HHS Public Access

Author manuscript

Eur J Clin Nutr. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Eur J Clin Nutr. 2019 March ; 73(3): 487–490. doi:10.1038/s41430-018-0297-5.

Consuming glucose-sweetened, not fructose-sweetened, beverages increases fasting insulin in healthy humans[1]

Jessica N. Kuzma[2,5], **Gail Cromer**[2], **Derek K. Hagman**[2], **Kara L. Breymeyer**[3], **Christian L. Roth**[6], **Karen E. Foster-Schubert**[4], **Sarah E. Holte**[2], **David S. Weigle**[4], and **Mario Kratz**[2,4,5,*]

[2]Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Prevention Center, Fred Hutchinson Cancer Research Center, Seattle, WA

[4]Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, Seattle Children's Hospital, University of Washington, Seattle, WA

[5]Department of Epidemiology, Seattle Children's Hospital, University of Washington, Seattle, WA

[6]Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA

Abstract

Fructose-, compared to glucose-, sweetened beverages increase liver triglyceride content in the short-term, prior to weight gain. In secondary analyses of a randomized cross-over design study during which 24 healthy adults consumed 25% of their estimated energy requirement in the form of glucose-, fructose-, and HFCS-sweetened beverages in addition to an identical *ad libitum* diet for three periods of 8 days each, we investigated the hypothesis that fructose in sweetened beverages also triggers insulin resistance in the short term. Total energy intake, body weight, and fasting glucose did not differ among diet phases. However, there was a significant trend for higher fasting insulin ($p = 0.042$ for trend) and, among normal weight participants, HOMA-IR ($p=0.034$ for diet x adiposity interaction) according to the glucose content of the beverages. In conclusion, in contrast to our hypothesis, insulin resistance was increased with higher glucose vs. fructose content of the beverages in this short-term trial.

Keywords

Sugar-sweetened beverages; fructose; insulin resistance

*To whom correspondence should be addressed. mkratz@fredhutch.org.

Authors' last names for PubMed indexing: Kuzma, Cromer, Hagman, Breymeyer, Roth, Foster-Schubert, Holte, Weigle, Kratz

This trial was registered at clinicaltrials.gov as NCT01424306.

The authors' responsibilities were as follows—JNK: completed laboratory procedures, statistical analysis of the data, and the first draft of the manuscript; JNK and GC: were responsible for collection of the data; DKH: provided technical assistance; KLB: oversaw preparation of all study meals; CLR: provided input on study design and data analysis and interpretation; KEF-S: served as the physician of record for the study; SEH: provided statistical guidance; DSW: was involved in the design of the studies as well as in data analysis and interpretation; MK: initiated the studies and had overall responsibility for the design and conduct of the studies as well as the data analyses; and all authors: contributed to the preparation of the manuscript and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

Introduction

The consumption of sugar-sweetened beverages (SSBs) increases *ad libitum* energy intake, body weight, and the risk of obesity and type 2 diabetes mellitus (T2DM) (1, 2). While both glucose- and fructose-sweetened beverages equally promote excess energy intake and body weight gain (3, 4), it has been suggested that the fructose component of HFCS is driving the increased risk of T2DM in individuals consuming SSBs. When consumed with a solid food diet in caloric excess, fructose-sweetened, but not glucose-sweetened, beverages promote hepatic *de novo* lipogenesis (DNL), ectopic fat deposition, dyslipidemia, and insulin resistance compared to glucose-sweetened beverages (4–6). It is not clear, however, whether the insulin resistance is due to the greater increase in overall fat mass that results from long-term consumption of fructose-sweetened beverages, or whether fructose acutely triggers insulin resistance through mechanisms that are independent of changes in fat mass. Schwarz et al. (6) suggest it might be the latter, as an increase in hepatic triglyceride content was seen within 9 days on a eucaloric diet in which 25% of total calories were provided by fructose-sweetened beverages (6). This suggests that fructose-triggered hepatic steatosis could be associated with insulin resistance in the short term, before substantive changes in fat mass occur.

We carried out a secondary analysis based on a previously published study (3, 7) to determine whether consuming beverages sweetened with fructose vs. HFCS vs. glucose differentially affected fasting glucose, insulin, and the homeostasis model assessment index of insulin resistance (HOMA-IR). We hypothesized that fasting insulin and HOMA-IR would be elevated following the fructose-diet phase followed by the HFCS- and glucose-diet phases.

Study Design and Methods

Detailed descriptions of this double-blinded, randomized, three-phase crossover study have been published previously (3, 7). Specifically, the randomization scheme was generated by the principal investigator using block randomization, stratified for sex and adiposity group (normal weight vs. overweight/obese). Each participant completed three 8-d dietary intervention periods during which subjects were provided with 150% of their estimated energy requirements: 25% of energy from sweetened beverages (glucose, HFCS, and fructose, in random order), and 125% as identical solid foods. The diet was designed as a 4-day rotating menu identical in all three phases of the study, and patterned after the average American diet (50% carbohydrate, 34% fat, and 16% protein). Participants were asked to drink all four servings of the SSB every day, and to consume the provided solid foods *ad libitum*, i.e. to eat only to satiety and return all leftover foods for weigh-backs. While the dietary intervention was not planned as hypercaloric, the mandatory inclusion of SSBs led to a similar increase in energy intake in all three diet groups, as reported previously (3). Beverages were prepared by individuals who did not communicate with participants or members of the study or kitchen teams, such that neither study team members, kitchen personnel, or study participants were aware of the order in which participants received the three SSBs. Subjects were asked to maintain their normal physical activity pattern across the

entire study period (~2.5 months). Physical activity, as assessed by modified Blair Physical Activity Questionnaires, did not differ significantly among diet periods (p=0.203) (3). Each dietary period was separated by a 20-day washout period during which subjects were asked to return to their habitual diet.

Subjects were 18–65 years old with a body mass index (BMI) 20–40 kg/m2. Twenty-four participants were enrolled into the normal weight (BMI 20.0–24.9, n=12) or overweight/obese (BMI 25.0–39.9, n=12) group. Written informed consent was obtained from all subjects, and the study was approved by the Fred Hutch institutional review board.

Fasted subjects were admitted to clinic the morning after each 8-d diet period for anthropometric assessment and blood draws. Endpoints of interest were fasting glucose (Roche Module P; Roche Diagnostics, Indianapolis, IN), fasting insulin (Tosoh Biosciences, San Francisco, CA) (both at the Northwest Lipid Research Laboratories, Seattle, WA), and HOMA-IR (8).

Repeated measures analysis of variance (RM-ANOVA) was used to assess whether ‘diet’ explained any variation in glucose, insulin, or HOMA-IR measured on day 9 of each diet period. We also used RM-ANOVA to test whether there was a linear trend in the effect of diet on the three variables from glucose- to HFCS- to fructose-sweetened beverages. The analysis was then stratified by adiposity category to assess whether fasting glucose or insulin were differentially affected by the three diet periods in normal weight vs. overweight/obese individuals. All statistical tests were performed using the SPSS version 20.0 for Macintosh (IBM, Armonk, NY), with an alpha-error level of 5%.

Results

There was no effect of diet on day 9 fasting concentrations of glucose, insulin, or HOMA-IR in the overall RM-ANOVA analysis (Table 1). However, there was a significant linear trend in fasting insulin among diet periods. Fasting insulin was lowest at the end of the fructose phase, followed by the HFCS phase, and was highest after the glucose phase (p=0.042). A similar non-significant trend was observed for HOMA-IR (p=0.075).

We also observed a statistically significant diet x adiposity group interaction for a trend across the three diet phases for fasting insulin and HOMA-IR (p=0.023 and p=0.034, respectively, for diet x adiposity category, Table 2). In normal weight subjects, mean fasting insulin and HOMA-IR values were lowest following the fructose period, followed by the HFCS period, and were highest following the glucose-beverage period. This trend was not observed in overweight/obese subjects.

Sensitivity analyses adjusted for diet order, physical activity, self-reported minor illness, age, and sex, did in some cases slightly attenuate the effect of diet, but did not fundamentally affect the results for overall or subgroup analyses on any endpoint.

Discussion

Given that excessive fructose intake promotes hepatic DNL and triglyceride accumulation in as little as 9 days even on a eucaloric diet (6), it was surprising to discover that, in our study, fasting insulin and HOMA-IR on day 9 of each diet period were higher following the consumption of glucose- rather than the fructose-sweetened beverages, at least in normal weight subjects, with no difference among overweight/obese individuals. While the effect size of the differential effect is relatively modest, similarly modest differences in fasting insulin have been shown to be associated with a substantial increase in the risk of pre-diabetes (9).

A recent meta-analysis of the effect of fructose on insulin sensitivity concluded that substitution of fructose for other dietary carbohydrate, whether under isocaloric or hypercaloric (25% excess energy) conditions, resulted in hepatic insulin resistance, as measured by euglycemic hyperinsulinemic clamp, in healthy normal and overweight/obese adults while fasting insulin and HOMA-IR values remained unchanged (10). It is unclear why our findings differ from those published in the meta-analysis. It could be that by including a HFCS beverage phase, which was a novel aspect of our study, we were able to detect the graded increase in fasting insulin and HOMA-IR in normal weight subjects according to the glucose content of the beverages. It may also be that the shorter duration of our study compared to previous studies may have contributed to the differential finding.

Our data may also suggest that glycemic load may be a determinant of fasting insulin concentrations. It has been shown experimentally that chronic, compensatory hyperinsulinemia leads to the development—and perpetuation—of insulin resistance (11). It could well be that in our study, 8 days of 25% of calories as a glucose beverage was sufficient to induce chronic hyperglycemia and concomitant hyperinsulinemia. This was reflected by the significant increasing trend in fasting insulin and HOMA-IR values according to glucose content of the beverages in normal weight subjects.

In conclusion, we observed no evidence that the consumption of excessive amounts of fructose from SSB differentially increases insulin resistance compared to SSB sweetened with HFCS or glucose. To the contrary, in the short-term, higher glucose content of the beverages was significantly related to higher fasting insulin and HOMA-IR in a concentration-dependent manner.

Acknowledgments

We thank Pamela Y Yang, Xiaoling Song, Michelle A Wurscher, Peggie Bates, Sara Bennett, Linda Glockling, and David Hatten.

[1]Supported by NIH grant R21HL108257 (to M. Kratz), NIH grant P30 DK017047 (University of Washington Diabetes Research Center), and NIH grant P30 CA015704 (FHCRC Cancer Consortium Cancer Center Support Grant). J.N. Kuzma was supported in part by grant R25CA094880 from the National Cancer Institute.

Abbreviations:

SSB	Sugar-Sweetened Beverages

HFCS	High-Fructose Corn Syrup
CRP	high-sensitivity C-reactive protein
IL-6	Interleukin-6

References

1. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, and Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care. 2010;33(11): 2477–83. [PubMed: 20693348]
2. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004;292(8):927–34. [PubMed: 15328324]
3. Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, Foster-Schubert KE, et al. No difference in ad libitum energy intake in healthy men and women consuming beverages sweetened with fructose, glucose, or high-fructose corn syrup: a randomized trial. Am J Clin Nutr. 2015;102(6):1373–80. [PubMed: 26537945]
4. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest. 2009;119(5):1322–34. [PubMed: 19381015]
5. Stanhope KL, Griffen SC, Bremer AA, Vink RG, Schaefer EJ, Nakajima K, et al. Metabolic responses to prolonged consumption of glucose- and fructose-sweetened beverages are not associated with postprandial or 24-h glucose and insulin excursions. Am J Clin Nutr. 2011;94(1): 112–9. [PubMed: 21613559]
6. Schwarz JM, Noworolski SM, Wen MJ, Dyachenko A, Prior JL, Weinberg ME, et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. J Clin Endocrinol Metab. 2015;100(6):2434–42. [PubMed: 25825943]
7. Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, Foster-Schubert KE, et al. No differential effect of beverages sweetened with fructose, high-fructose corn syrup, or glucose on systemic or adipose tissue inflammation in normal-weight to obese adults: a randomized controlled trial. Am J Clin Nutr. 2016;104(2):306–14. [PubMed: 27357093]
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, and Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9. [PubMed: 3899825]
9. Johnson JL, Duick DS, Chui MA, and Aldasouqi SA. Identifying prediabetes using fasting insulin levels. Endocr Pract. 2010;16(1):47–52. [PubMed: 19789156]
10. Ter Horst KW, Schene MR, Holman R, Romijn JA, and Serlie MJ. Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials. Am J Clin Nutr. 2016;104(6):1562–76. [PubMed: 27935520]
11. Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, and DeFronzo RA. Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. Diabetologia. 1994;37(10):1025–35. [PubMed: 7851681]

Table 1.

Fasting plasma glucose, insulin, and HOMA-IR in all subjects on day 9 of each dietary period[1].

	Fructose (n=24)	HFCS (n=24)	Glucose (n=24)	p-value (RM-ANOVA)[2]	p-value (trend)[3]
Glucose (mg/dL)	96 ± 7 96 (92, 98)	94 ± 7 94 (91, 97)	96 ± 6 94 (91, 98)	0.240	0.793
Insulin (uU/mL)	8.2 ± 6.5 5.4 (4.0, 9.3)	8.6 ± 6.6 6.8 (4.9, 11.1)	9.3 ± 6.9 7.0 (5.1, 11.1)	0.206	**0.042**
HOMA-IR	1.9 ± 1.6 1.2 (0.95, 2.2)	2.0 ± 1.5 1.5 (1.2, 2.4)	2.2 ± 1.6 1.6 (1.2, 2.5)	0.264	0.075

[1] Values are mean ± standard deviation, and median (IQR) if non-normally distributed data. HFCS, high-fructose corn syrup; HOMA-IR, Homeostatic model assessment of insulin resistance.

[2] Reflects an overall comparison of the 3 dietary phases by repeated-measures ANOVA.

[3] Reflects linear test for trend.

Eur J Clin Nutr. Author manuscript; available in PMC 2019 March 01.

Table 2.

Fasting glucose, insulin and HOMA-IR on day 9 of each diet period, separately for participants that were normal weight vs. overweight or obese [1].

	Fructose	HFCS	Glucose	RM-ANOVA			Test for trend	
				p-value (adiposity)	p-value (diet)	p-value (diet x adiposity)	p-value (diet)	p-value (diet x adiposity)
Glucose (mg/dL)								
Normal weight (n=12)	93 ± 4 95 (92, 96)	92 ± 5 93 (90, 94)	94 ± 4 94 (91,97)	**0.049**	0.250	0.685	0.796	0.512
Overweight/obese (n=12)	98 ± 8 98 (93, 103)	97 ± 8 97 (92, 99)	97 ± 7 97 (92, 102)					
Insulin (uIU/mL)								
Normal weight (n=12)	4.4 ± 1.1 4 (3.7, 5.3)	5.8 ± 2.5 5.8 (4.5, 7.2)	6.4 ± 2.9 5.7 (4.5, 7.0)	**0.002**	0.193	0.144	**0.027**	**0.023**
Overweight/obese (n=12)	11.9 ± 7.5 9.3 (5.7, 17.3)	11.4 ± 8.2 10.4 (6.7, 13.0)	12.2 ± 8.5 8.3 (7.0, 15.6)					
HOMA-IR								
Normal weight (n=12)	1.0 ± 0.23 0.95 (0.82, 1.2)	1.3 ± 0.54 1.4 (1.0, 1.6)	1.5 ± 0.70 1.3 (1.0, 1.6)	**0.001**	0.252	0.166	0.055	**0.034**
Overweight/obese (n=12)	2.9 ± 1.8 2.2 (1.4, 4.1)	2.6 ± 1.8 2.3 (1.5, 2.9)	2.9 ± 2.0 2.0 (1.6, 3.5)					

[1] Values are means ± standard deviations, and medians (IQR) if non-normally distributed data.