Metabolic and clinical aspects of sugar, fructose, soft drinks

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Added sugar

• Sugar added to a food including: sucrose, HFCS, honey, molasses, and other syrups

• Contributes 80% of the dietary fructose consumed

The dark side of sugar

Fructose

Added sugar

Sugared soft-drinks

- Obesity
- Increased HTN
- Increased VAT
- NAFLD
- Increased uric acid

Bray GA., Diabetes Care 2014
Added sweeteners pose dangers to health that justify controlling them like alcohol.

The toxic truth about sugar

Lustig RH., NATURE 2012
Drinking soft drinks daily

Adolescents' food habits: results of the Health Behavior in School-aged Children survey

Harel – Fisch Y, et al. HBSC survey, Bar Ilan University
Soft drinks consumption in Israel 2006

Youth in Israel – Findings from the 5th International HBSC survey
(Health Behaviors of School-aged Children 11-15 y)

Harel – Fisch Y, et al. HBSC survey, Bar Ilan University
AHA & WHO recommend upper limit of intake for added sugars

- < 5 teaspoons/day
- < 9 teaspoons/day
- ≈ 8 teaspoons of added sugar and/or fructose

Johnson RK., Circulation 2009
www.who.int/mediacentre/multimedia/sugar 2014
Cardiovascular risk and dietary sugar/fructose intake: is the link so sweet?

Sugar sweetened beverages and weight gain and metabolic alterations
Epidemiological studies
Changes in diet and lifestyle and long-term weight gain in women and men

Three separate prospective cohorts including 120,877 U.S. women and men

**Beverages**

- Sugar-sweetened beverages
- 100%-Fruit juice
- Low-fat or skim milk
- Whole milk
- Diet (zero-calorie) soda

Weight Change Associated with Each Increased Daily Serving, per 4-Year Period (lb)

~0.5 Kg

Mozaffarian D, et al. NEJM 2011
Weight according to trends in SSB consumption

- Prospective cohort conducted from 1991 to 1999
- Women in the Nurses’ Health Study II
- 51,603 women

Mean Change in Energy Consumption

Mean Weight

Schulze MB, et al. JAMA 2004
SSB and Risk of metabolic syndrome and type 2 diabetes
A meta-analysis of prospective cohort studies in adults

Metabolic syndrome
19,431 participants

All studies adjusted for potential confounding by diet and lifestyle factors, suggesting an independent effect of SSBs

Type 2 diabetes
310,819 participants

Malik VS, et al. Diabetes Care 2010
HDL levels by intake of added sugars among US Adolescents

- Cross-sectional study of 2,157 US adolescents in the NHANES 1999 to 2004
- 24-hour recall of food intake
- Adjusted for
  - body weight
  - ethnicity
  - sex

HOMA-insulin resistance by intake of added sugars among US Adolescents


Overweight/obese
P for trend 0.004

Normal weight
P for trend 0.41

### Relative risk of type 2 diabetes according to frequencies of SSBs consumption in women from the NHS II

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>&lt;1/mo</th>
<th>1-4/mo</th>
<th>2-6/wk</th>
<th>≥1/d</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sugar-sweetened soft drinks</td>
<td>1</td>
<td>1.06 (0.9-1.3)</td>
<td>1.49 (1.2-1.9)</td>
<td>1.83 (1.4-2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sugar-sweetened cola</td>
<td>1</td>
<td>0.99 (0.8-1.2)</td>
<td>1.56 (1.2-2.0)</td>
<td>1.87 (1.4-2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fruit punch</td>
<td>1</td>
<td>0.90 (0.7-1.2)</td>
<td>1.15 (0.8-1.7)</td>
<td>2.0 (1.3-3.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Relative risks are adjusted for age, lifestyle habits and dietary confounders, family history of diabetes & relevant medications.

The RR for extreme categories further controlling for BMI was 1.39 (1.1-1.8 CI)

Schulze MB, et al. JAMA 2004
Sugar sweetened beverages and risk of CHD
A meta-analysis of prospective studies

• Four prospective studies with 7396 CHD cases among 173,753 participants

Huang C., Atherosclerosis 2014
Added Sugar Intake and CVD Mortality

Figure 1. Adjusted Hazard Ratio (HR) of the Usual Percentage of Calories From Added Sugar for Cardiovascular Disease Mortality Among US Adults 20 Years or Older: National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006

Yang Q., JAMA Intern Med 2014
Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure

- 810 hypertensive adults
- 18-month behavioral intervention trial

Adjusted for known risk factors for BP including changes in lifestyle and in body weight

Chen L, et al. Circulation 2010
Sugar-sweetened vs. diet soft drinks and serum uric acid levels

• Hyperuricemia is considered the precursor of gout
• Soft drinks contain large amounts of fructose, which is the only carbohydrate known to increase uric acid levels
• 14,761 adults from the Third NHANES

Serum uric acid levels according to categories of sugar-sweetened vs. diet soft drink consumption

Adjusted for: age, sex, smoking, body mass index, relevant medications, hypertension, alcohol, meats, seafood, dairy foods, coffee, tea, total energy

Fructose promotes steatosis & inflammation

Fructose
• Insulin resistance
• Oxidative stress

Uric acid

Steatohepatitis
NAFLD

Real-world data from Maccabi Healthcare System, n= 82,608

P for trend <0.001

Afzali A, Hepatolog 2010
Stanhope KL, J Clin Invest  2009
The independent association between serum uric-acid and elevated serum ALT

Adjusted for age, BMI, glucose, lipids, smoking, statins

Zelber-Sagi S, Liver Int 2015
Putative mechanisms linking excess fructose consumption to the metabolic syndrome

Tappy L, et al. Nutrition 2010
Lipotoxicity

The adverse effect of an excess of fatty acids on the function of non-adipocytes liver, pancreas, muscle
7-day fructose overconsumption causes hepatic lipid deposition in healthy men

- Crossover trial
- Subjects with and without a family history of type 2 diabetes
- 7-d isocaloric diet or a hypercaloric high-fructose diet

Sucrose-sweetened beverages increase fat storage in the liver

- 47 overweight subjects
- Randomized to 4 different test drinks
- 1 L/d for 6 mo

<table>
<thead>
<tr>
<th></th>
<th>Regular Cola</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate (g/100 mL)</td>
<td>10.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Fat (g/100 mL)</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Energy (kJ/d)</td>
<td>1800</td>
<td>1900</td>
</tr>
</tbody>
</table>

NAFLD according to beverages consumption in the Framingham cohort

CT in 2634 participants

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Consumers</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 serving/mo-&lt;1 serving/wk</td>
<td>1 serving/wk-&lt;1 serving/d</td>
</tr>
<tr>
<td><strong>Sugar-sweetened beverages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Ref)</td>
<td>1.16 (0.88-1.54)</td>
<td>1.32 (0.93-1.86)</td>
<td>1.61 (1.04-2.50)</td>
</tr>
<tr>
<td><strong>Diet soda</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Ref)</td>
<td>1.02 (0.76-1.36)</td>
<td>1.12 (0.82-1.54)</td>
<td>0.91 (0.66-1.24)</td>
</tr>
</tbody>
</table>

Adjusted for: energy intake, macronutrients intake and BMI

Ma J., Journal of Hepatology 2015
NAFLD patients consume twice the amount of soft drinks

Carbohydrates from soft drinks

Fructose calories from soft drinks

Regardless of BMI & total calories

Controls matched for and BMI


Why is fructose bad for Satiety?
**Fructose vs. glucose in Satiety**

- Fructose vs. Glucose
  - No Glut-5 in pancreatic beta cells
  - Suppression of ghrelin
  - Stimulation insulin secretion
  - Stimulation leptin secretion
  - Satiety signals

Why sweetened beverages are the worst?

1. Large amounts of rapidly absorbed sugars

2. Sweetened liquids only modestly reduce food intake

3. Contain a lot of:
   - Fructose
   - HFCS
   - Sucrose

4. Caramel coloring which is rich in AGEs

Advanced Glycation End-Products
- Increase insulin resistance and inflammation

Vlassara H, et al. PNAS 2002
Advanced-Glycation End-Products (AGEs) glycotoxins

- Reaction of sugars (glucose and mainly fructose) with fat, amino acids, proteins and nucleic acids

- Exogeneous AGEs from processed food
  - Serum levels correlate with the amount ingested

- Associated with metabolic alterations
  - Oxidative stress
  - Insulin resistance & DM
  - Cardiovascular disease

- Associated with liver damage
  - Steatosis
  - NASH
  - Activation of HSCs
  - HCC

Zelber-Sagi S., submitted
Iwamoto K., J Gastroenterol 2008
Hyogo H., J Gastroenterol Hepatol 2007
Yilmaz Y., Clinical Biochemistry 2009
Moy KA., Hepatology 2013
### AGE content in common foods and beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Content, g/cup Carbohydrate</th>
<th>AGEs, units/cup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprite</td>
<td>26</td>
<td>475</td>
</tr>
<tr>
<td>Orange juice</td>
<td>23</td>
<td>600</td>
</tr>
<tr>
<td>Classic Coca Cola</td>
<td>27</td>
<td>8,500</td>
</tr>
<tr>
<td>Diet Coke</td>
<td>0</td>
<td>9,500</td>
</tr>
</tbody>
</table>

Sugar sweetened beverages and weight gain and metabolic alterations

Clinical trials
Liquid versus solid carbohydrate: effects on food intake

- Cross-over design
- 7 males and 8 females
- Dietary carbohydrate loads of 450 kcal/d during 4 week
  - liquid (soda)
  - solid (jelly beans)
- Diet records

Mean reported energy intake prior to and at the end of both intervention periods

Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight

- RCT
- Overweight subjects
- 10 wk daily supplements containing
  - sucrose (n = 21) •
  - artificial sweeteners (n = 20) △
- Sucrose supplements provided 152 g sucrose/d mostly from soft drinks

Blood pressure increased in the sucrose group but decreased in the sweetener group
Systolic BP (mm Hg) +6.9
Systolic BP (mm Hg) +5.3

SSB consumption and body weight: meta-analysis of randomized trials

**Adding mandatory SSB consumption to persons’ diets**
- RCT’s, Lasting at least 3 weeks (up to 1 year)
- Population: adults
- Daily energy loads ranged from ~150 kcal to 530 kcal
- Sample sizes 30-133

**Healthy lifestyle education program to reduce SSB consumption**
- RCT’s, Lasting at least 4 weeks (up to 39 weeks)
- Population: children/adolescents/adults
- Sample sizes 103-1140

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**Estimated weight gain effect of SSB**

![Dose-Response Graph](image)

Mattes RD, et al. obesity reviews 2011
SSB consumption and body weight: a meta-analysis of randomized trials


Forest plot of **reduced** SSB consumption in overweight/obese subjects

Forest plot of **added** SSB consumption

BMI change

- Forest plot of **reduced** SSB consumption in overweight/obese subjects
  - Std. mean difference
  - IV, fixed, 95% CI
  - 0.58 [0.88, 0.29]

- Forest plot of **added** SSB consumption
  - Std. mean difference
  - IV, fixed, 95% CI
  - 0.35 [0.49, 0.21]

**Consuming fructose-sweetened vs. glucose sweetened beverages**

- Double-blind clinical trial
- 32 overweight subjects
- Glucose- or fructose-sweetened beverages providing 25% of energy requirements for 10 weeks

*Despite comparable weight gain (+1.5~), there were differential effects of glucose and fructose on body fat distribution*

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Consuming fructose-sweetened vs. glucose sweetened beverages

24-hour circulating TG concentrations before and after the intervention

Nutrition

Microbiota

1. Determines susceptibility to diet
2. Influenced by diet – mediating factor

Metabolism

Fructose/ Fat-induced NAFLD is mediated by intestinal microflora

- Alterations in gut flora
- Increased intestinal permeability
- Increased translocation of bacterial endotoxin

Steatosis
Hepatic TNF

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

Rachel K. Johnson, PhD, MPH, RD, Chair; Lawrence J. Appel, MD, MPH, FAHA; Michael Brands, PhD, FAHA; Barbara V. Howard, PhD, FAHA; Michael Lefevre, PhD, FAHA; Robert H. Lustig, MD; Frank Sacks, MD, FAHA; Lyn M. Steffen, PhD, MPH, RD, FAHA; Judith Wylie-Rosett, EdD, RD;
on behalf of the American Heart Association Nutrition Committee of the Council on Nutri
Physical Activity, and Metabolism and the Council on Epidemiology and Prevention

Abstract—High intakes of dietary sugars in the setting of a worldwide pandemic of obesity and cardiovascular di
heightened concern about the adverse effects of excessive consumption of sugars. In 2001 to 2004, the usual
added sugars for Americans was 22.2 teaspoons per day (355 calories per day). Between 1970 and 2005, aver
availability of sugars/added sugars increased by 19%, which added 76 calories to Americans’ average daily
intake. Soft drinks and other sugar-sweetened beverages are the primary source of added sugars in America.
Excessive consumption of sugars has been linked with several metabolic abnormalities and adverse health
as well as shortfalls of essential nutrients. Although trial data are limited, evidence from observational studie
that a higher intake of soft drinks is associated with greater energy intake, higher body weight, and lower
essential nutrients. National survey data also indicate that excessive consumption of added sugars is curren
overconsumption of discretionary calories by Americans. On the basis of the 2005 US Dietary Guidelines
added sugars greatly exceeds discretionary calorie allowances, regardless of energy needs. In view of
considerations, the American Heart Association recommends reductions in the intake of added sugars. A pr
limit of intake is half of the discretionary calorie allowance, which for most American women is no more
than 150 calories per day and for most American men is no more than 150 calories per day from added sugars. (Circula
120:1011-1020.)
Summary and conclusions

• There is considerable evidence that SSBs produce weight gain & metabolic alterations

• The deleterious health effects of SSBs seem to be independent of body of weight and lifestyle factors

• Fructose seem to be responsible for most of the metabolic damage caused by SSBs consumption

Tappy L, et al. Nutrition 2010
Thank you and drink water