Bile Acid Malabsorption: When Detergents Are Too Much

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Bile Acid Diarrhea
BAD, BAD, BAD
Too Much Detergent or Too Many Bile Acids?

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The Intricacies of BAD

- Enterohepatic Circulation
- Classification of Bile Acid Diarrhea
- Mechanisms of Bile Acid Diarrhea
- Diagnosis
- Treatment
- Unresolved Issues

ENTEROHEPATIC CIRCULATION OF BILE SALTS

Hepatic synthesis from cholesterol by CYP7A1
Conjugated with glycine or taurine
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Secreted via biliary tree into intestine

Solubilise lipids in micelles for absorption
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Reabsorbed in distal intestine:
Active absorption in ileum (conjugated)

Reuptake by hepatocytes and resecreted
ENTEROHEPATIC CIRCULATION OF BILE SALTS

- Hepatic synthesis from cholesterol by CYP7A1
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- Reabsorbed in distal intestine:
  - Active absorption in ileum
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Bile salts entering the colon cause diarrhea

Colonic Secretion

- Stimulation of colonic enterocytes leads to Cl⁻ secretion
- H₂O losses
- Loss of ileum
- Unabsorbed bile acids

Effect of bile acids on colon
Bile Acids and the Colon

• Chloride Secretion
  – Initially a detergent effect (2-5 mM doses)
  – Low dose, Ca-mediated secretion (1-2 µM doses)
• Increased Motility, Decreased Transit Time
• Epithelial Proliferation

Bile Acids and the Microbiome

• Fecal BAs very different from biliary BAs
• Bacterial deconjugation of taurine/glycine conjugated bile acids
• 7αβ dehydroxylation via bacterial hydrolases
• Primary Bile Acids made in the liver
  – Chenodeoxycholic Acid
  – Cholic Acid
• Secondary Bile Acids from bacterial metabolism
  – Lithocholic Acid
  – Deoxycholic Acid
Diet, Bile Acids, Bugs & Colitis

- Dietary fat promotes changes in host bile acid composition: increased taurine conjugated BA
- Increased availability organic sulfur
- Expansion of a low abundance sulfite reducing *B. wadsworthia*
- Pro-inflammatory TH1 immune response
- Development of colitis in IL 10 -/- mice

BAD: Proof of Principle

- IBAT/ASBT: Apical bile salt transporter
- A3309, IBAT inhibitor
  - Rx for constipation
  - Colonic transit accelerated
  - Looser stool
A Classification of Types of Bile Acid Malabsorption


■ Type 1: Secondary
  Ileal resection, ileal disease (Crohn’s), bypass

■ Type 2: Primary
  “Idiopathic BA malabsorption (IBAM)”
  Primary BA Diarrhea (PBAD)

■ Type 3: Miscellaneous associated disorders
  Post-cholecystectomy, gastric surgery, chronic pancreatitis,
  celiac disease, SIBO, radiation enteropathy, microscopic colitis,
  etc.

Bile Acids and Diarrhea

• Ileal disease/surgery   Makes sense
• Post-GBX               Mechanism???
• IBAM                   Mechanism???
Mechanisms of BAD

- Disruption of enterohepatic circulation
  - Congenital deficiency of ileal transporter
  - Ileal resection
  - Ileal disease -> Crohn’s

Post Cholecystectomy Diarrhea

Common -- >10% of patients
- Why?
  - Bile acid malabsorption??
  - Greater resident time in the gut yields greater bacterial dehydroxylation, increasing the “diarrheogenic” bile salts??
  - Decreased colonic transit time
Post-Cholecystectomy Diarrhea

• Bile Acid Malabsorption

• Cholestyramine Works
Increased Fecal Primary Bile Acids in IBS-D

Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome.

- Total fecal bile acids associated with phenotype (p=0.03); ↑ in IBS-D
- Fecal levels of unconjugated primary UBAs (cholic and chenodeoxycholic acids) ↑ in IBS-D (p<0.01)

Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome.

- In feces in IBS-D patients:
  - ↑ % of primary bile acid (CA & CDCA)
  - ↓ % of secondary bile acids (DCA)
  - ↑ in E. coli, ↓ in leptum and bifidobacteria

Mechanisms of BAD

- Overflow phenomena?
  - Expanded bile acid pool
  - Limited ileal absorptive capacity overwhelmed
  - Not “true” malabsorption
  - Net result similar: colonic bile acids stimulate chloride secretion
  - Limited evidence
Diagnosing Bile Acid Malabsorption / Diarrhea

- Fecal bile acids
- $^{14}$C-glycocholate breath tests
- $^{75}$SeHCAT retention
- $7\alpha$-hydroxy-4-cholesten-3-one ($C4$, $7\alpha$-$C4$)
- Therapeutic trials


Diagnosis of Bile Acid Malabsorption

- **SeHCAT**
  - Synthetic $^{75}$Se radiolabelled bile acid analogue
  - Detected by gamma-camera
  - Limited radiation exposure
  - Kinetics similar to taurocholate
  - Measure of BA retention
  - 7 day retention:
    - normal > 15%
    - < 10% diagnostic

Available in many European countries
Not available in USA
Abnormal SeHCAT Values in D-IBS


<table>
<thead>
<tr>
<th>Reported SeHCAT value</th>
<th>&lt; 5%</th>
<th>&lt; 10%</th>
<th>&lt; 15%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies reporting</td>
<td>5</td>
<td>17</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>429</td>
<td>1,073</td>
<td>618</td>
<td>1,223</td>
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<tr>
<td>Number abnormal</td>
<td>43</td>
<td>339</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>% abnormal</td>
<td>10%</td>
<td>32%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>[95% confidence intervals]</td>
<td>[7 – 13]</td>
<td>[29 – 35]</td>
<td>[23 – 30]</td>
<td></td>
</tr>
<tr>
<td>% response to cholestyramine</td>
<td>96%</td>
<td>80%</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

Bile Acid Malabsorption: Frequency of Abnormal SeHCAT

Bile acid malabsorption in persistent diarrhoea


<table>
<thead>
<tr>
<th>SeHCAT retention &lt;10%</th>
<th>Response in these to BA sequestrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s with resection</td>
<td>36 / 37 (97%)</td>
</tr>
<tr>
<td>Crohn’s without resection</td>
<td>24 / 44 (54%)</td>
</tr>
<tr>
<td>Vagotomy / pyloroplasty (+/- cholecystectomy)</td>
<td>15 / 26 (58%)</td>
</tr>
<tr>
<td>Diarrhoea-predominant IBS</td>
<td>65 / 197 (33%)</td>
</tr>
</tbody>
</table>
SeHCAT in Diagnosis of Bile Acid Malabsorption & Prediction of Response to Cholestyramine


Low SeHCAT in proportion of patients with functional diarrhea

Low SeHCAT predicts response to cholestyramine

SeHCAT retention inversely related to faecal bile acids

Idiopathic Bile Acid Malabsorption

• SeHCAT: Only in Europe
  – Consistent increases in bile salt excretion
  – Responds to cholestyramine

• But
  – No change in ileal bile salt transporters
  – Enlarged bile acid pool
  – Increased bile acid synthesis
**IBAM: An explanation?**

- “Classic” IBAM patients
  - Decreased SeHCAT retention
  - Response to cholestyramine
- Decreased FGF19, increased C4 suggests increased bile acid pool
- Overflow rather than malabsorption
- What controls FGF19 ???

**Enterohepatic Circulation**

- Intestinal BA’s inhibit hepatic synthesis
- FGF 19
  - Made in intestine
  - Represses Hepatic BA synthesis
- C4: Circulating bile acid intermediate
  - Indicator of overall BA synthesis


**FGF19 & Primary Bile Acid Diarrhea**

![Diagram showing the relationship between FGF19 and bile acid diarrhea]

- Normal
- Bile acid diarrhea:
  - ↓ FGF19
  - ↑ BA synthesis
  - ↑ BA entering colon
  - ↑ Secretory diarrhea
Raised 7aOH-4-Cholesten-3-one (C4) in Patients with Chronic Bile Acid Diarrhea

Fasting blood samples from 17 patients and 19 healthy controls
SeHCAT in 13 patients (all < 8%)
Medians & quartiles
p < 0.001

Reduced FGF19 in Patients with Chronic Bile Acid Diarrhea

Significantly lower FGF19 in patients
p < 0.005
FGF19 in Prospective Groups with Chronic Diarrhea

Significantly lower median fasting FGF19 in patients with primary or secondary BAD compared with chronic diarrhea controls with normal SeHCAT values

\[ p < 0.001 \]

Treatment of Bile Acid Diarrhea

- **Bile acid sequestrants are effective treatments**
  - Bind Bile Salts in intestine
  - Cholestyramine (Questran®) & Colestipol (Colestid®) – powders
  - Colesevelam (Cholestegel®, Welchol®) – tablets

- **Therapeutic problems**
  - Poor long-term compliance
  - Bloating may worsen
  - Sequestrants can bind other drugs / vitamins
  - Optimal dosing regimes uncertain
  - Titration to individual needs

- Therapeutic trials not necessarily successful
- **Non-specific therapy may also work**
  - If the diagnosis is firmly established then the various therapeutic options can be refined to obtain the best clinical response.
FXR Agonists as Treatment for BAD?

- FXR agonists
- Stimulate FGF19
- Inhibit excessive hepatic Bile Acid synthesis
- Reduce colonic secretions / symptoms

BAD: Unresolved Issues

- How much of IBS is due to BAD?
- True Etiology or Epiphenomenon?
  - Primary motility disorder leads to secondary BAD?
  - Associations w/ infections, microscopic colitis, IBS
  - Sometimes transient (stopping rx)
  - BAD and SIBO
- Why does FGF decrease?
- Why do symptoms wax and wane?
**BAD Today/BAD Tomorrow**

- Bile Acid Diarrhea is a common condition which is poorly recognized
- Diagnostic tests are not widely available
- Treatment with bile acid sequestrants: therapeutic trial
- The role of FGF19 in pathogenesis may help define the primary disorder
- Potential for therapy with FXR agonists?

**Altered Bacterial Metabolism?**

- Abnormal sulfation abolishes secretory effect of BA’s in a subset of pediatric constipation.
- Increase in unconjugated primary BAs in d-IBS
- Lower unconjugated primary BAs in c-IBS
Additional Roles of FGF 19?

- Serum FGF19 levels increased following bariatric surgery
- Diabetic patients who went into remission had the greatest increases ($P<0.001$)
- Diabetic patients in remission also had the greatest increases in total bile acids
- Different relationship than BAD?
  - Cholic acid has been inversely related with insulin resistance
    - Argyropoulos G. 2013; ADA meeting

Diagnostic Dilemmas

- Fecal Bile Acid Assays are difficult, require timed stool collections
- Breath Test is not specific (double peak)
- C4 elevated with ETOH, chronic liver disease, elevated Triglycerides
- FGF 19 altered in cholestatic liver disease, obesity.
FGF19 is a Negative Regulator of Hepatic Bile Acid Synthesis

FGF19 in humans
FGF15 in mice

Could defective FGF19 signalling cause primary BA diarrhea?

Mechanism of Bile Acid Diarrhea

- Excess bile acids in colon
  - Unabsorbed by the small intestine
  - Increased bile acid synthesis

- Bacterial transformation of bile acids
  - Deconjugation
  - Dehydroxylation

- Stimulation of colonic secretion
  - Anion secretion
  - Watery stool
  - Motility changes

FGF19 in Different Types of Bile Acid Diarrhea

Figure 2
Chronic diarrhea due to excessive bile acid synthesis and not defective ileal transport: a new syndrome of defective FGF19 release.

Systemic Review of SeHCAT in Chronic Diarrhea


<table>
<thead>
<tr>
<th>Author (date)</th>
<th>Number of patients tested</th>
<th>Number of positive patients (SeHCAT retention &lt;10%)</th>
<th>% BAM-positive patients (confidence interval)</th>
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<tbody>
<tr>
<td>Merrick (1985)</td>
<td>43</td>
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<td>12 (5-28)</td>
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<tr>
<td>Sciarretta (1986)</td>
<td>13</td>
<td>6</td>
<td>46 (9-61)</td>
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<tr>
<td>Sciarretta (1987)</td>
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<td>32 (18-49)</td>
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<tr>
<td>Williams (1991)</td>
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<tr>
<td>Ford (1992)</td>
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<tr>
<td>Galizia (1993)</td>
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<td>57 (47-67)</td>
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<td>Dasu (1993)</td>
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<td>Sciarretta (1994)</td>
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<td>Brydon (1996)</td>
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<td>Rudberg (1996)</td>
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<td>Smith (2000)</td>
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<td>Ung (2000)</td>
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<td>Fernandez-Baneras (2001)</td>
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<tr>
<td>Maier (2004)</td>
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<td>15</td>
<td>41 (25-56)</td>
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<tr>
<td>Wild (2003)</td>
<td>133</td>
<td>21</td>
<td>16 (10-23)</td>
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<tr>
<td>Total</td>
<td>1073</td>
<td>339</td>
<td>32 (29-35)</td>
</tr>
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Table 4. Studies reporting patients with 7d SeHCAT retention <10%