The trouble with fructose

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The First Law of Thermodynamics

Weight Gain
Calories Out

Calories In

National Institute of Environmental Health Sciences (NIEHS), January 23, 2007
What happened to willpower? I love fat people. Every fat person says it’s not their fault, that they have gland trouble. You know which gland? The saliva gland. They can’t push away from the table.


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**Total Caloric Intake**

↑ 275 kcal in teen boys

Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Fat Intake: Grams

↑ 5 g (45 cal) in teen boys

Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Carbohydrate Intake: Grams

↑ 57 g (228 cal) in teen boys

Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95
Prevalence of Obesity Compared to Percent Calories from Fat Among US Adults

Beverage Intake

Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95
Beverage Intake

Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

One can of soda/day = 150 cal x 365 d/yr ÷ 3500 cal/lb = 15.6 lbs/yr!

Curtailing soft drinks limits childhood obesity

James et al. BMJ 328:1237, 2004
Influence of corn sweeteners on the price of sugar

U.S. Producer Price Index

International price of refined sugar

U.S. Retail Price

U.S. Department of Agriculture

ANNUAL PER CAPITA AVAILABILITY OF SUGAR AND HFCS ADJUSTED FOR LOSS

TOTAL HFCS & SUGAR

SUGAR*

HFCS**

USDA FOOD DISAPPEARANCE DATA

YEAR

POUNDS PER YEAR

Source: USDA, Economic Research Service, Sweetener Yearbook, Tables 41 and 52

*Estimated annual per capita sugar consumption calculated by adjusting sugar volumes for domestic food and beverage use for food losses.

**Estimated annual per capita HFCS consumption calculated by adjusting HFCS volumes for domestic food and beverage use for food losses.
High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose

Juice is sucrose:
Change in BMI z-score in lower socioeconomic status children versus number of fruit juice servings per day

**Fructose is not glucose**

- Fructose is 7 times more likely than glucose to form Advanced Glycation End-Products (AGE’s)
- Fructose does not suppress ghrelin
- Acute fructose does not stimulate insulin (or leptin)
- Hepatic fructose metabolism is different
- Chronic fructose exposure promotes the Metabolic Syndrome

Elliot et al. Am J Clin Nutr, 2002  
Bray et al. Am J Clin Nutr, 2004  
Teff et al. J Clin Endocrinol Metab, 2004  
Gaby, Alt Med Rev, 2005  
Le and Tappy, Curr Opin Clin Nutr Metab Care, 2006  
Wei et al. J Nutr Biochem, 2006

**Ethanol is a carbohydrate**
Ethanol is a carbohydrate

$\text{CH}_3\text{-CH}_2\text{-OH}$

But ethanol is also a toxin
Acute ethanol exposure

- CNS depression
- Vasodilatation, decreased BP
- Hypothermia
- Tachycardia
- Myocardial depression
- Variable pupillary responses
- Respiratory depression
- Diuresis
- Hypoglycemia
- Loss of fine motor control

Acute fructose exposure

- Diuresis
- Hypoglycemia
- Loss of fine motor control

UCSF Weight Assessment for Teen and Child Health (WATCH) Clinic

294 patients 2003-2006

- Biochemistry

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>33.2</td>
<td>20.0</td>
<td>92.4</td>
<td>&lt;25</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>2.5</td>
<td>1.3</td>
<td>4.4</td>
<td>0</td>
</tr>
<tr>
<td>FBG</td>
<td>87</td>
<td>58</td>
<td>119</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Insulin</td>
<td>20.7</td>
<td>2</td>
<td>117.5</td>
<td>5-20</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.3</td>
<td>0.34</td>
<td>28.1</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Maternal BMI</td>
<td>28.9</td>
<td>17.7</td>
<td>58.6</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Paternal BMI</td>
<td>28.9</td>
<td>16.7</td>
<td>48.8</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

- Race/Ethnicity

Caucasian 30%
Latino 27%
African-American 14%
Mixed 10%
Asian 12%
Unknown 7%

Mietus-Snyder et al. (submitted)
Metabolism of Glucose

- Glucose (20%)
- 24 kcal
- 96 kcal (80%)

Hepatocyte

- Blood Vessel
- Insulin

Muscle

TG
Metabolism of Glucose

1. Glucose
2. Glucokinase
3. ATP
4. ADP
5. Glycogen Synthase
6. Akt
7. pTyr-IRS-1
8. SREBP1
9. Pyruvate
10. TG

Blood Vessel
Insulin
Glucose
Muscle

Fructose-6-P, Fructose-1,6-bis-P, Dihydroxyacetone-P + Glyceraldehyde-3-P

TCA cycle
Acetyl-CoA
Citrate
Pyruvate
ATP
CO₂
15 kcal (+ 12 kcal glucose)

48 kcal

Detrimental Effects of Fructose
Relations between uric acid, hypertension, obesity, and fructose in NHANES IV children

![Graph showing the relationship between BMI Z-scores and uric acid levels.](image1)
P < 0.0001

![Box plot showing uric acid concentrations in normal and hypertensive 8-18 year olds by BMI category in NHANES 1999-2004.](image2)
P < 0.0001

S Nguyen et al. (in preparation)
Xylulose-5-phosphate increases after sucrose refeeding in rats

Wei et al. J Nutr Biochem epub, 2006
Detrimental Effects of Fructose

Fructose

Fructose-1-P

ATP

Fructokinase

Fructose

Dihydroxyacetone-P

Glyceraldehyde

Xylulose-5-P

Fructose-6-P *

Fructose-1,6-bis-P

PP2A

ChREBP

ACL, TGC, PAG

Citrate → Acetyl-CoA → Acyl-CoA

Pyruvate

TCA cycle

O₂

ATP

CO₂

TG

Insulin

BP

NO

PI → AMP → IMP → Uric Acid

NO

ATP

CO₂

TG

Insulin

BP

NO

PI → AMP → IMP → Uric Acid

NO

ATP

CO₂
Fructose increases de novo lipogenesis in normal adults

Fructose increases de novo lipogenesis, triglycerides and free fatty acids in normal adults

Faeh and Schwarz, Diabetes 54:1907, 2005

Detrimental Effects of Fructose
Relation between ALT and liquid calorie consumption

UCSF WATCH Clinic

210 observations

Univariate regression:

- Every 120 kcal/d increases ALT by 1 point (p = 0.013)

Multivariate regression:

- HOMA-IR (insulin resistance) predicts ALT (p = 0.048)
- liquid calories correlates with ALT less well (p = 0.1)

Mietus-Snyder et al. (in preparation)
Chronic ethanol exposure

- Hematologic disorders
- Electrolyte abnormalities
- Hypertension
- Cardiac dilatation
- Cardiomyopathy
- Dyslipidemia
- Pancreatitis
- Malnutrition
- Obesity
- Hepatic dysfunction (ASH)
- Fetal alcohol syndrome
- Addiction
Chronic ethanol exposure
• Hematologic disorders
• Electrolyte abnormalities
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• Addiction

Chronic fructose exposure
• Hypertension
• Myocardial infarction
• Dyslipidemia
• Pancreatitis (2° dyslipidemia)
• Obesity
• Hepatic dysfunction (NASH)
• Fetal insulin resistance
• Habituation, if not addiction

UCSF WATCH Clinic
Associations with the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Baseline Characteristic (mean ± SD)</th>
<th>HOMA-IR&gt;5* N=124</th>
<th>HOMA-IR&lt;5 N=147</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI z-score</td>
<td>2.5, 2.3-2.8</td>
<td>2.5, 2.2-2.7</td>
<td>0.06</td>
</tr>
<tr>
<td>BP syst</td>
<td>125 ± 13</td>
<td>113 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP diast</td>
<td>68 ± 9</td>
<td>64 ± 8</td>
<td>&lt;0.001</td>
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<tr>
<td>Triglyceride (mg/dl)</td>
<td>102, 69-136</td>
<td>63, 57-110</td>
<td>0.005</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>41 ± 10</td>
<td>43 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting Glc (mg/dl)</td>
<td>92 ± 9</td>
<td>85 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting Insulin (mU/ml)</td>
<td>33.7, 28.6-47.1</td>
<td>15.2, 11.2-19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.64 ± 0.14</td>
<td>0.58 ± 0.15</td>
<td>0.003</td>
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<tr>
<td>ALT (U/L)</td>
<td>35, 23-90</td>
<td>23, 18-31</td>
<td>&lt;0.001</td>
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<tr>
<td>MetS+</td>
<td>52%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sugared Beverage Intake (kcal/d)</td>
<td>269, 100-423</td>
<td>129, 21-288</td>
<td>0.002</td>
</tr>
<tr>
<td>Breakfast (days/ wk)</td>
<td>4, 0-7</td>
<td>7, 5-7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mietus-Snyder et al. (submitted)
**UCSF WATCH Clinic Lifestyle Intervention**

**Median Change in BMI z-score from Baseline**

<table>
<thead>
<tr>
<th>Median Time (mos) from initial visit</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>0</td>
</tr>
</tbody>
</table>

**Predictors of Lifestyle Intervention**

- Forward selection model, 4 variables

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>Number of obs =</th>
<th>F( 4, 125) =</th>
<th>Prob &gt; F =</th>
<th>R-squared =</th>
<th>Adj R-squared =</th>
<th>Root MSE =</th>
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</thead>
<tbody>
<tr>
<td>Model</td>
<td>.169200646</td>
<td>4</td>
<td>.042300161</td>
<td>130</td>
<td>6.49</td>
<td>0.0001</td>
<td>0.1720</td>
<td>0.1455</td>
<td>.08073</td>
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<tr>
<td>Residual</td>
<td>.81467663</td>
<td>125</td>
<td>.006517413</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.983877276</td>
<td>129</td>
<td>.007626956</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Delta z/yr | Coef. | Std. Err. | t    | P>|t| | Beta |
|------------|-------|-----------|------|--------|------|
| sugared bev | .012786 | .0048643 | 2.63 | 0.010 | .2268616 |
| HOMA | .0034239 | .0018131 | 1.89 | 0.061 | .1707474 |
| Baseline BMI | .0311507 | .006517413 | 1.56 | 0.122 | .1430862 |
| Baseline Age | .0027542 | .0018131 | 1.56 | 0.122 | .1430862 |
| _cons | -.1475346 | .0573037 | -2.57 | 0.011 | .1055135 |

Madsen et al. (submitted)
Fructose is a carbohydrate

Fructose is metabolized like fat
Fructose is a carbohydrate

Fructose is metabolized like fat

Fructose is also a toxin

Summary

• Fructose (sucrose vs. HFCS) consumption has increased in the past 30 years, coinciding with the obesity epidemic

• Fructose is everywhere

• Fructose is not glucose

• Hepatic fructose metabolism leads to all the manifestations of the Metabolic Syndrome:
  hypertension
  de novo lipogenesis, dyslipidemia, and hepatic steatosis
  inflammation
  hepatic insulin resistance
  obesity
  CNS leptin resistance, promoting continuous consumption

• Fructose ingestion interferes with obesity intervention

• Fructose is a chronic toxin
Collaborators

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