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Fructose Acute Effects on Glucose, Insulin, and Triglyceride After a Solid Meal Compared with Sucralose and Sucrose in a Randomized Crossover Study

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Fructose acute effects on glucose, insulin, and triglyceride after a solid meal compared with sucralose and sucrose in a randomized crossover study[1,2]

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ABSTRACT

Background: Fructose, which is a sweetener with a low glycemic index, has been shown to elevate postprandial triglyceride compared with glucose. There are limited data on the effect of fructose in a solid mixed meal containing starch and protein.

Objective: We determined the effects of sucrose, fructose, and sucralose on triglyceride, glucose, and insulin in an acute study in healthy, overweight, and obese individuals.

Design: The study had a randomized crossover design. Twenty-seven participants with a mean age of 44 y and a mean body mass index (in kg/m^2) of 26 completed the study. Fructose (52 g), sucrose (65 g), and sucralose (0.1 g) were delivered as sweet-taste–balanced muffins with a total fat load (66 g). Blood samples were taken at baseline and every 30 min for 4-h glucose, triglyceride, and insulin concentrations, and the area under the curve (AUC) and the incremental area under the curve (iAUC) were analyzed.

Results: No significant difference was shown between the 3 sweeteners for triglyceride and glucose concentrations and the AUC. The glucose iAUC was lower for fructose than for sucrose and sucralose ($P < 0.05$). Insulin concentrations differed significantly by the type of muffin ($P = 0.001$), the interaction of time by type of muffin ($P = 0.035$), the AUC ($P < 0.001$), and the iAUC ($P < 0.001$). Fructose had a significantly lower insulin response than that of either sucrose (P-treatment = 0.006) or sucralose (P-treatment = 0.041).

Conclusions: Fructose, at a moderate dose, did not significantly elevate triglyceride compared with sucrose or sucralose and lowered the glucose iAUC. These results indicate that these sweeteners, at an equivalent sweetness, can be used in normal solid meals. Fructose showed a lower insulin response, which may be beneficial in the long term in individuals at risk of type 2 diabetes. This trial was registered at the Australian New Zealand Clinical Trials Registry as ACTRN12615000279527. *Am J Clin Nutr* 2016;103:1453–7.

Keywords: fructose, insulin, postprandial, sucralose, sucrose

INTRODUCTION

Fructose consumed in beverages has been associated with increased incidences of obesity, type 2 diabetes, and cardiovascular disease in both cross-sectional and longitudinal studies (1). Short-term hypercaloric-consumption studies in obese subjects have shown that fructose consumed in beverages increased visceral fat, insulin resistance, and hypertriglyceridemia more than did a similar amount of glucose (2), although some of the differences, such as in visceral fat, were NS between groups. However in a meta-analysis of isocaloric-consumption studies ≥7 d in duration in which weight gain did not occur, fructose consumed as either beverages or foods did not have any differential effects than did other forms of carbohydrate on postprandial triglycerides (3). In acute studies in which fructose was consumed as part of a fat-tolerance test (4, 5) or as an addition to a mixed meal, fructose increased postprandial triglyceride concentrations (6–10) compared with the effect from glucose or other carbohydrate although some studies were negative (11–13). Despite these negative associations with fasting and postprandial triglyceride concentrations, fructose substitution in liquids or solid foods for starch in type 2 diabetes improves glycemic control (14). Fructose, itself, does not directly add to plasma glucose to a substantial degree over 4 h, and fructose-6-phosphate stimulates glucokinase regulatory protein-1 (15) and doubles the hepatic glucose content and enhances glycogen synthesis 4-fold (16), thereby leading to a 14% lower plasma glucose response and 21% lower plasma insulin in an oral glucose tolerance test with 7.5 g fructose added to the glucose.

Thus, it is possible that the consumption of fructose may be beneficial in people with insulin resistance or prediabetes provided that it is used in solid meals, such as in biscuits and cakes, which are more satiating than beverages are (17), and intake is restricted to<60g/d. Noncaloric sweeteners are widely used in beverages but are little used in solid foods, and thus, there is scope for an investigation of the replacement of sucrose with fructose to minimize the glycemic and insulinemic responses to

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[2] Supplemental Figures 1–9 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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sucrose. Optimally, sucrose-rich foods should not be consumed by people at risk of diabetes, but the reality is that this behavior does not occur as often as it should, and thus, alternative strategies are necessary to reduce risk of the progression to type 2 diabetes. Fructose has the advantage of being sweeter than sucrose is in a ratio of 0.8:1, and therefore, less fructose is needed and provides a lower caloric load when used instead of sucrose (18).

In this study, we investigated the use of fructose in solid starchy foods at a moderate dose (52 g/d), which is not much different from mean daily fructose intake from all sources, and compared it with both sucrose (65 g/d) and sucralose (0.1 g/d) to provide a sugar-free control. We hypothesized that fructose would enhance the uptake of glucose derived from starch and produce a lower insulin response than would either sucrose or sucralose without adversely affecting triglyceride concentrations in healthy normal-weight, overweight, and obese people.

METHODS

Participants

Participants were recruited with the use of a public advertisement and were screened over the telephone before their first visit. Participants were recruited from the general healthy population aged 18–81 y and with BMI (in kg/m^2) >17.5. Exclusion criteria were as follows: participants with renal, hepatic, active cardiac disease, known type 2 diabetes, cancer in the treatment phase, or an intolerance to the muffin ingredients (e.g., celiac disease), those who were pregnant or breastfeeding, or individuals who participated in another dietary study. The power analysis indicated that 24 participants were required to complete the study to provide 80% power to see a 30% difference in the triglyceride AUC; significance was set at $P < 0.05$. The power calculation was based on an SD of difference in triglyceride for both the AUC (0.4 mmol/L · h) and triglyceride at 4 h of 0.4 mmol/L, which produced similar numbers.

Participant recruitment is shown in **Supplemental Figure 1**. Twenty-nine healthy volunteers were recruited (11 men and 18 women). The experimental protocol was approved by the Human Ethics Committee at the University of South Australia, and all procedures were followed in accordance with ethical standards. The trial was registered at the Australian New Zealand Clinical Trials Registry as ACTRN12615000279527. All participants provided written consent. A gift of $58 was offered to participants once the study was completed.

TABLE 1
Composition of test meals[1]

	Sucrose	Fructose	Sucralose
Energy			
kJ	4721	4606	4177
kcal	1128	1101	998
Protein, g	17	17	19
Total fat, g	66	67	67
Saturated	41	41	41
Polyunsaturated	3	3	3
Monounsaturated	17	17	17
Total carbohydrate, g	119	109	80
Starch	54	57	80
Sugars	65	52	0

[1]Determined with the use of FoodWorks 7 2012 software [Xyris Software (Australia) Pty. Ltd.].

Study design

The study was a double-blind, randomized crossover study. Participants attended 3 study days. Before their first test day, subjects were randomly assigned to an order of sweetener consumption with the use of an online randomization website. The sweeteners were delivered via 3 muffins. Participants fasted overnight except for intake of water, and visits were separated by ≥1 wk. The muffin meals had a standardized amount of fat; the addition of cream was required with fructose and sucrose muffins (24 and 32 g, respectively) to reach the predetermined dose of 66 g fat. The fructose and sucralose muffins were adapted for an equivalent sweetness and consistent flavor from a recipe for blueberry muffins containing sucrose. The fructose dose was calculated at 80% of sucrose because fructose is sweeter than sucrose (18). Sucralose was used in equal volumes as sucrose, as per the manufacturer's instructions (19), so that the test meal contained 10 g Splenda (McNeil Nutritionals) of which 0.1 g was sucralose (21). Splenda contains 1% sucralose and 99% maltodextrin. The calories from 10 g maltodextrins were included in the starch component of the diet-composition table. The composition of muffin meals is shown in **Table 1**. Three small muffins made up the breakfast meal. Participants could have tea or coffee without sweeteners with their meal. Detailed intake of the beverage was recorded and replicated during the 3 visits. Details of any relevant medications and anthropometric measure (height and weight) were taken during visit 1. Body weight was measured at each visit with the use of electronic digital scales (Tanita Corp.) with participants wearing light clothing with their shoes removed. Height was measured on a wall-mounted stadiometer (Seca). Changes in medications, if any, were recorded during the 3 visits. Participants were asked to consume the 3 muffins within 15 min, which was timed to ensure consistency between test days. Participants could have tea or coffee with milk, if requested, but without sweeteners with their meal. Beverage intake was recorded and replicated during the 3 visits. One author (EP) was not blinded to the muffin identity but did not analyze the data.

Metabolic tests

An intravenous cannula was inserted at each study visit, and blood samples were taken at baseline and every 30 min for 4 h after the meal. For the analysis of glucose and triglyceride, 4 mL blood was collected in tubes that contained sodium fluoride glycolysis inhibitors and EDTA and stored on ice until processed. For the insulin analysis 8 mL blood was collected in serum separator clot-activator tubes, which were left to clot for ≥30 min. Whole blood samples were centrifuged at 4000 × *g* for 10 min (Universal 32R; Hettich Zentrifugen), and aliquots of serum

TABLE 2
Participant characteristics (n = 29)

	Minimum	Maximum	Mean ± SD
Age, y	19	81	44.3 ± 19
Weight, kg	41.10	114	73.9 ± 17.3
BMI, kg/m^2	17.5	36.2	26.3 ± 5.4

were stored at −80°C until analysis at the end of the study. Insulin measurements were performed with the use of an ELISA on kits (kit 0030N) provided by Alpha Diagnostic International. Glucose and triglyceride concentrations were determined on an autoanalyzer (Konelab 20XTi Thermo Electron Corp.). All reagents were supplied by Thermo Electron Corp.

Statistics

Data from the participants was analyzed with IBM SPSS software (version 20; IBM). The AUC and incremental AUC (iAUC) were calculated for glucose, insulin, and triglyceride with the use of the trapezoidal method. The Shapiro-Wilk test, quantile-quantile plots, and histograms were used to test for the normality of distribution. Insulin was not normally distributed and was log transformed. An analysis was performed with the use of a repeated-measures ANOVA. Significance was set at $P < 0.05$.

RESULTS

Twenty-nine healthy volunteers (11 men and 18 women) were randomly assigned and had a mean age of 44 y and mean BMI of 26. Baseline characteristics are shown in **Table 2**. Twenty-seven participants completed the study. Two volunteers dropped out after the first visit and provided no experimental data.

Glucose

There was no significant difference in baseline glucose concentrations during the 3 visit days. No significant difference was shown for the treatment or the time-by-treatment interaction (**Figure 1**). A significant difference (**Figure 2**) was shown between the 3 muffin meals for the glucose iAUC ($P = 0.019$) with post hoc differences between fructose and sucrose and between fructose and sucralose (both $P < 0.05$). There was no effect of age, sex, or BMI on the iAUC. Scatter plots of the data shown in Figure 2 are presented in **Supplemental Figures 2–5**.

Insulin

There were no significant differences in baseline concentrations during the 3 visit days. Insulin at baseline was significantly skewed and required a log transformation. Significance was shown for time ($P < 0.001$), treatment ($P = 0.001$), and the time-by-treatment interaction ($P = 0.035$) with treatment differences between fructose and both sucrose and sucralose ($P = 0.006$ and 0.04, respectively) but not between sucrose and sucralose (**Figure 3**). The log AUC ($P < 0.001$) and log iAUC ($P < 0.001$) (**Figure 4**) were highly significant with differences between fructose muffin meals and both the sucrose (AUC: $P = 0.004$; iAUC: $P < 0.001$) and sucralose meals (AUC: $P = 0.020$; iAUC: $P = 0.006$), but there was no significant difference between sucrose and sucralose. There was no influence of age, sex, or BMI on any of the differences between diets. Scatter plots of the data shown in Figure 4 are presented in **Supplemental Figures 6–9**.

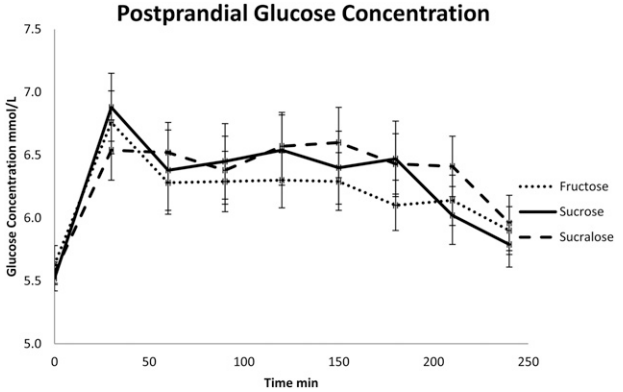

FIGURE 1 Mean ± SEM changes in glucose concentrations over time after the 3 muffin meals ($n = 27$). A repeated-measures ANOVA showed no significance for the treatment or time-by-treatment interaction.

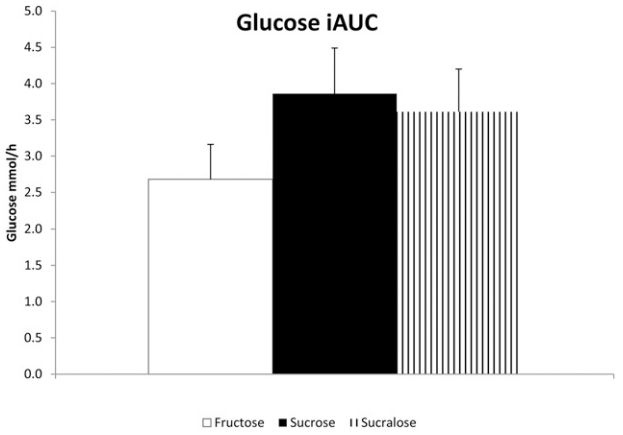

FIGURE 2 Mean ± SEM glucose iAUC ($n = 27$). $P = 0.019$ (repeated-measures ANOVA). Post hoc testing showed significant differences between fructose and sucralose and between fructose and sucrose (both $P < 0.05$). iAUC, incremental AUC.

Triglyceride

There were no differences for triglyceride for any of the measures (i.e., baseline values, repeated-measures ANOVA, AUC, or iAUC) (**Figure 5**).

DISCUSSION

In this group of mixed-weight individuals, a single amount of 52 g fructose as an intrinsic part of a high-fat solid meal containing starch and protein had no effect on plasma triglyceride over 5 h compared with that for 65 g sucrose or 0.1 g sucralose. However, fructose led to a lower incremental glucose AUC and a lower insulin concentration than was shown with both alternative meals. This result was expected with sucrose but somewhat unexpected with sucralose. However, we recognize that the sucrose test meal had 10 g more carbohydrate than the fructose meal did, which may have influenced the results to some degree. Although the total carbohydrate of the sucralose muffin meal was less than in the fructose meal, the glycemic carbohydrate was 23 g less in the fructose muffin meal, which accounted for the different responses. This lower glycemic response may have advantages in a population at risk of diabetes with impaired fasting glucose, impaired glucose tolerance, or an adverse family history. These results are in contrast with those of other acute studies of fructose that used liquid meals containing sugar and fat only (4, 5). These studies have focused on the determination of whether sugar exacerbated postprandial hypertriglyceridemia after a fat-tolerance test and whether fructose was worse than glucose

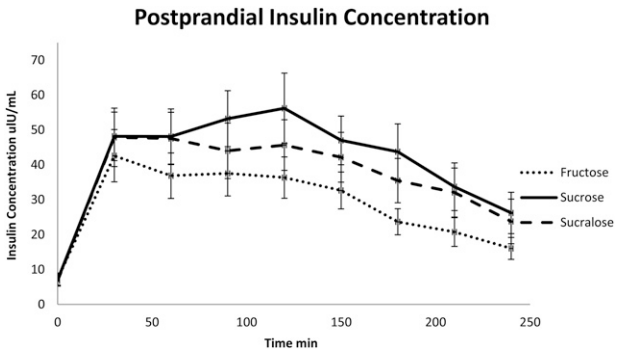

FIGURE 3 Mean ± SEM changes in insulin concentrations over time after the 3 muffin meals (n = 27). A repeated-measures ANOVA of log-transformed data showed significance for the treatment (P = 0.001) and time-by-treatment interaction (P = 0.035) with post hoc differences between fructose and sucrose and between fructose and sucralose in a repeated-measures ANOVA (P-treatment = 0.006 and 0.04, respectively).

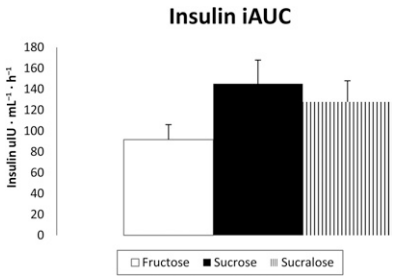

FIGURE 4 Mean ± SEM insulin iAUC (n = 27). A repeated-measures ANOVA showed that the log iAUC ($P < 0.001$) was highly significant with significant differences between fructose muffin meals and both the sucrose meal ($P < 0.001$) and sucralose meal (P = 0.006). iAUC, incremental AUC.

at exacerbating metabolic abnormalities, but these studies had no practical outcomes because glucose is rarely used as a caloric sweetener, whereas fructose has been extensively used in people with type 2 diabetes as an alternative to sucrose. In a fat-tolerance test in 14 lean healthy subjects, Chong et al. (5) showed that fructose at a dose of 0.75 mg/kg combined with fat at a dose of 0.5 mg/kg in beverage form but with no starch or protein increased postprandial triglyceride concentrations from 120 to 360 min after the meal with a maximum difference of 0.8 mmol/L at 300 and 360 min compared with the effects with glucose. More carbohydrate oxidation and more fatty acid esterification occurred with fructose. It was hypothesized that the higher triglyceride was cause by less activation of lipoprotein lipase by the lower insulin concentration after fructose. This result is in contrast with our study in which triglyceride concentrations were exactly the same despite marked differences in insulin concentrations. However, Chong et al. (5) showed no relation between triglyceride and insulin concentrations in their postprandial studies. Singleton et al. (11) showed that both glucose and fructose augmented the triglyceride response to a fat load, but no differences were seen between the 2 sugars. Saito et al. (12) used a population of 12 healthy, lean Japanese women and showed no differences between fructose and glucose in the AUC over 6 h for triglyceride, remnant lipoprotein triglyceride, or apolipoprotein B48 after a fat load. Jameel et al. (13) showed no differences in triglyceride concentrations between fructose, glucose, and sucrose over 2 h after a 50-g carbohydrate load without fat in 14 healthy subjects. Overall the triglyceride response in lean, healthy subjects has been variable with most studies showing no difference between glucose and fructose in acute studies. Thyetaz et al. (10) compared the addition of fructose to a liquid meal that contained both fat and protein in 8 healthy, nonobese men with the same meal without fructose and showed that the triglyceride AUC was doubled with the addition of fructose, with the triglyceride curves diverging at 6 h.

A second experimental model has been to add sugar-containing beverages to a solid fat-rich meal. Under these circumstances, a large amount of fructose enhances the triglyceride response to the meal. Teff et al. (20) compared the effects of a high-fructose or a high-glucose beverage added to meals over 24 h in 12 normal-weight women. Although the total nutrient distribution was normal at 55% carbohydrate, 30% fat, and 15% protein, 30% of energy came from the beverages with average intake of free sugars over the day of >130 g. With this large amount of fructose, serum triglyceride increased by 30–60% compared with glucose at the same time point and with a 35% increase in fasting triglyceride the next day. However, the maximum triglyceride concentration achieved was still low at 1.2 mmol/L. In a second study, Teff et al. (8) added fructose- and glucose-sweetened beverages (30% of energy) to meals consumed by 17 obese subjects and measured triglyceride over 23 h. The triglyceride AUC was ~3 times greater with fructose. Jin et al. (9) used a similar model in children with obesity and fatty liver disease or control children and showed a doubling of the 24-h triglyceride AUC. Parks et al. (7) showed that 65 g fructose doubled the de novo lipogenesis and stimulated the postprandial lipemia of a meal 4 h later by ~30% in 6 healthy subjects. Abraha et al. (6) compared a fructose-containing beverage (0.75 g/kg) added to a solid meal with toast added to the same meal and showed that triglyceride was higher with fructose from 180 to 360 min in both diabetic and non-diabetic men. It appears that doses of >60 g fructose/d enhance meal-induced triglyceride increases particularly in overweight subjects

However, to our knowledge, there have been no previous studies that have used fructose as an integral part of a mixed meal containing starch, and no study has compared fructose with sucralose, which is where our study offers unique insights compared with the results of fat-tolerance tests or beverage-plus-meal tests. Sucralose is an intense sweetener with ~600 times the sweetness of sucrose and can be used in baked goods (21). Sucralose constitutes ~30% of the US$1.22 billion high-intensity sweetener market, which is only ~2% of the world sucrose market. Concerns about cancer risk of all high-intensity sweeteners (22) have pushed consumers to revert to the use of sucrose again, but the apparent metabolic advantages of fructose at low to moderate doses, particularly in solid foods that have a more-satiating (17) value than beverages do, suggest that fructose should be re-evaluated for use as a sweetener in people with increased metabolic risk. One other study (23) has compared aspartame-containing beverages with high-fructose corn syrup beverages at 10–25% of energy over 2 wk and showed that, even at 10% of energy, the sugar-containing beverages increased the postprandial triglyceride concentration by 22 mg/dL, LDL-cholesterol concentration by 7.4 mg/dL, and uric acid concentration by 0.15 mg/dL, but to our knowledge, there has been no study that has compared solid foods containing fructose with sucralose-sweetened foods.

Although the lack of stimulation by fructose of insulin release has been cited as a disadvantage because of a reduction in the

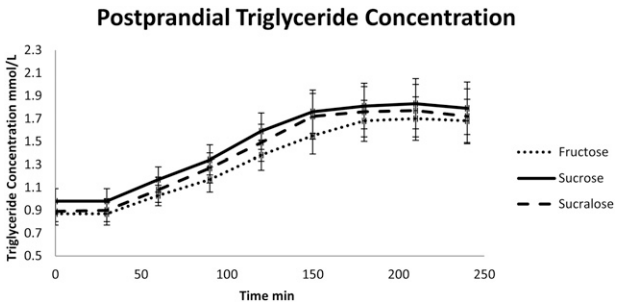

FIGURE 5 Mean ± SEM changes in triglyceride concentrations over time after the 3 muffin meals (n = 27). A repeated-measures ANOVA showed no significant differences for the treatment or time-by-treatment interaction.

stimulation of lipoprotein lipase and a reduction in satiety, neither of these concerns are well founded, and indeed, the insulin response to carbohydrate-rich foods has been inversely related to satiety (24). A relation between the insulin response and leptin response to carbohydrate-rich meals has been shown but neither response has been related to satiety, which suggests that a lack of an insulin response to fructose may have no negative effects (25). Uric acid increases with high-dose fructose consumption, but it is not clear if uric acid, per se, promotes cardiovascular disease although uric acid is strongly associated with disease (26).

We recognize that the responses observed reflected the intrinsic differences in the sweeteners used in the study. The starch content was similar in the sucrose and fructose muffins at 54 and 57 g, respectively. Future studies will need to examine the long-term impact of fructose at a moderate dose in place of both sucrose and sucralose over a period of 6–12 mo to examine the effect of fructose on weight and metabolic risk factors in people with obesity, metabolic syndrome, and prediabetes. Potential limitations of the applicability of the study findings were that a hedonic evaluation of the muffins was not carried out, and subjects were not asked if they could identify the sweetener in the different muffins.

In conclusion, the use of fructose as a sweetener in solid baked goods at a proportion of 0.8:1 compared with usual amounts of sucrose produces a better acute metabolic profile than does either sucrose or sucralose, but chronic studies are required.

The authors' responsibilities were as follows—CG, JBK, and PMC: wrote the manuscript; CG and EP: conducted the research; CG and PMC: analyzed the data; JBK and PMC: designed the research; PMC: had primary responsibility for final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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