Sweet Fructose with Sticky Consequences: A Look at IBS
1. The digestion of fructose compared to glucose and galactose
2. The role of fructose in IBS/Journal article
3. Solutions/MNT for IBS and fructose malabsorption
4. What HFCS has to do with IBS and the general population
Digestion of Fructose Compared to Glucose and Galactose
Glucose, Fructose, Sucrose Structure

**Glucose**

**Fructose**

**Sucrose**
Glucose Metabolism

Fructose Metabolism in Non-Liver Cells

Fructose Metabolism in Liver Cells

Fructose Transport

\[ \text{Na}^+ - \text{Glucose symport} \]

Glucose  \[\rightarrow\]  Fructose  \[\rightarrow\]  Fructose

Galactose  \[\rightarrow\]  Glucose  \[\rightarrow\]  Galactose

GLUT5  \[\rightarrow\]  GLUT5

GLUT2  \[\rightarrow\]  Glucose  \[\rightarrow\]  Fructose
Intestinal Mucosa

Blood
<table>
<thead>
<tr>
<th>Transporter Protein</th>
<th>Insulin Regulatable</th>
<th>Major Sites of Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>NO</td>
<td>Erythrocytes, blood brain barrier, placenta, fetal tissues in general</td>
</tr>
<tr>
<td>GLUT2</td>
<td>NO</td>
<td>Liver, β-cells of pancreas, kidney, small intestine</td>
</tr>
<tr>
<td>GLUT3</td>
<td>NO</td>
<td>Brain, neurons</td>
</tr>
<tr>
<td>GLUT4</td>
<td>YES</td>
<td>Muscles, heart, brown and white adipocytes</td>
</tr>
<tr>
<td>GLUT5</td>
<td>NO</td>
<td>Intestine, testis, kidney</td>
</tr>
<tr>
<td>GLUT6</td>
<td>NO</td>
<td>Spleen, leukocytes, brain</td>
</tr>
<tr>
<td>GLUT7</td>
<td>NO</td>
<td>Unknown</td>
</tr>
<tr>
<td>GLUT8</td>
<td>NO</td>
<td>Testis, blastocyst, brain</td>
</tr>
<tr>
<td>GLUT9</td>
<td>NO</td>
<td>Liver, kidney</td>
</tr>
<tr>
<td>GLUT10</td>
<td>NO</td>
<td>Liver, pancreas</td>
</tr>
<tr>
<td>GLUT11</td>
<td>NO</td>
<td>Heart, muscle</td>
</tr>
<tr>
<td>GLUT12</td>
<td>NO</td>
<td>Heart, prostate</td>
</tr>
</tbody>
</table>

**Glucose**
- Active transport
- Dependent on Na/K-ATPase pump
- SGLT1 carrier
- Transported from cell into circulation by GLUT2
- 4 kcal/g

**Galactose**
- Active transport
- Dependent on Na/K-ATPase pump
- SGLT1 carrier
- Transported from cell to liver by GLUT2
- Absorbed by liver so there is no circulating blood galactose
- Not subject to hormonal regulation
- 4 kcal/g

**Fructose**
- Facilitated transport
- GLUT5
- Slower rate of absorption, but empties stomach quicker
- Can use GLUT2, but dependent on glucose concentration
- Absorbed by liver so there is no circulating blood fructose
- Not subject to hormonal regulation
- 4 kcal/g
Role of Fructose in IBS/Journal Article
Fructose Malabsorption—Fructosemia (hereditary fructose intolerance)

- 1-phosphofructaldolase
- Autosomal recessive disease
- Hypoglycemia; progressive liver disease
- Exclude:
  - Fructose
  - Sucrose
  - Sorbitol
  - Invert sugar
  - Maple syrup; honey; molasses
  - Foods high in fructans

Fructose Malabsorption Non-hereditary

- Fructose fermented by bacteria in intestine to give off hydrogen or methane

- FODMAPs
  - Fermentable oligo-, di-, and monosaccharides and polyols (short-chain carbohydrates)

- FODMAPs known to cause abdominal pain, bloating, distension, altered bowels, nausea, vomiting
How do they diagnose fructose malabsorption?

- Not a consensus
- ≥20 ppm
- Positive symptoms
- Peak at 1.5-3 hrs
- 25 g or higher

Saad RJ, Chey WD. Breath Tests for Gastrointestinal Disease: The Real Deal or Just a lot of Hot Air? *Gastroenterology(Imaging and Advanced Technology)*. 2007; 133:1763-1766.
What is IBS?

- Abdominal pain/discomfort with altered bowel habits
- 3 types
  - Diarrhea prominent
  - Constipation prominent
  - Alternating
- No known medical cause
- ≥ 3 months of continuous or recurrent symptoms with altered stools
- R/O other conditions, like Crohn’s or celiac
- 10-15% of the U.S. population
- One of the most common ‘functional’ GI disorders, representing 3% of all primary care consultations

Comparison of breath testing with fructose and high fructose corn syrup in health and IBS
Grade I

“Our hypothesis was that fructose intolerance (i.e. positive hydrogen breath test and gastrointestinal symptoms) would occur more frequently with pure fructose compared to fructose provide as HFCS in healthy subjects and in IBS.”

Skoog SM, Bharucha AE, Zinsmeister AR. Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterol Motil.* 2008;20:505-511.
Hydrogen Breath Test

- Alternative to the invasive, expensive endoscopy
- Works by measuring the hydrogen expelled due to the gut bacteria fermenting the carbohydrate substrate

Bacterial fermentation of malabsorbed sugar produces hydrogen (H₂) & methane (CH₄) gas.

These gases are absorbed into the bloodstream and carried to the lungs.

Concentrations of exhaled breath H₂ & CH₄ are measured in the test.

Concentrations of breath hydrogen and methane are used to indicate if the test sugar is malabsorbed or if proximal bacterial overgrowth is present.
Limitations

- False-positives
  - Smoking
  - Poor oral hygiene
  - If test subjects do not brush teeth and rinse with antibacterial mouthwash
  - Eating fermentable carbohydrates like pasta/bread
  - Physical exertion/hyperventilation

- Some produce methane

- The test lasts 3-5 hrs

- Lack of uniformity in interpreting results

Saad RJ, Chey WD. Breath Tests for Gastrointestinal Disease: The Real Deal or Just a lot of Hot Air? *Gastroenterology (Imaging and Advanced Technology)*. 2007; 133:1763-1766.
Methods

- Double-blind, randomized, crossover study
- 20 healthy subjects; 30 patients
- HBT

- Given 1 of 2 sugar solutions
  - 40 g fructose in 330 mL tap water (12%)
  - 40 g fructose as 95 g HFCS-55 in tap water for total 600 mL (12%)

- HFCS solution mimicked two cans of cola

- Breath samples every 30 minutes for 3 hrs using modified Haldane-Priestly bag

- Fructose malabsorption was defined as a rise in breath hydrogen of ≥20 ppm over the baseline value
Patient breakdown

- Diarrhea predominant IBS—12
- Constipation predominant IBS—4
- Alternating IBS—10
- Functional diarrhea—4
Symptoms

- Visual Analog Scales (VAS)
- Every 30 min for 3 hrs
- 10 mm increase in symptom scores was considered abnormal
- Bristol scale
- Done for both sugar solutions
## VAS and Bristol Stool Chart

### Visual Analog Scale (VAS)

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td></td>
</tr>
<tr>
<td>Pain as bad as it could possibly be</td>
<td></td>
</tr>
</tbody>
</table>

1. If used as a graphic rating scale, a 10 cm baseline is recommended.
2. A 10 cm baseline is recommended for VAS scales.

### Bristol Stool Chart

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces. Entirely Liquid</td>
</tr>
</tbody>
</table>
Statistical Analysis

- McNemar’s test for paired discrete data
- Paired t-tests used to compare AUC for hydrogen breath excretion after fructose and HFCS
- Relationship between symptoms and breath hydrogen tests were analyzed using Spearman’s correlation coefficient
- Breslow-Day test used to compare the association between health and IBS
- All stats analysis carried out using SAS software
Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=20)</th>
<th>Patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs) (mean ± SE)</strong></td>
<td>28 ± 3</td>
<td>41 ± 2</td>
</tr>
<tr>
<td><strong>Number of females</strong></td>
<td>14 (60)</td>
<td>21 (60)</td>
</tr>
<tr>
<td><strong>BMI (mean ± SE)</strong></td>
<td>24 ± 1</td>
<td>26 ± 1</td>
</tr>
<tr>
<td><strong>Breath hydrogen test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal—fructose</td>
<td>13 (65)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Abnormal—HFCS</td>
<td>4 (20)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Abnormal—fructose and HFCS</td>
<td>4 (20)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Normal—fructose and HFCS</td>
<td>7 (35)</td>
<td>9 (30)</td>
</tr>
<tr>
<td><strong>Symptoms after fructose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (20)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Bloating</td>
<td>5 (25)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (10)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (10)</td>
<td>9 (30)</td>
</tr>
<tr>
<td><strong>Symptoms after HFCS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (10)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Bloating</td>
<td>1 (5)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

All values except age and BMI are N (%) of group total. HFCS, high fructose corn syrup; BMI, body mass index.
Comparison of symptoms and breath hydrogen response in controls and IBS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=20)</th>
<th>Patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal fructose breath test</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Number with symptoms</td>
<td>2/7</td>
<td>3/9</td>
</tr>
<tr>
<td>Abnormal fructose breath test</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Number with symptoms</td>
<td>5/13</td>
<td>12/21</td>
</tr>
<tr>
<td>Normal HFCS breath test</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Number with symptoms</td>
<td>2/16</td>
<td>12/21</td>
</tr>
<tr>
<td>Abnormal HFCS breath test</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Number with symptoms</td>
<td>0/4</td>
<td>2/9</td>
</tr>
</tbody>
</table>
Discussion of fructose and HFCS

- 65% healthy subjects and 70% patients incompletely absorbed pure fructose
- 20% healthy subjects and 30% patients incompletely absorbed HFCS
- Other studies found similar results
- Fructose intolerance may be present in a minority
HBTs may overestimate prevalence of fructose malabsorption at 25 g d/t being unrealistic

Suggest using smaller fructose dose
Discussion of Conclusions

- Glucose increases fructose absorption
- Fructose intolerance is more prevalent after fructose alone than after HFCS in health and IBS
- Prevalence of fructose intolerance is not significantly different between health and IBS
Theoretical Relationship

Competition for luminal fructose

Small intestinal bacterial overgrowth

Fructose malabsorption

“Fast food” promotion of biofilm

Solutions/MNT for IBS/fructose malabsorption
Medical Approaches

- Anemia, fever, persistent diarrhea, rectal bleeding, weight loss, infections, and nocturnal symptoms
- Medications only if nonprescription methods do not work
- Antibiotics
- Psychotherapy/antidepressants
- Be aware of pain, constipation, and diarrheal medications

Most IBS patients attribute their symptoms to a food sensitivity

Identify the culprit

ADA (AND) suggests 3 dietitian visits

Increase physical activity, fluid, and fiber

Food diary

Avoid high-fat and high sugar

Avoid spicy or gas-forming oligosaccharides, like Brussels sprouts, cabbage, beans

Ensure adequate quantity of food intake
FODMAP elimination diet

- Lactose
- Fructose
- Fructans (also called inulin, fructo-oligo-saccharide, or oligofructose)
- Sugar alcohols
- Galactans

FODMAPs elimination diet—what can you eat??

- Lactose-free dairy
- Small servings of berries and citrus fruits
- Potatoes, rice, oats, corn products
- Lean meats
- Salad vegetables
- Plant based oils
- Very small servings of sugar, honey, or syrup


How does it work?

- 1-2 wks eliminate all FODMAPs, including alcohol
- Reintroduce 1 FODMAP group at a time
- Goal: Find the elimination diet that works for that pt
- Perhaps they will be able to tolerate small amounts of foods they need to eliminate
- Dry wines tolerated best, beer has no fructose, hard liquors need to read label

What HFCS has to do with IBS and the general population
High Fructose Corn Syrup

- Refined sweetener
- Introduced in the 1970s
- Treat cornstarch with acid and enzymes to break down the starch into glucose; different enzymes convert about half the glucose to fructose
- HFCS-55 (soft drinks) and HFCS-42 (beverages, processed foods, cereals, etc.)
- Corn sugar

http://www.youtube.com/watch?v=jisBG3egS8o

Comparison of Sugar and Sweetener Intake in America

• Highest intake in adolescence

• Sweetened soft drinks make up 1/3 of added sugar intake

• 14-18 yrs
  ○ Carbonated soft drink intake exceeded milk and fruit drinks (2004)

Purpose: To distinguish at what dose malabsorption happens in healthy subjects to determine an appropriate amount to diagnose fructose malabsorption.

Tested both amount (15, 25, 50g) and concentration (10, 30%) in 20 healthy subjects

What happened?

- **15 g fructose dose**
  - 20 out of 20 tolerated
  - No symptoms reported

- **25 g fructose dose**
  - 18 out of 20 tolerated
  - No symptoms reported

- **50 g fructose dose at 10% concentration**
  - 4 out of 20 absorbed
  - 69% with a positive breath test reported symptoms
  - 25% with a negative breath test reported symptoms

- **50 g fructose dose at 33% concentration**
  - 8 out of 20 absorbed
  - 75% with a positive breath test reported symptoms
  - 25% with a negative breath test reported symptoms
What is this study saying about fructose malabsorption?

- BOTH a positive hydrogen breath test and symptoms
- Suggest 25 g dose to determine if malabsorption is present
- Food diary and dietary consult highly recommended
- Amount of fructose matters more than the concentration
What is the ADA saying about fructose/IBS/HFCS?

- When following nutrition recommendations, nutritive sweeteners can be consumed in moderation
- RD’s role is to provide scientific evidence
- Obesity is caused by an entire host of factors
- Sucrose/fructose have GRAS status
- Malabsorption can be detected in 37% to 80% of healthy people at 50 g and in >70% of children to a 2 g/kg bw/d load
- Fructose is better absorbed as sucrose and worse when amount of fructose exceeds amount of glucose

What is the ADA saying about fructose/IBS/HFCS?

- Increase in consumption of HFCS “could have implications for absorption and lipid profiles in susceptible individuals.”

- HFCS consumption may cause a hypertriglyceride effect

- There may be an association between sweeteners and obesity, but no “direct link”

- The concern that fructose/HFCS decreases insulin and leptin response needs further research

- Fructose is not recommended for diabetic patients d/t lipid effects

- RD needs to monitor intakes of fructose in relationship to GI dysfunction and hyperlipidemia
Questions

1. Has anyone ever tried the FODMAP diet on a patient?
2. Have RDs considered fructose as a condition that needs to be treated?
3. Will this information change the way you conduct your clinical work and educations?
4. Do you think that fructose malabsorption is often mistaken for something else, like lactose malabsorption or a gluten intolerance?


References