Disclosures

None
Objectives

- Epidemiology of Obesity
- The Evolution of Artificial & Natural Alternative Sweeteners
- The Effects of Sugar Substitutes on Energy Consumption
- The Effects of Sugar Substitutes on the Neuronal, Hormonal Response & Glucose Homeostasis
- The Effects of Sugar Substitutes on the Microbiome
Epidemiology of Obesity
The Obesity Epidemic

Global Health Crisis
Exhibits no boundaries
All ages, ethnicities, races

1980-2000
Prevalence Obesity in Adults: 35%
Prevalence Obesity <20 yo: 20%

Obesity prevalence remained stable since 2000
Increase in obesity among women & extreme obesity

References:
The Cost of Obesity

Greater healthcare costs vs Drug/Alcohol Use

Americans spend $38 billion/year trying to lose weight

NIH spends <1% of its budget on obesity research

The Healthcare Costs of Obesity

Obesity is one of the biggest drivers of preventable chronic diseases and healthcare costs in the United States. Currently, estimates for these costs range from $147 billion to nearly $210 billion per year. In addition, obesity is associated with job absenteeism, costing approximately $4.3 billion annually and with lower productivity while at work, costing employers $506 per obese worker per year.


OBESITY AND WEIGHT LOSS ≠ NOT THIS SIMPLE...

Energy IN > Energy OUT ≠ Obesity
Obesity is Multifactorial

Energy Dense Foods

Genetics

Larger portions

Physical Activity

Microbiome Changes

Artificial sweeteners
High omega 6:3 FA
Immunizations
Abx

De Filippo, C., et al., Proc Natl Acad Sci USA, 2010
Sugar
The Sugar Addiction: The Gut-Brain axis

Pour some sugar on me, in the name of love
Pour some sugar on me, c'mon fire me up
Pour your sugar on me, I can't get enough
I'm hot, sticky sweet, from my head to my feet, yeah

Sugar ingestion → Dopamine, opioid receptor binding, Ach release in nucleus accumbens → Reward → Excessive sugar intake
Pseudo-Sugar: What defines an artificial sweetener/non-nutritive sweetener?

- Low calorie
- Not metabolized by host
The Evolution of Sugar Substitutes

Sugar-laden diets are ubiquitous. Humans & animals display preferences for sweet taste, starting early in life. As awareness of the obesity epidemic increases, so has the popularity of sugar substitutes. Over 6000 products are available on the market in the US alone.
Saccharin
- Increased WWI sugar shortages
- Use increased 1960s low-calorie foods
- Developed to combat obesity epidemic & insulin resistance
Artificial sweetener use in agriculture

Artificial sweeteners have been used since the 1950's

- Promote feeding & weight gain in agricultural animals
- Cheaper alternative to sugar
Types of Sugar Substitutes

AKA Non-nutritive sweeteners (NNS)

Artificial Sweeteners
- Aspartame,
- saccharin,
- sucralose

Natural Alternative Sweeteners
- Stevia,
- rare sugars,
- sugar alcohols,
- monk fruit
## Common FDA Approved Sugar Substitutes

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Trade Names</th>
<th>FDA Approved</th>
<th># X sweetness of sucrose</th>
<th>Common Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin</td>
<td>Sweet ‘N Low, Sugar Twin Necta Sweet</td>
<td>1879</td>
<td>200-700</td>
<td>Soft drinks, candy, medicine, toothpaste, lip gloss, baked goods, dressing</td>
</tr>
<tr>
<td>Aspartame</td>
<td>NutraSweet, Equal</td>
<td>1981</td>
<td>200</td>
<td>Gum, diet soda, instant tea/coffee, yogurt, pudding</td>
</tr>
<tr>
<td>Acesulfame-K</td>
<td>Sweet One, Sweet and Safe, Sunette, Swiss Sweet</td>
<td>1967</td>
<td>200</td>
<td>Soft drinks, baked goods, gum, gelatin</td>
</tr>
<tr>
<td>Sucralose</td>
<td>Splenda</td>
<td>1998</td>
<td>600</td>
<td>Baked goods</td>
</tr>
<tr>
<td>Stevia/Erythritol</td>
<td>Truvia, PureVia</td>
<td>1955</td>
<td>300</td>
<td>Baked goods, soft drinks</td>
</tr>
<tr>
<td>Sugar alcohols</td>
<td>Sorbitol, Mannitol, Xylitol</td>
<td>Naturally occurring</td>
<td>0.5-1</td>
<td>Candy, gum, naturally in fruits/vegetables</td>
</tr>
</tbody>
</table>
Artificial sweeteners: the details

**Saccharin**
- Drinks, candy, medicine, toothpaste
- Not in baking products (unstable w/ heat)

**Aspartame**
- Dipeptide (aspartic acid + PHA)
- Gum, drinks, desserts, candy
- Not used for baking (loses sweetness)

**Sucralose**
- Stable hot & cold temp
- Baking

**Acesulfame potassium**
- Bitter taste in large amounts
Natural Alternative Sweeteners
Studies in healthy & DM pts

**Stevia (stevioside and rebaudioside A metabolites)**
- Native plant South America
- Studies show reduction in blood glucose, less calorie consumption

**Rare sugars (i.e. D-sorbose, Allulose, Tagatose)**
- Monosaccharaides found in nature
- Studies show reduction in BW vs HFCS

**Sugar alcohols (polyols i.e. sorbitol)**
- Hydrogenated mono and disaccharides, some alter gastric emptying
- Less post-prandial glucose response vs sucrose/glucose, no change in satiety

**Monk fruit (luo han guo)**
- Native fruit in China, plant
- Improvement in glucose tolerance testing
Major limitations: human studies

- Majority of large studies are based on dietary recall
  - Poor awareness of foods/beverages that contain artificial sweeteners
    - Toothpaste, mouthwash, frozen dinners, sauces
- Small human sample sizes
- Short study durations (<3 months)
CONSUMPTION OF ARTIFICIAL SWEETENERS

NHANES database
1999-2007 increased from 6.1 → 12.5% children
18.7% → 24.1% adults

Nurses Health Study (NHS)
Prevalence 56%

Health Professionals Follow-up study (HDFS)
Prevalence 54%

San Antonio Heart Study
Prevalence 48%
Consumer Use of Low-Calorie, Sugar-Free Foods & Beverages
(in millions of adult Americans consuming these products)

- 78 in 1986
- 101 in 1991
- 151 in 1996
- 180 in 2004
- 187 in 2010

Source: Calorie Control Council National Consumer Survey, 2010
Dietary Trends
Why are we discussing artificial sweeteners in an obesity talk, aren’t they supposed to help people lose weight?
What a Conundrum

Despite increased use of artificial sweeteners:

Prevalence of obesity has stayed stable over the past decade

Suggests NOT good weight loss tool
Artificial sweeteners vs sugar = similar risk

HTN
CAD
Insulin Resistance
Obesity

O'Connor L et al., Diabetologia. 2015
Gardener H et al., J Gen Intern Med. 2012
Sakurai M et al., Eur J Nutr. 2014
Fowler SP et al., Obesity. 2008
Energy balance
Energy Balance

Energy demand and drive to eat

Tonic inhibition of energy intake

Leptin and other adipokines

Resting metabolic rate

Fat-free mass

Fat mass

Tonic appetite signals

Energy intake

Energy balance

Energy expenditure

Gastrointestinal tract

Appetite stimulating hormones

Appetite inhibiting hormones

CCK, PYY, GLP-1

Ghrelin

Exercise

Acute and long-term effects

obesity reviews (2015) 16 (Suppl. 1), 6
Key peripheral hormones → hypothalamus

- **Ghrelin**

- **Cholecystokinin (CCK)**
  - Polypeptide Y (PYY)
  - Glucagon-like-peptide 1 (GLP-1)
What happens after sugar ingestion: In a cellular uptake of glucose for energy:

- Sugar ingestion
- Increase blood glucose
- Upregulation GLP-1, GIP, PYY
- Pancreatic beta cell stimulation
- Insulin secretion
- Cellular uptake of glucose for energy
The Effects of Artificial Sweeteners on the Hormonal Response and Glucose Homeostasis:

GLP-1

- Incretin hormone & neuropeptide (gut hormone)
- Primary source is intestinal L cell in ileum
- GLP-1 secretion dependent on presence of nutrients in small intestine
- (+) pancreatic beta cells \(\rightarrow\) release insulin in response to rising blood sugar
- (-) glucagon secretion

Glucose ingestion (+) GLP-1 and GIP at greater levels vs sucralose \(\rightarrow\) more delayed gastric emptying & increased satiety

Skibicka KP., Front Neurosci. 2013
Food reward: INVOLVES TWO PATHWAYS

**Sensory Pathway**
- Sweet taste receptors in oropharynx (G protein receptors)
- Send signals to hypothalamus & amygdala (reward centers)

**Post- Ingestion Pathway**
- Depends on energy content of food/beverage

References:
- Yang Q., Yale J Biol Med. 2010
- Stice E et al., J Abnorm Psychol. 2008
- Avena NM et al., Neurosci Biobehav Rev. 2008
- Smeets PA et al., Am J Clin Nutr. 2005
Normal physiology after sugar consumption

Anticipatory/Cephalic Phase

- Flavor and taste cues
- Food ingestion (+) sweet taste receptors oral cavity prior to nutrient absorption in anticipation of sugar
- (+) physiologic responses & hormone release
  - Insulin secretion
  - Heat production
  - Satiety hormones i.e. GLP-1

Teff KL., Physiol Behav. 2011
Swithers SE., Behav Anal. 2015
Altered physiology after ingestion

- Artificial sweetener ingestion

- Dampened hormonal response (no sugar load)
  - No insulin release
  - No heat production
  - No satiety hormone release (GLP-1) → less satiety (more hunger)

- Future sugar exposure
  - Abnormal response persists → insulin resistance, increased caloric intake
In a

- The body develops a dampened hormonal response because the intake of sweets is no longer predictably followed by a sugar load.
- Artificial sweeteners interfere with basic learned, predictive relations between sweet tastes (sensory) & post-ingestion pathways.
  - (-) anticipatory responses that normally serve to maintain physiological homeostasis.
The Effects of Artificial Sweeteners on Energy Consumption

Improved palatability promotes feeding (rodent & human models)
Overcompensation Phenomenon

- 8 obese patients

When patients were aware they were consuming aspartame containing products, caloric intake was maintained or slightly increased vs caloric intake from conventional diet w/o AS

When diet covertly changed to aspartame containing products, patients had 25% reduction in caloric intake vs conventional diet

Suggests part of increased caloric consumption attributed to AS is conscious decision to overcompensate

Effects of Artificial Sweeteners on subjective appetite & food appeal

Consuming aspartame with and without taste: Differential effects on appetite and food intake of young adult males

Richard M. Black, Lawrence A. Leiter, G. Harvey Anderson

18 normal weight males: Each wk received beverage @ 11 am

- 280 ml carbonated mineral water (CMW) (control)
- 560 ml CMW
- 280 ml CMW w/ APM powder
- 280 ml CMW w/ encapsulated APM
- 560 ml APM soft drink
Subjective hunger & food appeal measured 9:30 am

Test beverage 11 am

Buffet lunch 12:05 pm

Subjective hunger & food appeal measured 12:30 pm
Conclusions

560 ml CMW & 560 ml APM soft drink
- Suppressed appetite
- Volume not APM content

280 ml CMW w/ APM powder
- Increased subjective appetite vs 280 CMW control (improved palatability)

280 ml CMW w/ encapsulated APM
- No effect on appetite
- Importance of activating taste oral taste receptors (Sensory pathway in reward)
The Effects of Artificial Sweeteners on the Neuronal, Hormonal Response & Glucose Homeostasis
Goal: Compare effects of artificial sweeteners to sucrose:

- Energy intake
- Blood glucose
- Insulin response
Study design

30 healthy males, Randomized crossover study
ALL Standardized breakfast

Aspartame (mid morning)
Ad libitum lunch 1 hr post
BS & insulin q15 min x 1 hr, q30 min x 2 hrs, food diary

Monk Fruit (mid morning)
Ad libitum lunch 1 hr post
BS & insulin q15 min x 1 hr, q30 min x 2 hrs, food diary

Stevia (mid morning)
Ad libitum lunch 1 hr post
BS & insulin q15 min x 1 hr, q30 min x 2 hrs, food diary

Sucrose 65 g (mid morning)
Ad libitum lunch 1 hr post
BS & insulin q15 min x 1 hr, q30 min x 2 hrs, food diary
Artificial sweetener groups: greater ad libitum lunch intake compared to sucrose group.

Energy saved from replacing sucrose with artificial sweetener was fully compensated for at subsequent meals.

No difference in daily energy intake between test groups.

Sucrose group had larger spikes in BS and insulin w/in 1st hr of test beverage.

Artificial sweetener groups had higher BS and insulin 2 hrs post lunch.
The Effects of Artificial Sweeteners: Microbiome
Intestinal Microbiome

- Heterogenous population of bacteria
- Immense spatial distribution throughout GI tract
  - Surface area ~ 300 to 400 m²
- Influenced by host internal and external environment
  - Dietary intake and physical activity
  - Host disease state

Xu J et al., Science. 2003
Turnbaugh PJ et al., Nature. 2006
Schloss PD et al., PLoS One. 2011
Backhed F et al., Proc Natl Acad Sci USA. 2004
Microbiome: The basics

- **Bacteroidetes**
- **Firmicutes**

- Majority are strict anaerobes
- Facultative anaerobes
- Aerobes

Backhed F et al., Science. 2005
Ley RE et al., Proc Natl Acad Sci USA. 2005
Qin J et al., Nature. 2010
Artificial sweeteners: effects on the microbiome

Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat.

Palmnäs MS¹, Cowan TE², Bomhof MR², Su J³, Reimer RA⁴, Vogel HJ¹, Hittel DS⁴, Shearer J⁴.

Goal of study:

- Evaluate effects of low dose aspartame x8 wks on fat composition in obese rats
  - Anthropometrics
  - Metabolic parameters
  - Changes in microbiome
Study Design

Male Sprague-Dawley Rates

- Standard Chow (12% kcal fat)
  - Ad libitum water control
  - Low dose aspartame

- High Fat Chow (60% kcal fat)
  - Ad libitum water control
  - Low dose aspartame
Conclusions

HFD + ASP vs HFD + water: fewer calories, less weight gain

ASP groups in both standard chow & HFD: higher blood sugar, worse insulin tolerance test independent of body fat composition

Fecal analysis: ASP groups had increased total bacteria, greater abundance of Enterobacteriaceae & Clostridium leptum

HFD + ASP: increased Firmicutes: Bacteroidetes ratio which is typically seen in an obese host
Summary

- Artificial sweeteners are marketed as a healthy alternative to sugar & for weight loss
- Data suggests the intended effects do not correlate with evidence
- More promising data on natural alternative sweeteners
- Future research
  - Longer study durations to determine the long-term effects
  - Larger patient populations
    - Healthy individuals & DM
That’s a WRAP
Michelle Pearlman, MD
University of Miami
Division of Gastroenterology
Physician Nutrition Specialist, Obesity medicine
M.pearlman@med.miami.edu