Fructose and the liver: More than just extra calories?

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• No disclosures
Secular trend in diabetes among U.S. adults, 1988-2012

Now
Criticism from the nutritional community

Misconceptions about fructose-containing sugars and their role in the obesity epidemic

Vincent J. van Baal, Leon Tappy and Fred J. P. H. Brouns

To say that fructose is toxic is a total misconception of the nature of the molecule. If you have too much oxygen, it is toxic. If you get too much water, you have water intoxication. That doesn’t mean we say oxygen is toxic.

– Fred Brouns, Atlantic Monthly, USA, June 5, 2014
Criticism from the nutritional community

Toxicity: The degree to which a substance can damage an organism

- Does not distinguish acute vs. chronic toxicity

Requisites:
- Must be an "independent risk factor"
- Exclusive of calories
- Exclusive of obesity
- Must establish causation

Criticisms of Fructose Toxicity

- Animal models, not human studies
- Administration of excessive doses of fructose
Criticisms of Fructose Toxicity

• Animal models, not human studies
• Administration of excessive doses of fructose

WILL LIMIT DISCUSSION TO:
HUMAN DATA,
HUMAN CONSUMPTION,
AND IN DOSES ROUTINELY INGESTED

Sugar and Diabetes
(Prospective Correlation)

SSB’s and BMI-adjusted risk of diabetes in EPIC-Interact (Europe)

<table>
<thead>
<tr>
<th>Variable and model</th>
<th>&lt; 4 glasses (g/d)</th>
<th>≥ 4 glasses (g/d)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.51 (0.37, 0.71)</td>
<td>0.54 (0.40, 0.74)</td>
<td>0.67 (0.51, 0.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total model</td>
<td>0.51 (0.37, 0.71)</td>
<td>0.54 (0.40, 0.74)</td>
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</tr>
<tr>
<td>Adjusted model</td>
<td>0.50 (0.37, 0.71)</td>
<td>0.53 (0.40, 0.74)</td>
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</tr>
<tr>
<td>Model 1</td>
<td>0.51 (0.37, 0.71)</td>
<td>0.54 (0.40, 0.74)</td>
<td>0.67 (0.51, 0.92)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.50 (0.37, 0.71)</td>
<td>0.53 (0.40, 0.74)</td>
<td>0.67 (0.51, 0.92)</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.50 (0.37, 0.71)</td>
<td>0.53 (0.40, 0.74)</td>
<td>0.67 (0.51, 0.92)</td>
</tr>
<tr>
<td>Total model - BMI</td>
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</table>
Associations between consumption of sugar sweetened beverages and fruit juice and incident type 2 diabetes: meta-analysis of prospective cohort studies

<table>
<thead>
<tr>
<th>Sugar Sweetened Beverages</th>
<th>Not Adjusted for Adiposity: Relative Risk</th>
<th>Adjusted for Adiposity: Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis, crude</td>
<td>1.25 (1.18 to 1.33)</td>
<td>1.18 (1.09 to 1.28)</td>
</tr>
<tr>
<td>Relative Risk I2</td>
<td></td>
<td>1.13 (1.06 to 1.21)</td>
</tr>
<tr>
<td>Not Adjusted for</td>
<td></td>
<td>1.43 (1.20 to 1.70)</td>
</tr>
<tr>
<td>Adiposity:</td>
<td></td>
<td>1.28 (1.12 to 1.46)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.18 (1.09 to 1.28)</td>
<td>1.07 (1.01 to 1.14)</td>
</tr>
<tr>
<td>Information bias</td>
<td></td>
<td>1.10 (1.01 to 1.20)</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Fruit Juices

| (n=13)                   |                                          |                                      |
| Meta-analysis, crude     | 0.97 (0.90 to 1.06)                      | 1.05 (0.99 to 1.11)                  |
| Relative Risk I2          |                                          | 1.07 (1.01 to 1.14)                  |
| Not Adjusted for          |                                          | 1.06 (0.98 to 1.14)                  |
| Adiposity:                |                                          | 1.10 (1.01 to 1.20)                  |
| Multivariable adjusted   | 1.05 (0.99 to 1.11)                      | 1.07 (1.01 to 1.14)                  |
| Information bias         |                                          | 1.10 (1.01 to 1.20)                  |
| Publication bias          | Not detected                             | Not detected                         |

Sugar and Diabetes

(Econometric Analysis)

An international econometric analysis of diet and diabetes

Food and Agriculture Organization (FAO); FAOSTAT

Food Supply data in Kilocalories/day calculation:
Food Supply = Supply Elements - Utilization Elements = (Production + Import Quantity + Stock Variation - Export Quantity) - (Feed + Seed + Processing + Waste). Only industrial waste factored in.

Extracted Food Supply data for 2000 and 2007:
Total Calories; Roots & Tubers, Pulses, Nuts, Vegetables; Fruits-Excluding Wine; Meat; Oils; Cereals; Sugar, Sugarcrops & Sweeteners

International Diabetes Federation (IDF)

2000 (1st ed) and 2010 (3rd ed)

The World Bank World Development Indicators Database

GDP expressed in purchasing power parity in 2005 US dollars for comparability among countries

An international econometric analysis of diet and diabetes

Total 175 countries; complete data for 154 countries (21 not different)

Data monitoring and quality
- Generalized estimating equations
- Conservative fixed effects approach (Hausman test)
- Hazard model to control for selection bias (Heckman selection model)
- Longitudinal data to determine what preceded diabetes (Granger causality)
- Period effects controlled for secular trends that may have occurred as a result of changes diabetes detection capacity or importation policies.

Controlled for:
- GDP per capita
- % population living in urban areas
- Obesity
- % of population over age 65
- Physical inactivity
An international econometric analysis of diet and diabetes

Diabetes prevalence rose from 5.5% to 7.0% for 175 countries 2000-2010

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Effect of Sugar on Diabetes Prevalence

<table>
<thead>
<tr>
<th>Model</th>
<th># countries</th>
<th>Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar+controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar+control+period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Adjusted Association of Sugar with Diabetes Prevalence

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An international econometric analysis of diet and diabetes

Only changes in sugar availability predicted changes in diabetes prevalence

Every extra 150 calories increased diabetes prevalence by 0.1%

But if those 150 calories were a can of soda, diabetes prevalence increased 11-fold, by 1.1% (95% CI 0.03 — 1.71%, p <0.001)

This study meets the Bradford Hill criteria for Causal Medical Inference:

—dose  —duration  —directionality  —precedence

We estimate that 25% of diabetes worldwide is explained by sugar

Sugar and Fatty Liver Disease

NAFLD and Metabolic Syndrome are congruent (if not the same)

References:
NAFLD is a primary predictor of T2DM in Korean adults

<table>
<thead>
<tr>
<th>Value z</th>
<th>OR for T2DM at 5 yr. Follow-up</th>
<th>95% CI of coefficient estimated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 100</td>
<td>1.017 (0.995, 1.038)</td>
<td>0.066</td>
<td>0.367</td>
</tr>
</tbody>
</table>

MRI Fat Fraction Maps

Obese

Low Liver Fat = 2.6%

MRI Fat Fraction Maps

Obese

Low Liver Fat = 2.6%
Intrahepatic fat explains metabolic perturbation better than visceral fat

Hepatic Insulin Sensitivity Index
Insulin Stimulated Glucose Disposal Rate
Insulin Stimulated Palmitate Suppression Rate

B

Contribution Of Free Fatty Acids To VLDL

A

VLDL Secretion Rate

Fabbrini et al. Proc Natl Acad Sci 106:15430, 2009

MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%
Obese
High Liver Fat = 24%
Thin
High Liver Fat = 23%

Metabolism of Glucose

(20%) Glucose
Glycogen
Insulin (80%) Glucose
Muscle
Insulin
TG

(572x25) 12
Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it
Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love anyway
Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love anyway

**Answer: Ethanol**

**Histology of (N)AFLD**

- Normal
- Alcohol?
- Sugar?

**Metabolism of Ethanol**

- (80%) Ethanol
- Acetaldehyde
- Inflammation
- ROS
- Insulin
- Dyslipidemia
- Aldehyde dehydrogenase 2
- Acetyl CoA
- Acetyl CoA:ACP
- TG
**Strategy**

- Isocaloric fructose restriction x 9 days in children who are habitual sugar consumers
- No change in weight
- Substitute complex carbs for sugar
- Maintain baseline macronutrient composition of the diet
- Study in PCRC at Day 0 and Day 10
- Assess changes in organ fat, *de novo* lipogenesis, and metabolic health

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**DNL is the Conversion of Dietary Carbohydrates into Lipids**

Sugar → Fructose → Acetate → Palmitate

[Diagram showing the conversion process]

*New Tracer Method using MIDA: Hellerstein and Neese, AJP 1999*

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**DNL AUC Pre and Post Fructose Restriction**

[Graph showing AUC comparison between Day 0 and Day 10]

[Graph legend: Black line represents control group; other lines represent different treatment groups].

*Endocrine Society, March 5, 2015*
Triglyceride-rich Lipoprotein
DNL AUC (n=17)

Fructose Restriction Reduced Liver Fat

Changes in fat depots by Magnetic Resonance Spectroscopy
Oral glucose tolerance test before and after isocaloric fructose restriction

For pediatric subjects with hepatic steatosis (n = 25)

Change in Liver Fat and Insulin Sensitivity

-30% (-50, -20); p <0.001
+0.65 (0.41, 0.88); p <0.001

Adjusted for change in weight
### Correlation between Insulin Sensitivity & Liver Fat vs Visceral Fat

<table>
<thead>
<tr>
<th>Spearman R</th>
<th>Day 0</th>
<th>Day 10</th>
<th>Change in fat (Absolute)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver Fat Fraction</td>
<td>Visceral Fat</td>
<td>Liver Fat Fraction</td>
</tr>
<tr>
<td>Insulin Sensitivity (CISI) DAY 0</td>
<td>- 0.36 §</td>
<td>- 0.57*</td>
<td></td>
</tr>
<tr>
<td>Insulin Sensitivity (CISI) DAY 10</td>
<td></td>
<td></td>
<td>- 0.28</td>
</tr>
<tr>
<td>Change in Insulin sensitivity (ΔCISI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05  § 0.05<p<0.1

Lustig et al. Obesity Society, Nov. 4, 2015

### Association between Insulin Sensitivity (CISI) and Liver Fat vs. Visceral Fat

**Liver Fat**

- Every unit decrease in liver fat increases CISI by 10.49 (p = 0.008).
- Every unit decrease in %liver fat increases %CISI by 0.8 (p = 0.03).

**Visceral Fat**

- Every unit decrease in visceral fat is non-significantly increases CISI by 0.002 (p = 0.77).
- Every unit decrease in %visceral fat non-significantly increases %CISI by 0.69 (p = 0.28).

Lustig et al. Obesity Society, Nov. 4, 2015

### Summary

- **Prospective correlational** data demonstrate associations between added sugar and heart disease, exclusive of calories or obesity
- **Econometric** data show causal medical inference for added sugar and diabetes, exclusive of calories or obesity
- **Interventional isocaloric glucose for fructose** study shows improvements in fatty liver disease, insulin resistance and metabolic health in children in 10 days, and insulin resistance is driven by liver fat
Toward a unifying hypothesis of metabolic syndrome

FRUCTOSE

Lactate

ROS

Mitochondria

Peroxisome

Cell death

FRUCTOSE

Acetyl-CoA

ROS

ATP

Cellular/metabolic dysfunction

NH2

Endoplasmic Reticulum

Acyl-CoA

Lipid droplet

pSer-IRS-1

PKC

JNK1

Insulin resistance

Fat deposition

Insulin Receptor

Toward a unifying hypothesis of metabolic syndrome

Weiss et al., Ann NY Acad Sci 1281:123, 2013

Collaborators

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