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Change in postprandial substrate oxidation after a high fructose meal is related to Body Mass Index (BMI) in Healthy Men

Anne C. Smeraglio¹, Emily K. Kennedy², Angela Horgan³, Jonathan Q. Purnell⁴, and Melanie B. Gillingham^{5,3}

¹School of Medicine, Oregon Health & Science University, Portland, OR

²Graduate Programs in Human Nutrition, Oregon Health & Science University, Portland, OR

³Oregon Clinical and Translational Research Institute, Oregon Health & Science University, Portland, OR

⁴Department of Medicine, Oregon Health & Science University, Portland, OR

⁵Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR

Abstract

Oral fructose decreases fat oxidation and increases carbohydrate (CHO) oxidation in obese subjects, but the metabolic response to fructose in lean individuals is less well understood. The purpose of this study was to assess the effects of a single fructose-rich mixed meal on substrate oxidation in young healthy non-obese males. We hypothesized that a decrease in fat oxidation and an increase in carbohydrate oxidation would be observed following a fructose-rich mixed meal compared to a glucose-rich mixed meal. Twelve healthy males, normal to overweight and age 23–31 years old, participated in a double-blind, cross-over study. Each participant completed two study visits, eating a mixed meal containing 30% of the calories from either fructose or glucose. Blood samples for glucose, insulin, triglycerides, and leptin as well as gas exchange by indirect calorimetry were measured intermittently for 7 hours. Serum insulin was higher after a fructose mixed meal but plasma glucose, plasma leptin and serum triglycerides were not different. Mean postprandial respiratory quotient and estimated fat oxidation did not differ between the fructose and glucose meals. The change in fat oxidation between the fructose and glucose rich meals negatively correlated with BMI ($r=-0.59$, $P=0.04$ and $r=-0.59$, $P=0.04$ at the 4 and 7 hour time points, respectively). In healthy non-obese males, BMI correlates with altered postprandial fat oxidation after a high-fructose mixed meal. The metabolic response to a high fructose meal may be modulated by BMI.

Keywords

Fructose; Glucose; Fat oxidation; Carbohydrate oxidation; RQ; NPRQ; BMI; Obesity; Energy expenditure; Indirect calorimetry

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Corresponding author: Melanie B. Gillingham, RJH 4549, Oregon Health & Science University, 3181 SW Sam Jackson Park Road Portland, OR 97239, Phone: 503-494-1682, Fax: 503-494-6886, gillingm@ohsu.edu.

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1. Introduction

The prevalence of obesity in the United States (US) has more than doubled since 1980 and is now estimated to be 33.8% of the adult population [1,2]. This dramatic increase in obesity has corresponded to a rise in consumption of fructose containing sweeteners in the US [3]. From 1970 until 2008, the average daily US household fructose intake increased from 37g to 54.7g per day with the main sources of fructose being sucrose and high fructose corn syrup sweetened beverages and grains [4]. While these data are correlative, the association has led some researchers to suggest a causative relationship between increased fructose consumption and societal weight gain [5,6]. Still other researchers suggest that the observed increase in obesity is more likely related to an increase in total energy consumption which also increased 18% from 1977 to 2004 and total carbohydrate intake which increased 41% over the same period of time [3].

While both fructose and glucose are 6-carbon sugars, they have different metabolic fates in the liver. The liver efficiently takes fructose up from the portal vein on first pass metabolism. It is converted to fructose-1-phosphate and without further regulation immediately enters glycolysis [7–9]. In contrast, glucose enters glycolysis via the enzyme 6-phosphofructo-1-kinase, a highly regulated enzyme that is sensitive to energy needs [10,11]. The ability of fructose to bypass this enzymatic control allows glycolysis to proceed independent of energy demand. This leads to a hepatic surplus of energy production and glycolytic intermediates that are shunted to other metabolic pathways, including fatty acid synthesis and glucose production [12].

Fructose consumption has been shown to lower postprandial glucose response, increase serum triglyceride levels, visceral adiposity, insulin resistance, and reduce leptin levels in humans in some but not all studies [6,13–17]. The variable results observed in research studies of fructose consumption may be related to the dose and form of fructose used in the study with beneficial effects on glycemic control at lower doses and more pronounced adverse triglyceride effects at higher doses [18,19]. Recently, fructose consumption has also been shown to decrease fat oxidation in obese subjects fed a high fructose diet over a ten-week period [20]. This change in substrate oxidation has been hypothesized to occur as a result of increased de-novo lipogenesis and increased gluconeogenesis when fructose is metabolized in the liver [7,21]. Fat oxidation is suppressed during lipogenesis via the control of malonyl-CoA levels and inhibition of carnitine-palmitoyltransferase-1, the rate limiting step in fatty acid oxidation [22,23]. Gluconeogenesis stimulated by fructose intake provides a constant supply of glucose to skeletal muscles thus encouraging glucose oxidation preferentially over fat oxidation [13]. Both mechanisms could contribute to the decreased fat oxidation reported with fructose consumption and, in the context of excess total energy, potentially lead to increased lipid storage and weight gain.

Based on these mechanisms fructose might be expected to decrease fat oxidation in both lean and obese individuals. However, most prior fructose research has focused on obese or diabetic populations. In healthy normal weight populations the data remains sparse with mixed results regarding the metabolic effects of fructose [24–27]. Thus we hypothesized that fructose would have the same metabolic effects in a normal to mildly overweight population as those observed in obese populations. Furthermore, these changes in metabolism with a high fructose meal would alter postprandial substrate oxidation causing increased lipogenesis, decreased fat oxidation and increased CHO oxidation. This hypothesis was evaluated in a double blind crossover trial where 12 healthy men with BMI's 20–30kg/m² were given single meals rich in either fructose or the control substance, glucose. Metabolic

parameters were then followed using indirect calorimetry and blood markers at hours 0, 1, 4 and 7 to evaluate for acute metabolic differences post glucose vs fructose rich meals

2. Methods & Materials

2-1. Subjects

Twelve healthy men without diabetes, mean age 25 (23–31) years old and a BMI < 30 kg/m² were recruited from Oregon Health & Science University (OHSU) through campus advertisements. Participants were at their lifetime maximal body weight and had been weight stable for at least 1 month. Those with any acute or chronic medical conditions that could affect metabolic rate were excluded from the study, as were smokers and individuals that consumed more than 2 drinks of alcohol daily. This protocol was approved by the OHSU Institutional Review Board, and all subjects gave written consent prior to participation in the study.

2-2. Experimental Design

Study visits were conducted at the Clinical and Translational Research Center (CTRC) of the Oregon Clinical and Translational Research Institute (OCTRI). Participants were evaluated on two separate occasions, greater than one week but less than one month apart, in a double-blind, cross-over design. All participants were assigned to consume a single meal high in glucose or fructose in random order. The Bionutritionists and kitchen staff of the CTRC Bionutrition Unit maintained the randomization assignments and prepared the study meals, accordingly. Study staff and participants were blinded to beverage type during participant visits as well as during data analysis.

2-3. Study Visit Protocol

Participants arrived early in the morning after fasting from food, drink (except water), caffeine and alcohol for >12 hours. A research nurse or study staff obtained vital signs, height, and weight measurements. Fasting blood markers including serum leptin, triglycerides, glucose and insulin were obtained as well as baseline indirect calorimetry. Participants were fed a standardized breakfast as described below containing either glucose or fructose. Following breakfast participants again fasted from food and drink except water for another 7 hours while testing was conducted. Repeated blood markers and metabolic activity by indirect calorimetry were measured at 1, 4 and 7 hours postprandial.

2-4. Diet Composition

Participants were fed an egg omelet, bagel with cream cheese, and sweetened beverage breakfast consisting of 1/3 of their estimated daily caloric needs as calculated from the average of the Harris Benedict and Mifflin-St Jeor equations multiplied by an activity factor of 1.4 [28–30]. The meal consisted of 30% of energy from fat, 15% from protein, and 55% from carbohydrate. The carbohydrate energy was further divided into complex and simple carbohydrates; 25% of the total calories were from complex carbohydrates and 30% of the calories were from either glucose or fructose added to the beverage[31]. Breakdown of each participant's meal characteristics can be found in Table 1. Participants were required to ingest all the food provided within 15 minutes and observed for compliance.

2-5. Energy Expenditure Measurement

Participants were not allowed to perform any vigorous physical activity 24 hours prior to admission to decrease variability in substrate oxidation due to prior exercise. During testing participants remained inactive, allowed only to watch TV or perform quiet activities. Oxygen consumption and CO₂ production were measured by indirect calorimetry to

calculate resting energy expenditure (REE) and respiratory quotient (RQ) [32] (Sensormedics Corp. model 29n, Yorba Linda, CA). Non-protein respiratory quotient (NPRQ) was calculated based on the equation from Simonson et al [32]. A 24-hour urine collection was analyzed for markers of protein metabolism (urinary urea nitrogen). Substrate oxidation was calculated using resting VO_2 (L/min), VCO_2 (L/min), and 24 hour urine urea excretion (g/min) based on the equations from Frayn [33].

2-6. Blood samples

Blood samples were drawn before meal consumption, 1 hour post meal, 4 hours post meal, and 7 hours post meal to evaluate markers of metabolic activity (glucose, insulin, leptin, triglycerides). An intravenous catheter was placed in the peripheral arm vein of the subjects to minimize harm to the patient from repeated blood draws. A maximum of 30 mL of blood was collected from each patient per admission. The following tubes were collected at each admission.

Glucose—1 ml of blood was collected in a potassium oxalate (grey-top) tube for glucose analysis. Whole blood was centrifuged and plasma was separated and stored at -80°C until analysis. Plasma glucose was measured using a glucose oxidase assay purchased from Raichem Inc. (San Diego, CA). Plasma samples were assayed in duplicate in 96 well plates. The sensitivity of the assay was 12.5 mg/dl. The intra- and inter- assay coefficients of variation were 10.79% and 9.49% respectively.

Insulin—2 ml of blood were collected in a serum (red-top) tube for insulin and leptin analysis. The tube was allowed to stand at room temperature before whole blood was centrifuged and serum was separated and stored at -80°C until analysis. Insulin samples were processed at OCTRI, and concentrations of insulin were measured in the OCTRI core lab using an immulite autoanalyzer. The sensitivity of the assay was 2 mU/L. The intra- and inter- assay coefficients of variation were 7.01% and 7.91% respectively.

Leptin—Serum leptin was measured by radioimmunoassay kits purchased from Millipore Inc. (Billerica, MA). The sensitivity of the assay was 0.5 ng/ml. The calculated intra-assay coefficient of variation was 16% and the calculated inter-assay coefficient of variation for the two kits used were 1.6 and 6.6%.

Triglycerides—1 ml of blood was collected in a lithium heparin (green-top) tube for analysis of triglycerides. Whole blood was sent to the OHSU hospital pathology lab for analysis. Triglyceride concentrations were measured using an enzymatic reaction and autoanalyzer (Beckman Coulter Counter). Triglycerides were hydrolyzed to glycerol and fatty acids by lipase. Glycerol was converted to H_2O_2 by glycerol kinase and glycerolphosphate oxidase. Change in absorbance was read at 520 nm.

Urine Samples—Participants' urine was collected over a 24-hour period beginning with the subject arrival at OCTRI. Subjects continued the urine collection after their discharge from OCTRI and returned the completed sample the following morning. All urine collected was mixed and the volume recorded. An aliquot of each urine sample was measured for urine urea nitrogen, at the OHSU hospital pathology lab using an enzymatic reaction and autoanalyzer (Beckman Coulter counter). Urea was hydrolyzed to ammonia and CO_2 by urease. Glutamate dehydrogenase condensed ammonia and alpha-ketoglutarate to form glutamate and NAD. Change in absorption of NADH to NAD was measured at 340 nm.

2-7. Statistical Analyses

A sample size of 8 to 11 subjects was estimated to provide 80 to 90% power based on our preliminary results of a difference in postprandial RQ at 7 hours (RQ after the fructose meal = 0.81; RQ after the glucose meal = 0.71 with standard deviation of 0.07) in the initial 3 subjects; we recruited a total of 12 subjects. Insulin sensitivity was estimated by the homeostatic model assessment (HOMA-IR) as fasting glucose (mmol/l) x fasting insulin (mU/l)/22.5 [34]. Differences between the effects of fructose and glucose consumption on RQ, NPRQ, carbohydrate (CHO) oxidation, fat oxidation, plasma insulin, glucose, insulin, leptin, triglycerides, were analyzed using a two-factor repeated measures ANOVA. If the overall F-test was significant, post-hoc analysis of the differences between individual time points was compared by Bonferroni posttest. Relationship between BMI and CHO and fat oxidation was assessed by Pearson's correlation. Statistical analysis was conducted with Prism software v.5.0 (Graphpad Software, La Jolla, Ca), and $P \leq 0.05$ was considered significant.

3. Results

General subject characteristics are provided in Table 2. The mean age of participants was 25.2 ± 2.2 years with BMI's of 24.2 ± 2.1 . They had estimated mean caloric needs of 2290 ± 196 kcal/day. The estimated insulin sensitivity in our subjects using the homeostatic assessment model for insulin resistance (HOMA-IR) was 1.33 ± 1.05 , suggesting our population was insulin sensitive as reported by others (Table 2) [34].

3-1. Glucose, insulin, triglyceride and leptin levels

All fasting blood work showed inter-test statistical equivalence between the fructose and glucose study visits, indicating good baseline congruence between the two visits. Averaged fasting values between both visits were: insulin $5.0 \pm 1.3 \mu\text{IU/mL}$, triglyceride 82.6 ± 8.0 mg/dL, glucose 106.5 ± 0.7 mg/dL and leptin 2.9 ± 0.3 ng/mL (Table 1). Serum insulin was significantly lower 1 hour postprandially following fructose compared to the glucose study visit (Figure 1A; 2-way ANOVA $P < 0.05$, 1 hour postprandial insulin means 26.3 vs. $50.5 \mu\text{IU/mL}$ with Benferroni posttest $P < 0.001$). Overall post-prandial plasma triglycerides, plasma glucose and serum leptin were not significantly different between the fructose and glucose meals (Figure 1B; Triglycerides, Figure 1C; Glucose: Figure 1D; Leptin).

3-2. RQ, NPRQ, Fat and Carbohydrate Oxidation

Baseline respiratory quotient (RQ) between the fructose and glucose study visits were equivalent (0.82 ± 0.08 and 0.81 ± 0.10 respectively). In this healthy young male population we saw no divergence in the RQ response after fructose vs glucose administration ($P = 0.72$). Even when protein utilization was accounted for by evaluating non-protein RQ (NPRQ), the two study-visits remained equivalent at all time points (Figure 2A; $P = 0.75$). Consistent with RQ and NPRQ, estimated fat oxidation (Figure 2B; $P = 0.77$) and carbohydrate oxidation (Figure 2C; $P = 0.49$) showed no difference between the two study visits.

3-4. BMI vs Change in Fat Oxidation and NPRQ

Although the absolute values for fat and CHO oxidation were not different between the fructose and glucose study visits, we did find a correlation between BMI and change in fat oxidation as a result of consuming the high fructose meal compared to the high glucose meal. The difference in fat oxidation (fat oxidation following the fructose meal minus fat oxidation following the glucose meal) was negatively correlated with BMI at the 4 and 7 hour time points (Figure 3; $r = -0.59$, $P = 0.04$ and $r = -0.59$, $P = 0.04$ for 4 and 7 hour time points respectively) but not the 1 hour time point (Figure 3; $r = -0.52$, $P < 0.09$). NPRQ displayed these same trends but did not reach significance. This suggests the postprandial fat

oxidation following the fructose meal was less than the fat oxidation following the glucose meal only among subjects with a higher BMI.

4. Discussion

Based on the results of our study, we rejected our hypothesis that fat oxidation decreases and carbohydrate oxidation increases following a fructose-rich mixed meal compared to a glucose-rich mixed meal in normal to overweight healthy males. However, we found that the difference in postprandial fat oxidation between the fructose and the glucose rich meals was negatively correlated with BMI in non-obese men. Our data contrasts with that of Tappy, Blaak and Schwarz [35–38], which found an overall significant decrease in fat oxidation amongst both lean and obese individuals. However, these previous studies used a pure CHO source with a fixed caloric amount when evaluating substrate oxidation. Our study adjusted caloric content to be 1/3 of each participant's estimated daily caloric need. We also used a mixed CHO source with 25% of the calories from complex CHO and 30% from either fructose or glucose. This was intended to provide a representation of the American diet, which often includes mixed carbohydrate ingestion. It is possible that we did not observe an absolute difference in fat oxidation following the fructose meal because the changes in substrate oxidation following a mixed meal are subtle compared to changes seen with prior studies using a pure CHO source. Together this suggests fructose-mediated changes in postprandial substrate oxidation appear to be associated with both dietary composition and increasing BMI.

Why would a higher BMI alter the substrate oxidation observed following oral fructose ingestion? Several mechanisms have been proposed to mediate the decreased fat oxidation with high fructose consumption. For instance, the decreased insulin release with oral fructose leads to decreased insulin-stimulated upregulation of lipoprotein lipase in visceral adipose tissue. Decreased fatty acid uptake into tissues will limit fatty acid oxidation and promote use of alternative substrates such as carbohydrate. We did not see a correlation with change in insulin release and BMI in our data. Another proposed mechanism is enhanced hepatic de novo lipogenesis with fructose consumption. Consumption of high doses of fructose has previously been seen to increase hepatic de novo lipid synthesis [23], which in turn can suppress fatty acid oxidation with high levels of malonyl-CoA. It is possible that increased BMI leads to greater de novo lipogenesis in the liver and therefore less fat oxidation following a high fructose meal.

In our study, serum insulin followed a predicted path of rise and fall post glucose ingestion that was blunted with fructose ingestion. This is similar to previous reports of blunted insulin response with fructose consumption compared to glucose consumption [31,39]. Interestingly blood glucose levels were not significantly different between the two study visits at any time point. This differs from other reports on the acute effects of fructose consumption [16,40,41], and may be explained in part by less frequent sample acquisitions than other studies leading to missing a glucose peak at 30 minutes [36,42]. Other possibilities to explain this difference could be the total dose of fructose or glucose and use of a mixed meal altering the expected effects.

Leptin levels were not statistically different post fructose versus glucose ingestion. This is in contrast to the previous study by Teff et al [31] who showed a reduced leptin response following fructose versus glucose consumption in healthy women. Our different findings may stem from both participant gender, blood sampling timeline differences, dose of fructose/glucose and use of a mixed meal. Teff et al looked at leptin response over a twelve-hour increment and multiple meals as compared to our seven-hour timeline following a single meal. It is possible that with longer evaluation we may have seen a divergence in

leptin levels between the two study diets. It is also possible that sex differences play a role in metabolic response.

There were several limitations to this study in addition to those mentioned above. The most notable is the small sample size. An evaluation of a larger spectrum of individuals with varied BMI's would provide a much better analysis of BMI's interaction with fat oxidation. Furthermore longer-term consumption of fructose would provide a better representation of the "American diet" and allow evaluation of metabolic impacts of chronic consumption as opposed to a single meal. However, in the context of an acute feeding study, we observed no significant differences in the utilization of a single meal high in fructose compared to a meal high in glucose among normal healthy men.

We conclude that there was no absolute difference in postprandial fat or CHO oxidation following a fructose compared to glucose rich mixed meal in a group of normal to overweight men. However, there was a significant correlation between the change in fat oxidation following consumption of a fructose rich meal compared to a glucose rich meal and BMI. That these correlations were observed within a very narrow BMI range in a small population suggests that BMI may have a significant effect on the metabolic changes associated with fructose consumption. There were blunted insulin concentrations post fructose consumption as compared to glucose consumption regardless of changes in substrate oxidation. Interestingly leptin response was not statistically different postprandially between the glucose and fructose study visits. Future studies with chronic fructose ingestion will be needed to further characterize the results of this short term feeding trial and determine if there is indeed a relationship between BMI and altered substrate oxidation post fructose consumption.

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Abbreviations

AUC	area under the curve
BMI	body mass index
CHO	carbohydrate
RQ	Respiratory quotient
NPRQ	Non-protein respiratory quotient
US	United States
OHSU	Oregon Health & Science University
CTRC	Clinical and Translational Research Center
REE	resting energy expenditure
HOMA-IR	homoeostatic model assessment of insulin resistance
SD	standard deviation
Fru	fructose

Glu glucose
OCTRI Oregon Clinical and Translational Research Institute

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Figure 1.

Standard Blood Analysis

2 factor ANOVA analysis before and after an isocaloric mixed meal high in fructose (open circles) versus glucose (closed squares) in 12 healthy males at hours 0, 1, 4, 7. A) Serum Insulin (2 factor ANOVA * $P < 0.05$, 1 hour postprandial Bonferonni posttest * $P < 0.001$).

There were no significant differences in B) plasma triglycerides, C) plasma glucose and D) serum leptin. Data is presented as means $\pm$ standard deviation. * Indicates significant differences at $p < 0.05$

Figure 2.

Indirect Calorimetry and Substrate Oxidation

2 factor ANOVA analysis performed before and after an isocaloric mixed meal high in fructose (open circles) versus glucose (closed squares) in 12 healthy males at hours 0, 1, 4, 7. Indirect calorimetry estimates of A) non-protein RQ $P=0.75$, B) fat oxidation $P=0.77$, and C) carbohydrate oxidation $P=0.49$ were not significantly different. Data is presented as means $\pm$ standard deviation.

Figure 3.

Correlation of BMI with Change in Fat Oxidation

Pearson's correlation with linear regression trend lines between BMI and change in fat oxidation (fat oxidation following the fructose study visit minus fat oxidation following the glucose study visit) 1 hour; $r=-0.52$ $P<0.09$ n.s., 4 hours; $r=-0.59$ $*P=0.04$, 7 hours; $r=-0.59$ $*P=0.04$. All data points given for hours 1, 4 and 7 postprandial in 12 healthy volunteers. * Indicates significant differences at $p = 0.05$

Table 1

Individual Meal Characteristics

Subject #	Fru/Glu (g/meal)	Total Kcal/meal	Carbohydrate (g/meal)	Protein (g/meal)	Fat (g/meal)
1	56.3	737.5	37.5	28.1	29.2
2	52.5	689.7	35	26.3	27.2
3	63.8	841.7	42.5	31.9	33.1
4	60.0	787.4	40	30.0	31.1
5	52.5	700.6	35	26.3	27.2
6	52.5	704.7	35	26.3	27.2
7	56.3	754.1	37.5	28.1	29.2
8	67.5	900.2	45	33.8	35
9	63.8	836.7	42.5	31.9	33.1
10	56.3	753.9	37.5	28.1	29.2
11	56.3	752.5	37.5	28.1	29.2
12	52.5	715.2	35	26.3	27.2

Individual meal characteristics for each participant detailing grams of glucose/fructose per meal, total kilocalories per meal, carbohydrates, fat and protein in each participants meal.
Abbreviations Fru=fructose and Glu=glucose.

Table 2

Participant Characteristics

Age (<i>years</i>)	25.2 ± 2.2
BMI (<i>kg/m²</i>)	24.2 ± 2.1
Estimated Caloric Need (<i>kcal/day</i>)	2290 ± 196
HOMA-IR	1.3 ± 1.5
Fasting Triglyceride (<i>mg/dL</i>)	82.6 ± 8.0
Fasting Leptin (<i>ng/mL</i>)	2.9 ± 0.3
Fasting Insulin (<i>μIU/mL</i>)	5.0 ± 1.3
Fasting Glucose (<i>mg/dL</i>)	106.5 ± 0.7

Results are means ± standard deviation. Fasting triglyceride, leptin, insulin and glucose values are averaged from baseline values for each participant at fructose and glucose study visits.