Fructose and metabolic syndrome: Is there a link?

Robert H. Lustig, M.D., M.S.L.
Division of Endocrinology, Department of Pediatrics
Institute for Health Policy Studies
University of California, San Francisco

Adjunct Faculty
UC Hastings College of the Law

Past

Currently there are 30% more obese than undernourished people worldwide
(World Health Organization)

371 million diabetics in 2012
(5% of the world’s population)
(International Diabetes Federation)

Present

Experts predict:

165 million Americans will be obese by 2030
(4 part obesity series in Lancel, 8/26/11)

42% of Americans will be obese by 2030

100 million Americans will have diabetes by 2050
(CDC Division of Diabetes Translation, 2011)

Obesity is the problem

Medicare will be broke by 2026

No disclosures
• Obesity is increasing worldwide by 1% per year
• Diabetes is increasing worldwide by 4% per year

“Exclusive” view of obesity and metabolic dysfunction

“Inclusive” view of obesity and metabolic dysfunction
Obese (30%)  
Normal weight (70%)

240 million adults in U.S.

Obese and sick (80% of 30%)  
Normal weight, metabolic dysfunction (40% of 70%)

Total: 124 million sick

57 million

67 million

Relation between visceral and subcutaneous obesity: TOFI (thin on the outside, fat on the inside)

72 million

168 million

Obesity is not the problem

Obesity is not the problem

Obesity is not the problem

Obesity is not the problem

Obesity is not the problem

Obesity is not the problem

Metabolic syndrome is difficult to define in adults

- WHO 1998
- AACE 2003
- EGIR 1998
- IDF 2005
- NCEP/ATP III 2001
- AHA 2005
Metabolic syndrome is difficult to define in adults

- WHO 1998
- EGIS 1998
- NCEP/ATPIII 2001
- AHA 2005

And even more difficult to define in children

Because each of these definitions sought to define the metabolic syndrome phenomenologically, with cutoffs

Circulation 119:628, 2009

It is easier to define the metabolic syndrome mechanistically

Where’s the insulin resistance?

The standard model of insulin resistance

Comparing between lipodystrophy and obesity

Familial Partial Lipodystrophy: Dunningan or Type 2

- X-linked or autosomal dominant
- Absence of limb fat
  - Easily visible veins
  - Defined musculature
- Normal or excess facial fat
- Cushionoid facies (moon facies)
- Dorsocervical fat pad
- Acanthosis nigricans
- Metabolic Syndrome

Fat mass
Leptin
Adiponectin
Inflam. Cytokines
Metabolic Syndrome

LD obesity

++ ±
Comparison between lipodystrophy and obesity

- Fat mass
- Leptin
- Adiponectin
- Inflam. Cytokines
- Metabolic Syndrome

So the metabolic syndrome can arise from too much, or too little fat i.e. it’s not the fat that counts

Obesity and lipodystrophy share insulin resistance

Obesity and Lipodystrophy

Relation between obesity, T2DM, and Metabolic Syndrome

REFRAMING THE DEBATE

Obesity doesn’t CAUSE metabolic syndrome
Obesity is a MARKER for metabolic syndrome

OBESITY IS A “RED HERRING” ONE IS AT RISK OF METABOLIC SYNDROME
Obesity isn’t enough!
Insulin resistance isn’t enough!
What kind of obesity?
What kind of insulin resistance?
In which tissue?
Are all insulin pathways affected?

Insulin Receptor Knockouts (IRKO)
Kahn Lab, Joslin 1998-present

Obesity, Metabolic Syndrome
Liver (LIRKO)
Brain (NIRKO)

Protected from Obesity
Muscle (MIRKO)
White Adipose Tissue (FIRKO)
Brown Adipose Tissue (BATIRKO)
β-cell (βIRKO)
Vascular Smooth Muscle (VSMCIRKO)
Glomerular Podocyte (PODIRKO)

Insulin has two effects on the liver

Result: Obesity
Hyperglycemia, hyperinsulinemia, DM
Low TG, VLDL
Normal BP
NOT Metabolic Syndrome

Result: Obesity
Hyperglycemia, hyperinsulinemia, DM
High TG, VLDL
Low BP
Metabolic Syndrome
In order to explain Metabolic Syndrome:

- We are looking for a ubiquitous factor that
  - promotes obesity (preferably visceral)
  - promotes hypertension
  - induces selective hepatic insulin resistance
    - blocks Foxo1 to promote gluconeogenesis
      (hyperglycemia, hyperinsulinemia, and diabetes)
    - stimulates de novo lipogenesis
      (dyslipidemia, atherosclerosis)

U.N. General Assembly
Sept 20, 2011

- Non-communicable disease is now a bigger problem
  than acute infectious diseases worldwide
- Plan to target, tobacco, alcohol, and diet

U.N. General Assembly
Sept 20, 2011

- Non-communicable disease is now a bigger problem
  than acute infectious diseases worldwide
- Plan to target, tobacco, alcohol, and diet
- But exactly what about diet?
  Total calories?
  Fat?
  Red meat?
  Dairy?
  Carbohydrate?

The Fiction

“Beating obesity will take action by all of us, based on one simple common sense fact: All calories count, no matter where they come from, including Coca-Cola and everything else with calories…”

- The Coca Cola Company, “Coming Together”, 2013
The Science

• Some Calories Cause Disease More than Others
• Different Calories are Metabolized Differently
• A Calorie is Not A Calorie

High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose

Actual fructose content in soft drinks

US Sugar Consumption, 1822-2005

Growth of Sugar Industry

Stabilization

WWII

HFCS + Sugar for Fat

Theoretical threshold based on EtOH

AHA threshold for CVD

Stabilization

WWII

HFCS + Sugar for Fat

Growth of Sugar Industry
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

Obesity is not the problem
Metabolic syndrome is the problem

A different model of insulin resistance
A different model of insulin resistance

Cytokines
Fructose
Fatty liver
Sensitivity
Hepatic insulin resistance

The second problem

Fatty liver

Aging and costal cartilage

The common link

The browning reaction or Maillard reaction or non-enzymatic glycation

Instead of roasting 1 hour at 375 degrees we slow cook at 98.6 degrees for 75 years

Aging and costal cartilage

Generation of reactive oxygen species by carbohydrate
The furan ring of fructose is more unstable, so at equilibrium, fructose exists in the linear form.

Non-enzymatic glycation: fructose >> glucose

Hepatocyte death in vitro upon fructose exposure (after generation of H$_2$O$_2$)

Treatment | ED$_{50}$
---|---
Fructose | 1.5 ± 0.13 M
Glucose | >1.5 M
 Glycoaldehyde | 20 ± 2 mM
 Glyoxal | 5 ± 0.5 mM

Prevented by addition of:
- antioxidant vitamins (VitB$_1$, VitB$_6$, VitC)
- P450 inhibitors
- hydroxyl radical and carbonyl scavengers
- heavy metal chelators

Sucrose is necessary for NAFLD in the Methionine-Choline deficient diet

Fastest animal model of NASH
- sucrose necessary to provide the substrate for steatosis
- methionine deficiency reduces glutathione, the hepatic hydroxyl radical scavenger
- choline deficiency reduces phosphatidyl choline, another mechanism of hepatic lipid export
TUNEL staining in the Methionine-Choline deficient diet

Association of fructose consumption with severity of steatosis and fibrosis

Grade of Steatosis

Stage of Fibrosis

Non
Occasional
Daily

Fructose consumption

Error bar = 95%CI


10 Most Obese States

> 30% obese

10 Most Laziest States

< 63% active

10 Most Unhappy States

Adult Obesity Rate
Hazard ratio for CV mortality based on percent calories as sugar for US adult population, 1988-2006

Figure 1. Adjusted Hazard Ratio of the Usual Percent of Calories from Added Sugar for CVD Mortality Among US Adults Aged > 20 Years – NHANES Linked Mortality Files, 1988-2006

Histogram is the distribution of usual percent of calories from added sugars in population. Lines show the adjusted HRs from Cox models. Mid-value of quintile 1 (7.5%) was the reference standard. Model was adjusted for age, sex, race/ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, family history of CVD, antihypertensive medication use, health eating index score, body mass index, systolic blood pressure, total serum cholesterol and total calories. Solid line indicates point estimates; dashed lines indicate 95% CIs. CVD indicates cardiovascular disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey.


Hazard ratio for CV mortality based on percent calories as sugar for US adult population, 1988-2006

Prevalence of diabetes, 2010

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

An international longitudinal panel analysis of diet and diabetes

Food and Agriculture Organization (FAO); FAOSTAT

Food Supply data in kcal/capita/day:
\[ \text{Food Supply} = \sum \text{Supply Elements} - \sum \text{Utilization Elements} = \left( \text{Production} + \text{Import Quantity} + \text{Stock Variation} - \text{Export Quantity} \right) - \left( \text{Feed} + \text{Seed} + \text{Processing} + \text{Waste} \right). \]

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)

The World Bank World Development Indicators Database

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

14
An international longitudinal panel analysis of diet and diabetes

Total 204 countries; complete data for 154 countries (50 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

Diabetes prevalence rose from 5.5% to 7.0% for 204 countries 2000-2007

Model | # countries | Effect (95% CI)
--- | --- | ---
Sugar | |  
Sugar+controls | |  
Sugar+controls+period | |  
Overall | |  

Adjusted Association of Sugar with Diabetes Prevalence

**Model # countries Effect (95% CI)**

<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+controls+period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
An international longitudinal panel analysis of diet and diabetes

Context

Only changes in sugar availability correlated with 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%; p < 0.001.
These data meet the criteria for Causal Medical Inference (Bradford Hill):
— dose
— duration
— directionality
— precedence
Controlled for many confounders; obesity exacerbated, but did not confound the effect.
These data estimate that 25% of diabetes worldwide is explained by sugar.

Limitations

Ecologic, not raw data analysis.
Ecologic fallacy: inferences about individuals are based on aggregates.
Could the sugar consumers and the diabetes be different people?
Food supply, not food consumption data (wastage, esp. in the U.S.?)
but wastage does not appear to be different based on different foods.
And leaving the U.S. out of the analysis did not change the findings.
Only one decade (but longitudinal time-series data, not 2 cross-sectional
points in time).
Not a complete dietary analysis.
Different techniques used to screen for diabetes in different countries.
Different diagnostic criteria for diabetes in different countries.
Some countries used self-reported data; many diabetics are undiagnosed.
Data includes both Type 1 and Type 2 diabetes.

Foodstuffs and metabolic syndrome

- Transfats
- Branched chain amino acids
- Ethanol
- Fructose
- Liver is the only site for energy metabolism
- Not insulin regulated
- No glycogen popoff, mitochondria are overwhelmed

Toward a unifying hypothesis of metabolic syndrome


Recognition at the American Heart Association

AHA Scientific Statement

Dietary Sugars Intake and Cardiovascular Health
A Scientific Statement From the American Heart Association

Recommends reduction in added sugar intake from 22 tsp/day
(100g) to 9 tsp/day (males) and 6 tsp/day (females).

No drug target

- Mitochondrial overload promotes lipogenesis, leading to hepatic insulin resistance, and metabolic syndrome.
- Mitochondrial overload releases ROS’s, which lead to cell dysfunction, aging, and death.
- Only options are:
  - reduce substrate availability (diet)
  - reduce hepatic flux (fiber)
  - increase clearance (exercise).
How our food dollars have been reallocated

Question 1:
Can our “toxic food environment” be changed without government/societal intervention? Especially when there are potentially addictive substances involved?

Question 2:
Can we afford to wait to enact public health measures when health care will be bankrupt due to chronic metabolic disease?

Further reading
Facts About Fructose
Fructose: It’s “Alcohol Without the Buzz”
Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol
The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome
Effects of Sugar-Sweetened Beverages on Children
Toward a Unifying Hypothesis of Metabolic Syndrome
The toxic truth about sugar
Furth​er reading

**Dietary treatment of nonalcoholic steatohepatitis**


*Current Opinion Gastroenterology, 29:170, 2013*

The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated Cross-Sectional Data

Sanjay Basu, Paula Yaffe, Nancy Milbrath, and Robert H. Lustig

*PloS One 8:e57873, 2013*

We have started a non-profit to provide medical, nutritional and legal analysis and consultation to promote personal and public health vs. Big Food

**INSTITUTE FOR RESPONSIBLE NUTRITION**

[www.responsiblefoods.org](http://www.responsiblefoods.org)

Please let me know if you would like more information!

rlustigmd@earthlink.net

---

**Collaborators**

UCSF Weight Assessment for Teen and Child Health (WATCH)

Andrea Garber, Ph.D., R.D.

Kristine Madsen, M.D., M.P.H.

Patrika T sai, M.D., M.P.H.

Stephanie Nguyen, M.D. M.A.S.

Emily Perito, M.D.

Jung Sub Lim, M.D., Ph.D.

UCSF Dept. of Epidemiology and Biostatistics

Nancy Mills, M.S.

Touro University Dept. of Biochemistry

Jean-Marc Schwarz, Ph.D.

San Francisco General Hospital Dept. of Medicine and Radiology

Sanjay Basu, M.D., Ph.D.

Susan Kosinski, Ph.D.

Kathleen Mulligan, Ph.D.

UC Berkeley Dept. of Nutritional Sciences and Integrative Biology

Pat Crawford, R.D., Ph.D.

Patsi Yaffe, R.S.

Vanderbilt University Dept. of Pediatrics

Andrew Bremer, M.D., Ph.D.

Children’s National Medical Center

Michele Mehta-Snyder, M.D.