinks, the effect was not significant (Fig. 2C).

3.4. *Glucose*

Glucose AUC, Cmax, and changes in postprandial glucose concentrations were very similar between HFCS and sucrose

Table 4 – Effects of consuming HFCS- vs sucrose-sweetened beverages on fructose, FE_fructose, and glucose

Variable	Parameter	Treatment				P value
		HFCS		Sucrose		
		Mean	95% CI	Mean	95% CI	
AUC (min *μmol/L)*	Fructose	38791 ± 1624	35533-42049	32327 ± 1614	29087-35567	<.0001
AUC/D [(min *μmol/L)/g]	Fructose	989.5 ± 43.3	902.6-1076.3	934.4 ± 43.0	848.0-1020.8	.1076
Cmax (μmol/L) *	Fructose	363.4 ± 17.6	328.1-398.8	317.0 ± 17.5	281.9-352.2	.0043
Cmax/D [(μmol/L)/g]	Fructose	9.3 ± 0.5	8.3-10.2	9.2 ± 0.5	8.2-10.1	.8039
Tmax (min)	Fructose	57.4 ± 4.2	49.1-65.8	59.7 ± 4.1	51.4-68.0	.6172
MRT (min)	Fructose	87.8 ± 2.0	83.8-91.8	89.6 ± 2.0	85.6-93.5	.3063
HL (min)	Fructose	35.4 ± 2.2	31.0-39.8	39.3 ± 2.2	34.9-43.7	.2079
Relative bioavailability[a]	Fructose	1.07 ± 0.24				.1219
ΔFE_fructose (%)	FE_fructose	311.8 ± 66.7	178.8-444.8	302.9 ± 66.0	171.4-434.4	.9249
AUC (min *mg/dL)	Glucose	29911 ± 323	29266-30557	30053 ± 320	29413-30694	.6492
AUC/D [(min *mg/dL)/g] *	Glucose	1038.2 ± 9.9	1018.4-1058.0	863.1 ± 9.8	843.5-882.7	<.0001
Cmax (mg/dL)	Glucose	120.3 ± 2.6	115.2-125.4	123.5 ± 2.5	118.4-128.6	.1778
Cmax/D [(mg/dL)/g] *	Glucose	4.2 ± 0.1	4.0-4.3	3.5 ± 0.1	3.4-3.7	<.0001
MRT (min)	Glucose	172.5 ± 0.9	170.8-174.3	170.4 ± 0.9	168.6-172.1	.0292
Tmax (min)	Glucose	30.1 ± 2.7	24.8-35.4	30.2 ± 2.6	24.9-35.4	.9842
Relative bioavailability *,[a]	Glucose	1.20 ± 0.07				<.0001

Data given as least square mean ± standard error. Linear mixed effect models were used to analyze the parameters. AUC/D indicates AUC divided by the respective sugar dose of the treatment; Cmax/D, Cmax divided by the respective sugar dose of the treatment. AUC, area under the curve; Cmax, maximum observed concentration; MRT, mean residence time; Tmax, time of Cmax; FE, fructose fractional excretion of fructose; CI, confidence interval.

[a] Paired *t*-test was used.

* P value < .005.

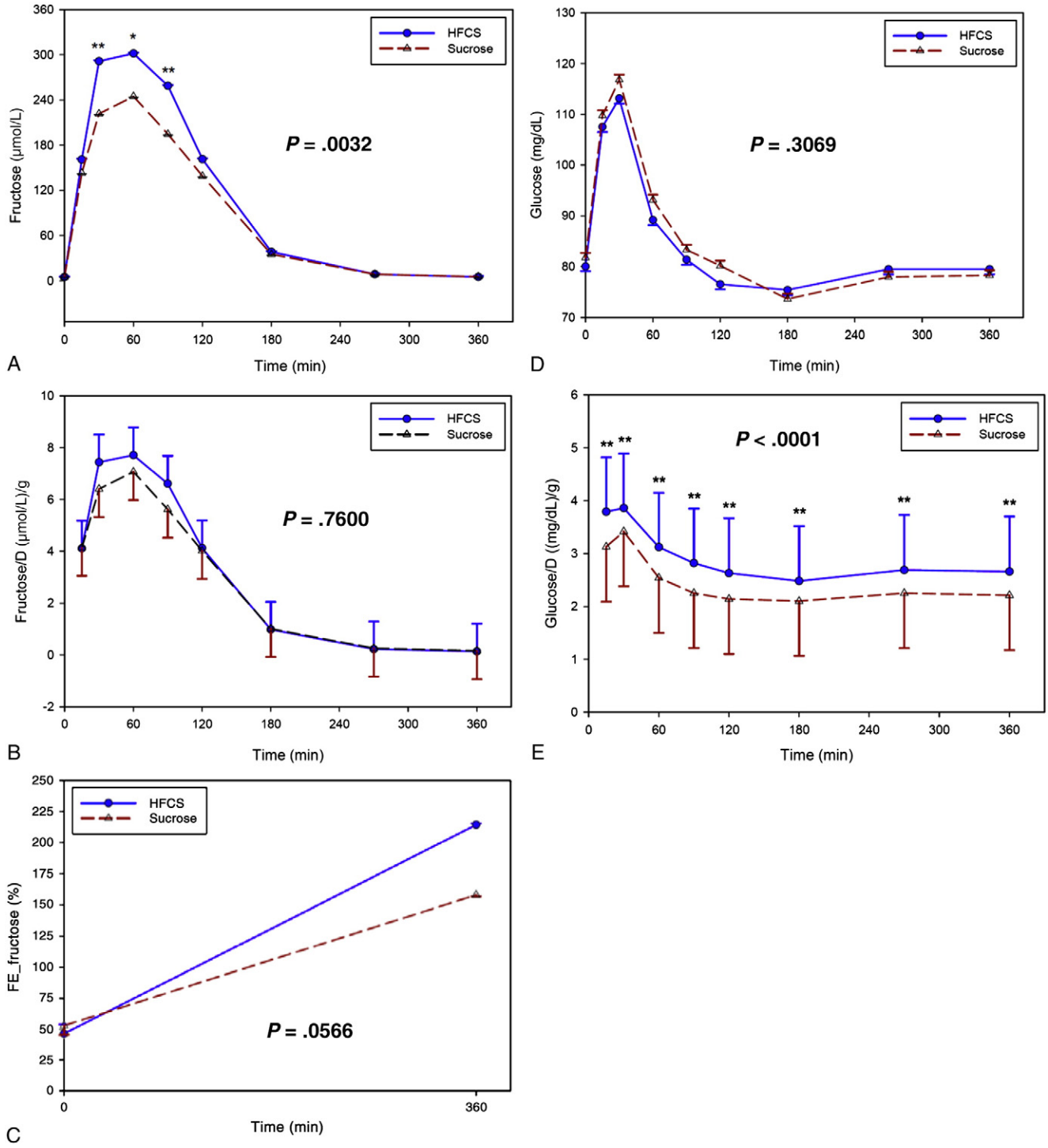

Fig. 2 – Effect of consuming HFCS- vs sucrose-sweetened beverages during a 6-hour period on (A) fructose, (B) normalized fructose by dose of each treatment, (C) FE_fructose, (D) glucose, and (E) normalized glucose by dose of each treatment. Values are least square means ± standard errors. *P*-value shown represents overall treatment effect. *p*-value: * = < 0.05; ** = < 0.005. FE_fructose fractional excretion of fructose; HFCS high fructose corn syrup.

(Table 4, Fig. 2D). However, dose-normalized glucose AUC and Cmax were significantly higher from the HFCS treatment compared with sucrose. In addition, dose-normalized glucose concentrations were higher at all time points (Fig. 2E). The relative bioavailability of glucose indicates that a gram of glucose from HFCS reaches the systemic circulation more efficiently than that from sucrose (1.20 ± 0.07, $P < .0001$).

Table 5 – Effects of consuming HFCS- vs sucrose-sweetened beverages on SBP, DBP, and HR

Variable	Parameter	Treatment				P value
		HFCS		Sucrose		
		Mean	95% CI	Mean	95% CI	
AUC (min *mm Hg)	SBP	43832 ± 309	43214-44449	43588 ± 306	42977-44200	.4802
Observed max (mm Hg) *	SBP	133.5 ± 1.0	131.4-135.5	130.2 ± 1.0	128.1-132.2	.0047
AUC (min *mm Hg)	DBP	27460 ± 263	26935-27985	27363 ± 260	26842-27883	.7425
Observed max (mm Hg)	DBP	84.1 ± 0.8	82.4-85.7	84.0 ± 0.8	82.4-85.6	.9470
AUC (min *beat/min)	HR	23856 ± 263	23328-24384	23791 ± 262	23266-24316	.7745
Observed max (beat/min)	HR	75.3 ± 0.9	73.5-77.1	75.0 ± 0.9	73.2-76.8	.7488

Data given as least square mean ± standard error. Linear mixed effect models were used to analyze the parameters. AUC, area under the curve; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; CI, confidence interval.
* P value < .005.

3.5. *BP and HR*

The observed maximum systolic BP (SBP) was significantly different between the 2 treatments (Table 5). In contrast, diastolic BP (DBP) did not differ between the treatment groups; and neither did HR (Table 5).

3.6. *SUA and FEUA*

There were no treatment differences in AUC and Cmax of SUA or FEUA (Table 6). However, there was a significantly higher effect from HFCS than from sucrose on postprandial changes in levels of SUA (P = .0042, Fig. 3A). Although, FEUA was higher at the end of the 6-hour study visit from HFCS, the treatment effect did not meet our definition of statistical significance (P = .0254, Fig. 3B).

3.7. *TG, insulin, and lactate*

There were no treatment differences in AUC and Cmax of TG, insulin, and lactate (Table 6). There were also no contrast differences in postprandial concentrations at any time points between HFCS vs sucrose for TG (Fig. 3C), insulin (Fig. 3D), and lactate (Fig. 3E).

4. Discussion

In this study, we compared the acute metabolic and hemodynamic effects of HFCS and sucrose in 40 healthy subjects. We found treatment differences in fructose, glucose, SUA, and SBP. The following metabolic parameters were higher from the HFCS-sweetened beverages than from the sucrose-sweetened beverages: fructose AUC and Cmax, dose-normalized glucose AUC and Cmax, relative bioavailability of glucose, changes in postprandial concentrations of SUA, and observed maximum SBP. There were no differences in relative fructose bioavailability, FE_fructose, FEUA, DBP, HR, TG, insulin, and lactate. To our knowledge, this is the first study to show that HFCS is more likely to cause acute adverse effects than sucrose.

We hypothesized that the formulation of HFCS would result in greater systemic fructose exposure than from sucrose. First, HFCS contains more fructose than sucrose. Second, HFCS consists of free fructose and glucose, thus allowing for the immediate transport of these simple sugars in the intestine. Meanwhile, sucrose must first be metabolized by sucrase before fructose and glucose are available for uptake. Studies have shown that the expression of sucrase

Table 6 – Effects of consuming HFCS- vs sucrose-sweetened beverages on SUA, FEUA, TG, insulin, and lactate

Variable	Parameter	Treatment				P value
		HFCS		Sucrose		
		Mean	95% CI	Mean	95% CI	
AUC (min mg/dL)	SUA	1848.6 ± 15.1	1818.5-1878.7	1811.3 ± 14.9	1781.5-1841.0	.0827
Cmax (mg/dL)	SUA	5.4 ± 0.1	5.3-5.5	5.4 ± 0.1	5.2-5.5	.4947
ΔFEUA (%)	FEUA	7.6 ± 0.4	6.8-8.3	7.0 ± 0.4	6.2-7.7	.2671
AUC (min mg/dL)	TG	30661 ± 798	29069-32253	31964 ± 790	30387-33540	.1949
Cmax (mg/dL)	TG	101.7 ± 2.4	97.0-106.5	108.4 ± 2.4	103.7-113.1	.0108
AUC (min μIU/mL)	Insulin	3717.2 ± 304.4	3106.7-4327.8	3824.3 ± 302.2	3217.8-4430.7	.6846
Cmax (μIU/mL)	Insulin	58.1 ± 5.8	46.4-69.8	61.2 ± 5.8	49.6-72.8	.5905
AUC (min mg/dL)	Lactate	355.4 ± 11.1	333.1-377.8	354.2 ± 11.0	332.1-376.4	.8907
Cmax (mg/dL)	Lactate	2.0 ± 0.1	1.9-2.2	2.1 ± 0.1	1.9-2.2	.4401

Data given as least square mean ± standard error. Linear mixed effect models were used to analyze the parameters. AUC, area under the curve; Cmax, maximum observed concentration; FEUA, fractional excretion of uric acid; SUA, serum uric acid; Tg triglycerides; CI, confidence interval.

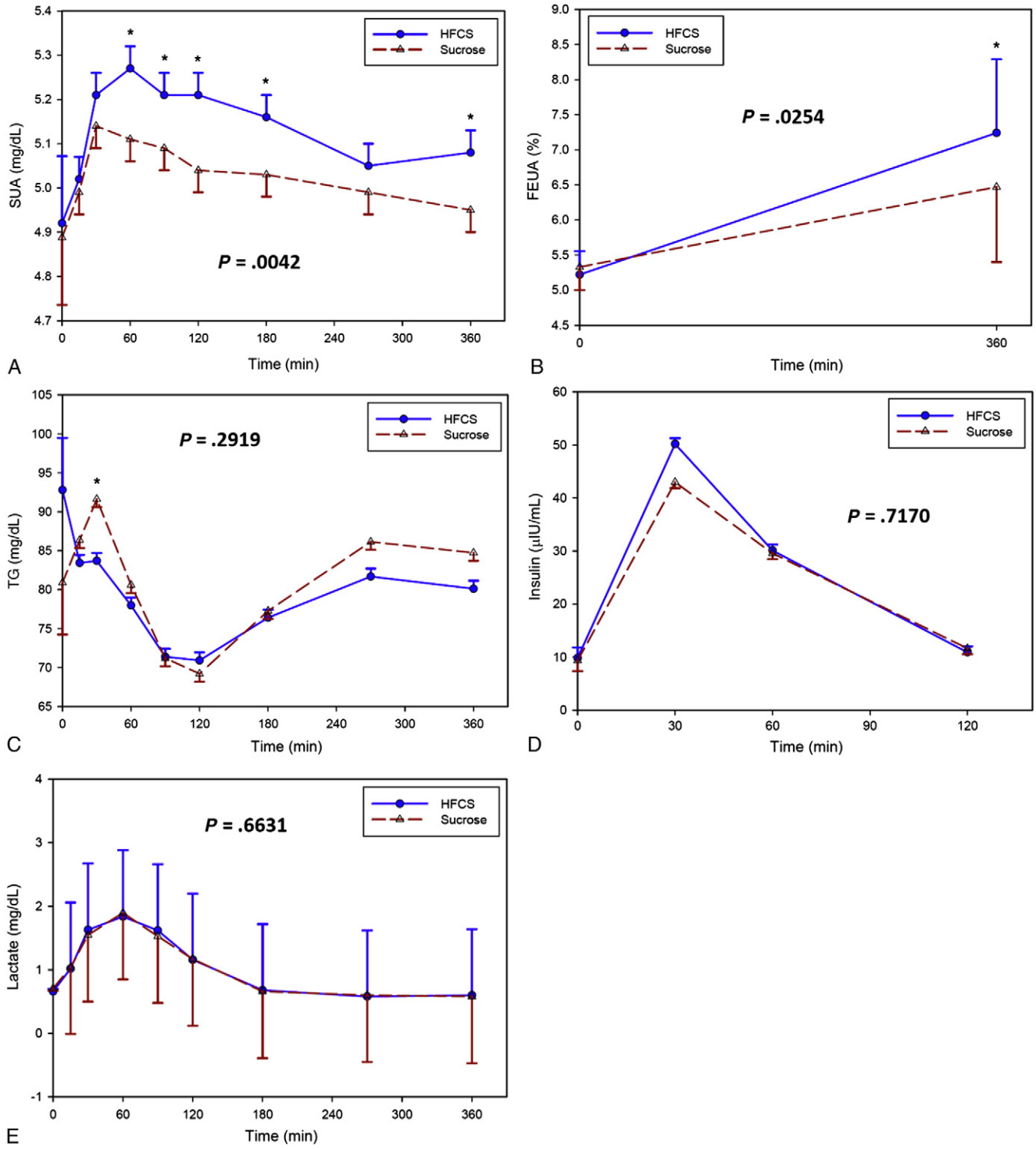

Fig. 3 – Effect of consuming HFCS- vs sucrose-sweetened beverages during a 6-hour period on (A) SUA, (B) FEUA, (C) TG, (D) insulin, and (E) lactate. Values are least square means ± standard errors. P-value shown represents overall treatment effect. * P-value < 0.05. FEUA fractional excretion of uric acid; HFCS high fructose corn syrup; SUA serum uric acid; Tg triglycerides.

can be negatively affected by genetic polymorphisms [26,27]. Its activity has also been shown to be inhibited by glucose [28,29]. Thus, we hypothesize that sucrase may potentially be a bottleneck, preventing complete metabolism of sucrose in the gut. Therefore, less fructose would be available for transport. In our study, we found that fructose AUC was about 20% greater and Cmax was about 15% greater from the HFCS-sweetened beverages than from sucrose-sweetened

beverages. However, the relative bioavailability was not different. Thus, the difference in fructose plasma concentrations between the sweeteners is most likely due to the higher fructose dose from HFCS, which was about 13% greater than that from sucrose. Interestingly, we also detected a significant difference in dose-normalized glucose AUC and Cmax. This was surprising because the glucose dose from sucrose was 6 g or about 21% higher than that from HFCS. This finding suggests that glucose is more efficiently absorbed into the body from HFCS than from sucrose. The mechanism for this enhanced bioavailability of glucose needs to be further elucidated.

Our study found a significant increase in SBP, about 3 mm Hg, from HFCS compared with sucrose. However, the increase was very acute. The impact of chronic exposure of higher fructose bioavailability on affecting sustained elevated BP needs to be investigated. Nevertheless, our finding potentially supports the postulated link between high fructose intake and increased SBP. Jalal et al [8] recently reported an association between high fructose intake from added sugars and increased risk of elevated SBP in the National Health and Nutrition Examination Survey. In a randomized study consisting of 74 men, Perez-Pozo et al [37] showed that the ingestion of fructose was associated with an increase in BP. Others have also found a relationship of sugar-sweetened soft drink intake with BP [38,39], although this was not observed in a study in which much of the fructose intake originated from fruits [40].

Several mechanisms have been proposed for fructose-induced high BP, including fructose-induced hyperuricemia [38]. This is an appealing mechanism because previous studies have shown that fructose can increase uric acid levels [16,41]. Fructose increases uric acid both by acute effects related to adenosine triphosphate consumption and purine degradation, but also via chronic effects to stimulate uric acid synthesis [16,41,42]. Importantly, Feig et al [43] showed that by lowering uric acid levels, there was a decrease in BP in hypertensive adolescents with newly diagnosed hypertension. Furthermore, Perez-Pozo et al [37] showed that by lowering uric acid with allopurinol, the effect of fructose (200 g/d for 2 weeks) on elevated BP was prevented in healthy adults. Finally, an epidemiological study has linked uric acid with soft drink ingestion and hypertension in adolescents [44]. In our study, we detected a treatment difference in SUA level, which was higher from HFCS than sucrose. Although the difference was small, about 0.2 mg/dL, our findings highlight that SUA levels can increase when fructose levels increase in the body. Thus, our data potentially support the link between higher fructose levels, elevated uric acid levels, and higher SBP levels, although other mechanisms by which fructose could raise BP remain possible [45].

Because of the similarity in composition between HFCS and sucrose, it has been speculated that the metabolic effects of these sweeteners are also similar. Studies directly comparing the effects of HFCS vs sucrose are limited. Nevertheless, Melanson et al [46], Akhavan and Anderson [47], Soenen and Westerterp-Plantenga [48], and Stanhope et al [14] conducted short-term studies comparing the 2 sweeteners. These studies found no significant differences on glucose, ghrelin, leptin, insulin, TG, uric acid, glucagon-like peptide 1, appetite, and food intake. Although their findings seemingly conflict with our results, these studies did not assess fructose bioavailability and did not account for fructose levels. If fructose is an important factor driving the development of various adverse metabolic effects, we hypothesize that higher fructose exposure would lead to greater effects. If, in these studies, there were no differences in exposure to fructose between their study groups, it would not be surprising that HFCS and sucrose resulted in similar effects. Importantly, fructose bioavailability can vary greatly because of various factors, such as individual differences in fructose absorption and metabolism, the effects of glucose on impacting fructose uptake, and liquid vs solid vs mixed sources of fructose-containing sweeteners [49-54]. In our study, we were able to detect a higher exposure to fructose from HFCS than from sucrose. Thus, this may explain why we were able to detect a difference in metabolic and hemodynamic effects between the 2 sweeteners, whereas other studies have not.

Our study has several limitations. First, it was determined from the sugar profile analyses that the sucrose in the soft drinks was being hydrolyzed. At the start of the study, about 60% of the sucrose had already been hydrolyzed; and by the end of the study, all of the sucrose had been broken down. As a result, the potential important role of sucrase was marginalized, which may have reduced our ability to detect a difference in fructose relative bioavailability between HFCS and sucrose and which may have resulted in greater differences in fructose AUC and Cmax. However, the external validity of the study is high because soft drinks are a major source of sucrose and HFCS. For future studies, a more controlled environment can be obtained by having the sugar mixtures made immediately before the study visits. Second, the study population consisted of young and healthy individuals. Their responses may have been less dramatic than older individuals who are metabolically at risk, such as those with abdominal obesity or those with metabolic syndrome.

In conclusion, our findings suggest that there are differences in various acute metabolic and hemodynamic responses between HFCS and sucrose. A major strength of our study was the fructose measurements. This allowed us to determine that the consumption of HFCS resulted in higher systemic fructose exposure, which may have driven the significant treatment differences detected on glucose, SUA, and, SBP. Although the treatment effects on acute metabolic responses were small, the effects may increase with continued chronic exposure to these sweeteners. Furthermore, it still needs to be determined if there are differences in fructose exposure and metabolic effects from HFCS and sucrose if the sweeteners were consumed over a longer period vs the acute bolus that was given in our study. Importantly, further studies are needed to evaluate the impact of variable fructose absorption and/or metabolism on higher fructose exposure and how that may affect long-term metabolic responses and disease risks. Although we did find differences between HFCS and sucrose, both sweeteners are currently consumed in excessive amounts, which may play an important role in driving the prevalence of cardiorenal diseases.

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Conflict of Interest

RJJ has a patent application on inhibition of fructokinase as a mechanism to treat sugar craving. RJJ also has a lay book, *The Sugar Fix: The High-Fructose Fallout That Is Making You Fat and Sick* (Rodale and Simon and Schuster, 2008). No other authors declared a conflict of interest.

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