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

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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
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 prediabetes (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.

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Abbreviations:

SSB Sugar-Sweetened Beverages
HFCS  High-Fructose Corn Syrup
CRP  high-sensitivity C-reactive protein
IL-6  Interleukin-6

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Table 1.

|                   | Fructose (n=24) | HFCS (n=24) | Glucose (n=24) |
|-------------------|-----------------|-------------|---------------|
| Glucose (mg/dL)   | ± 7             | ± 6.5       | ± 6           |
| Insulin (uU/mL)   | 96 (92-98)      | 94 (91-97)  | 94 (91-98)    |
| HOMA-IR           | 1.9 ± 1.6       | 1.8 ± 1.5   | 1.7 ± 1.6     |

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.

1 Reflects an overall comparison of the 3 dietary phases by repeated-measures ANOVA.
2 Reflects linear test for trend.
3 Reflects an overall comparison of the 3 dietary phases by repeated-measures ANOVA.
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  | p-value | p-value | p-value  | p-value       |
|                | (adiposity) | (diet) | (diet) | (diet x adiposity) | (diet x adiposity) |
| **Glucose (mg/dL)** |          |       |         |          |               |
| Normal weight (n=12) | 93 ± 4 | 92 ± 5 | 94 ± 4 | 0.049    | 0.250         | 0.685           | 0.796 | 0.512 |
|                   | 95 (92, 96) | 93 (90, 94) | 94 (91,97) |         |               |                 |       |      |
| Overweight/obese (n=12) | 98 ± 8 | 97 ± 8 | 97 ± 7 |          |               |                 |       |      |
|                   | 98 (93, 103) | 97 (92, 99) | 97 (92, 102) |         |               |                 |       |      |
| **Insulin (uIU/mL)** |          |       |         |          |               |
| Normal weight (n=12) | 4.4 ± 1.1 | 5.8 ± 2.5 | 6.4 ± 2.9 | 0.002    | 0.193         | 0.144           | 0.027 | 0.023 |
|                   | 4 (3.7, 5.3) | 5.8 (4.5, 7.2) | 5.7 (4.5, 7.0) |         |               |                 |       |      |
| Overweight/obese (n=12) | 11.9 ± 7.5 | 11.4 ± 8.2 | 12.2 ± 8.5 |          |               |                 |       |      |
|                   | 9.3 (5.7, 17.3) | 10.4 (6.7, 13.0) | 8.3 (7.0, 15.6) |         |               |                 |       |      |
| **HOMA-IR**|          |       |         |          |               |
| Normal weight (n=12) | 1.0 ± 0.23 | 1.3 ± 0.54 | 1.5 ± 0.70 | 0.001    | 0.252         | 0.166           | 0.055 | 0.034 |
|                   | 0.95 (0.82, 1.2) | 1.4 (1.0, 1.6) | 1.3 (1.0, 1.6) |         |               |                 |       |      |
| Overweight/obese (n=12) | 2.9 ± 1.8 | 2.6 ± 1.8 | 2.9 ± 2.0 |          |               |                 |       |      |
|                   | 2.2 (1.4, 4.1) | 2.3 (1.5, 2.9) | 2.0 (1.6, 3.5) |         |               |                 |       |      |

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