Bile acid diarrhoea and FGF19: new views on diagnosis, pathogenesis and therapy

Julian RF Walters
Professor of Gastroenterology
Imperial College London, UK
Julian RF Walters: Disclosures

Speaking and Teaching: GE Healthcare; Pendopharm

Consulting: Novartis; Albireo; NGMBio; Sanofi; Intercept

Research support: BRET; Broad Foundation; Albireo; Intercept
What is Bile Acid Diarrhoea?

- Clinical features of BA diarrhoea & malabsorption
- Diagnosis
- Causes: Malabsorption / overproduction
- Regulation of Bile Acid synthesis by FGF19
- Approaches to treatment: current and future
Bile Acid Malabsorption: Case History 1 – Ms MH

- **Aged 37**
  - Abdominal pain, weight loss
  - Resection of parts of small & large intestine
  - Histology: Crohn’s Disease

- **Aged 49**
  - Perforation, Peritonitis
  - Further resection

- **Aged 54**
  - Persistent bowel problems with diarrhoea up to 10x / day
  - No rectal bleeding, abdominal pain, weight loss, fever, joint pains, recent travel, drugs etc.
Investigations:
- No evidence of inflammation (bloods, colonoscopy)
- No fistulae, strictures or inflammatory changes on further imaging
- SeHCAT 5%

Treatment:
- Cholestyramine 4g, 1 – 2 /day
- Rapid clinical response – bowels open 1-2x /day

Diagnosis: Bile Acid-induced Diarrhoea, due to Bile Acid Malabsorption, secondary to intestinal (ileal) resections
Bile Acid Diarrhoea: Case History 2 – Mr AM

- Lifelong problems with diarrhoea
  - BO x 6-10 / d, watery stool (type 7), urgency

- Age 32
  - “Chronic pancreatitis” diagnosed
  - Pancreatic enzyme replacement: doubtful effectiveness

- Age 49
  - Referred to Hammersmith Hospital for diarrhoea
  - SeHCAT 3%

- Started cholestyramine
  - Complete response
  - Enzymes stopped
  - Still dependent on cholestyramine after 13 years: diarrhoea returns in one day if he stops it

Diagnosis: Primary (Idiopathic) Bile Acid Diarrhoea (Malabsorption)
A Classification of Types of Bile Acid-induced Diarrhoea / Bile Acid Malabsorption


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

- **Type 2: Primary**
  - “Idiopathic BA malabsorption (IBAM)”
  - Primary BA Diarrhoea (PBAD)

- **Type 3: Miscellaneous associated disorders**
  - Post-cholecystectomy, gastric surgery, chronic pancreatitis, coeliac disease, SIBO, radiation enteropathy, microscopic colitis, etc.
Bile Acid Diarrhoea: First Descriptions


The syndrome of ileal disease and the broken enterohepatic circulation: cholerheic enteropathy.

Hofmann AF.


Diarrhoea associated with idiopathic bile acid malabsorption. Fact or fantasy?

Thaysen EH, Pedersen L.

Idiopathic bile acid catharsis

E. HESS THAYSEN1 AND L. PEDERSEN

From the Department of Medical Gastroenterology, Aalborg Sygehus, Aalborg, Denmark

SUMMARY: In the course of extensive routine screening for bile acid malabsorption a few patients were detected in whom chronic diarrhoea was apparently induced by excess bile acid loss which was neither associated with demonstrable conventional ileopathy nor with any other disorder allied to diarrhoea. In three patients subjected to scrutiny the results obtained were in harmony with a concept of idiopathic bile acid catharsis. Ingestion of cholestyramine was followed by immediate relief, but the diarrhoea recurred whenever this treatment was withdrawn. It is suggested that idiopathic bile acid catharsis should be suspected in patients with unexplained chronic diarrhoea and especially in those with a diagnosis of irritable colon with diarrhoea.
Hepatic synthesis from cholesterol by CYP7A1
Conjugated with glycine or taurine
ENTEROHEPATIC CIRCULATION OF BILE ACIDS

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Conjugated with glycine or taurine

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Reabsorbed in distal intestine:

Active absorption in ileum (conjugated)
ENTEROHEPATIC CIRCULATION OF BILE ACIDS

Hepatic synthesis from cholesterol by CYP7A1

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Secreted via biliary tree into intestine

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Reabsorbed in distal intestine:
  Active absorption in ileum

Reuptake by hepatocytes and resecreted
Hepatic synthesis from cholesterol by CYP7A1

Conjugated with glycine or taurine

Secreted via biliary tree into intestine

Solubilise lipids in micelles for absorption

Reabsorbed in distal intestine:
  - Active absorption in ileum
  - Reuptake by hepatocytes and resecreted

Bile salts entering the colon cause diarrhoea
Mechanism of Bile Acid Diarrhoea

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

- Bacterial transformation of bile acids
  - Deconjugation
  - Dehydroxylation

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

Reviewed in Walters, Nat Rev Gastroenterol Hepatol 2014; 11:426–434
Bile Acid Kinetics in a Typical Adult

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA secretion</td>
<td>12 g/d (30 mmol/d)</td>
</tr>
<tr>
<td>BA pool size</td>
<td>2 – 3 g (5 - 7.5 mmol)</td>
</tr>
<tr>
<td>Cycling frequency</td>
<td>4 – 6 x/d</td>
</tr>
<tr>
<td>Amount absorbed / cycle</td>
<td>~ 95%</td>
</tr>
<tr>
<td>Faecal BA loss</td>
<td>&lt; 0.5 g/d (~ 1 mmol/d)</td>
</tr>
<tr>
<td>Average half-life</td>
<td>~ 3 d</td>
</tr>
</tbody>
</table>

Data from multiple studies reviewed in
Walters & Pattni, Therapeutic Advances Gastroenterology 2010; 3: 349
Methods for Diagnosis of Bile Acid Malabsorption in Clinical Practice

PRIYA VijYAVARGIYA,* MICHAEL CAMILLERI,* ANDREA SHIN,* and AMY SAENGER†

*Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER); and †Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

Table 1. Advantages and Disadvantages of BAM Diagnostic Methods

<table>
<thead>
<tr>
<th>BAM diagnostic methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{14}$C glycocholate</td>
<td>May identify small bowel bacterial overgrowth</td>
<td>Radiation exposure, β emission, long half-life \nVarying normal values</td>
</tr>
<tr>
<td>$^{76}$SeHCAT</td>
<td>Gamma emission, short half-life, with decreased \nradiation to extra-abdominal organs \nWell-defined normal values; level of isotope \nretention predicts response to bile \nacid sequestrant \nSimple test method: 2 patient visits</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>Serum C4</td>
<td>No radiation \nNormal values reported in adults \rNot dependent on age, gender, or cholesterol \nSimple blood test: 1 patient visit</td>
<td>Fasting sample, diurnal variation \nRequires further validation \nFalse positive in liver disease, treatment with statins, \nand altered circadian rhythm</td>
</tr>
<tr>
<td>Fecal BA</td>
<td>No radiation \nMeasures total and individual BAs</td>
<td>Variable daily fecal BA excretion, requires at least \n48-h sample</td>
</tr>
</tbody>
</table>
Diagnosis of Bile Acid Malabsorption

- Fecal bile acids
  - 24hr stool collection (or longer)
  - Only available in a few centres
  - Unpopular with patients and lab staff
  - Not easy to perform

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

Walters JRF. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. Expert Rev Gastroenterol Hepatol 2010; 4: 561-567
SeHCAT in Diagnosis of Bile Acid Malabsorption & Prediction of Response to Cholestyramine

Sciarretta *et al*, *Gut* 1987; 28: 970

Low SeHCAT in proportion of patients with functional diarrhoea

Low SeHCAT predicts response to cholestyramine

SeHCAT retention inversely related to faecal bile acids
Bile Acid Malabsorption: Frequency of Abnormal SeHCAT

<table>
<thead>
<tr>
<th>Condition</th>
<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>
<td>60%</td>
</tr>
<tr>
<td>Crohn's without resection</td>
<td>24 / 44 (54%)</td>
<td>40%</td>
</tr>
<tr>
<td>Vagotomy / pyloroplasty (+/- cholecystectomy)</td>
<td>15 / 26 (58%)</td>
<td>64%</td>
</tr>
<tr>
<td>Diarrhoea-predominant IBS</td>
<td>65 / 197 (33%)</td>
<td>70%</td>
</tr>
</tbody>
</table>

J R Coll Physicians Lond 2000; 34: 448-451
304 patients
Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome


Conclusions
Idiopathic adult-onset bile acid malabsorption is not rare. International guidelines for the management of irritable bowel syndrome need to be revised so that clinicians become more aware of this possibility.

Aliment Pharmacol Ther 30, 707-717
# Systemic Review of SeHCAT in Chronic Diarrhoea

**Wedlake et al. Aliment Pharmacol Ther 2009**

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>Number of patients tested</th>
<th>Number of positive patients (7d SeHCAT retention &lt;10%)</th>
<th>% BAM-positive patients (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merrick (1985)</td>
<td>43</td>
<td>5</td>
<td>12 (5–28)</td>
</tr>
<tr>
<td>Sciarretta (1986)</td>
<td>13</td>
<td>6</td>
<td>46 (9–61)</td>
</tr>
<tr>
<td>Sciarretta (1987)</td>
<td>38</td>
<td>12</td>
<td>32 (18–49)</td>
</tr>
<tr>
<td>Williams (1991)</td>
<td>181</td>
<td>39</td>
<td>22 (16–28)</td>
</tr>
<tr>
<td>Ford (1992)</td>
<td>74</td>
<td>15</td>
<td>20 (12–31)</td>
</tr>
<tr>
<td>Galatola (1992)</td>
<td>98</td>
<td>56</td>
<td>57 (47–67)</td>
</tr>
<tr>
<td>Eusufzai (1993)</td>
<td>24</td>
<td>11</td>
<td>46 (26–67)</td>
</tr>
<tr>
<td>Sciarretta (1994)</td>
<td>31</td>
<td>18</td>
<td>58 (39–75)</td>
</tr>
<tr>
<td>Brydon (1996)</td>
<td>46</td>
<td>13</td>
<td>28 (16–43)</td>
</tr>
<tr>
<td>Smith (2000)</td>
<td>197</td>
<td>65</td>
<td>33 (26–40)</td>
</tr>
<tr>
<td>Ung (2000)</td>
<td>36</td>
<td>13</td>
<td>36 (21–54)</td>
</tr>
<tr>
<td>Fernandez-Banares (2001)</td>
<td>23</td>
<td>15</td>
<td>65 (43–84)</td>
</tr>
<tr>
<td>Wildt (2003)</td>
<td>133</td>
<td>21</td>
<td>16 (10–23)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1073</strong></td>
<td><strong>339</strong></td>
<td><strong>32 (29–35)</strong></td>
</tr>
</tbody>
</table>

**Table 4. Studies reporting patients with 7d SeHCAT retention <10%**
### Summary of Studies Reporting Abnormal SeHCAT Values in D-IBS

Data from Wedlake *et al.;* *Aliment Pharmacol Ther,* 2009
Walters & Pattni; *Ther Adv Gastroenterol,* 2010

<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>1073</td>
<td>618</td>
<td>1223</td>
</tr>
<tr>
<td>Number abnormal</td>
<td>43</td>
<td>339</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>% response to cholestyramine</td>
<td>96%</td>
<td>80%</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of Bile Acid Malabsorption

Calculations from Wedlake et al. *Aliment Pharmacol Ther* 2009; 30: 707

In UK:
~10% of adults in the UK are currently under medical care for “IBS”
33% of these have diarrhoea-predominant symptoms (D-IBS),
and if approximately 33% have abnormal SeHCAT tests, then ...

Adult population prevalence may be about 1%

In Europe Union:
Adult population
1%

~ 400 million
= 4 million
**Comparisons of the Prevalence of Certain Intestinal Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Population Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s *</td>
<td>0.1 – 0.2 %</td>
</tr>
<tr>
<td>Ulcerative colitis *</td>
<td>0.2 – 0.3 %</td>
</tr>
<tr>
<td>Coeliac disease *</td>
<td>0.7 – 1 %</td>
</tr>
<tr>
<td><strong>Primary Bile Acid Diarrhoea</strong></td>
<td>~ 1 %</td>
</tr>
</tbody>
</table>

62 patients with chronic watery diarrhoea

- >3 loose stools / d, > 4 weeks
- HLA-DQ + duodenal biopsy
- SeHCAT
- SB follow-through
- H₂ breath test: lactose, fructose + sorbitol

- Bile acid malabsorption 45%
- Sugar malabsorption 16%
- Gluten-sensitive enteropathy 16%
- Bile acid + sugar malabsorption 3%

80% symptom-free at 12 months with specific treatment
Diagnosis of Bile Acid Diarrhoea

- 7α-hydroxy-4-cholesten-3-one (C4)
  - Intermediate step in BA synthesis (Cholesterol → C4 → Bile Acids)
  - Increased levels with increased BA synthesis
  - Measured by HPLC or LC-MS/MS
  - Inversely correlates with SeHCAT
  - Not widely available

26 patients with chronic diarrhoea
Bajor et al. 2006

164 patients with chronic diarrhoea
Brydon et al. 1996
Increased Bile Acid Biosynthesis Is Associated With Irritable Bowel Syndrome With Diarrhea

BANNY S. WONG,* MICHAEL CAMILLERI,* PAULA CARLSON,* SAVANNA MCKINZIE,* IRENE BUSCIGLIO,Olga Bondar,* ROY B. DYER,† JESSE LAMSAM,† and ALAN R. ZINSMEISTER‡

*Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Department of Internal Medicine, Immunohematology Core Laboratory, Center for Translational Science Activities, and ‡Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota.

**Overall univariate association P = .057
*P = .02 vs controls
**P = .017 vs IBS-C/FC
Prior cholecystectomy

Serum C4 ng/mL

IBS-C
N=26

IBS-D
N=21

Healthy
controls
N=23

Total stool bile acid µmol/24h (48h collection)

IBS-C
N=26

IBS-D
N=21

Healthy
controls
N=23

Serum C4 ng/mL

One fecal BA measurement missing, corresponding to C4 of 85 ng/mL.

Total stool bile acid µmol/24h (48h collection)

r = 0.606
P < .001
Pathophysiology of Primary Bile Acid Diarrhoea

- Malabsorption of bile acids does occur with ileal disease or resection

\textit{BUT}

- In primary “idiopathic” bile acid “malabsorption” diarrhoea
  - No defect in ileal bile acid absorption
  - No defect in ileal bile acid transporters
  - Larger bile acid pool size
  - Increased bile acid synthesis

- Hepatic bile acid synthesis is under negative feedback control by the ileal hormone Fibroblast Growth Factor 19 (FGF19)

\textit{Van Tilburg Gastro 1990; Gut 1991; Sc J Gastro 1992}
\textit{Bajor Eur J Gastro Hep 2006}
Primary bile acid diarrhoea without an ileal carrier defect: quantification of active bile acid transport across the ileal brush border membrane

A J P van Tilburg, F W M de Rooij, J W O van den Berg, M van Blankenstein

Abstract
Unexplained bile acid malabsorption associated with diarrhoea that responds to chenodeoxycholic acid was first described in 1973. Convincing evidence of the proposed mechanism – a defective active ileal bile acid transport – has never been substantiated.

### TABLE III

<table>
<thead>
<tr>
<th>Patient no, sex</th>
<th>INBAT (pmol/mg prot)</th>
<th>INBALTC (pmol/g tissue)</th>
<th>BBMV yield (mg prot/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients mean (range)</td>
<td>88 (30–136)</td>
<td>158 (85–268)</td>
<td>2.46 (0.67–7.63)</td>
</tr>
<tr>
<td>Control mean (range)</td>
<td>63 (1–244)</td>
<td>98 (1–408)</td>
<td>1.69 (0.45–7.61)</td>
</tr>
</tbody>
</table>

INBAT = in vitro Na$^+$ dependent bile acid transport (pmol taurocholate uptake/mg brush border membrane protein/15 seconds).
INBALTC = in vitro Na$^+$ dependent bile acid local transport capacity (pmol taurocholate uptake/g ileal biopsy tissue/15 seconds).
No Ileal BA Absorption Defect in Primary Bile Acid Diarrhoea

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=8)</th>
<th>Primary Bile Acid Diarrhoea (IBAM) (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal BA loss (mmol/d)</td>
<td>1.0 ± 0.1</td>
<td>2.5 ± 1.0 *</td>
</tr>
<tr>
<td>BA pool size (mmol)</td>
<td>3.7 ± 1.0</td>
<td>7.0 ± 4.4 *</td>
</tr>
<tr>
<td>$^{75}$SeHCAT retention</td>
<td>2.6 ± 0.7</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>(half-life in d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Means ± SD are shown. * $p < 0.05$

From Van Tilburg et al. Scand J Gastroenterology Supplement 1992; 194:66-70
Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis

Takeshi Inagaki, Mihwa Choi, Antonio Moschetta, Li Peng, Carolyn L. Cummins, Jeffrey G. McDonald, Guizhen Luo, Stacey A. Jones, Bryan Goodwin, James A. Richardson, Robert D. Gerard, Joyce J. Repa, David J. Mangelsdorf, and Steven A. Kliewer

Table 1. Genes regulated by FXR agonist GW4064 in ileum

<table>
<thead>
<tr>
<th>Average ratio</th>
<th>Gene title</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>Fibroblast growth factor 15</td>
</tr>
<tr>
<td>45</td>
<td>Small heterodimer partner</td>
</tr>
<tr>
<td>11</td>
<td>Ubiquitin D</td>
</tr>
<tr>
<td>4.0</td>
<td>iNOS</td>
</tr>
<tr>
<td>2.8</td>
<td>RNase A family 4</td>
</tr>
<tr>
<td>2.8</td>
<td>Transient receptor potential cation channel</td>
</tr>
<tr>
<td>2.6</td>
<td>Ubiquitin-specific protease 2</td>
</tr>
<tr>
<td>2.3</td>
<td>Angiogenin</td>
</tr>
<tr>
<td>2.3</td>
<td>Carbonic anhydrase 12</td>
</tr>
<tr>
<td>2.2</td>
<td>IL18</td>
</tr>
<tr>
<td>2.1</td>
<td>Ileal bile acid binding protein</td>
</tr>
</tbody>
</table>

PNAS 2006; 103: 3920–3925

FGF19 is a Negative Regulator of Hepatic Bile Acid Synthesis

Could defective FGF19 signalling cause primary BA diarrhoea?

FGF19 in humans
FGF15 in mice

Figure from
Inagaki et al 2005, modified by Hofmann, Mangelsdorf, Kliewer 2009
# Studies of the FGF19/FGFR4/βKlotho System & Diarrhoea

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>First Author</th>
<th>Date</th>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td>Inagaki</td>
<td>2005</td>
<td>Fgf15 -/-</td>
<td>Increased fecal bile acids</td>
</tr>
<tr>
<td>Animal</td>
<td>Yu</td>
<td>2000</td>
<td>Fgfr4 -/-</td>
<td>Increased fecal bile acids &amp; bile acid pool size</td>
</tr>
<tr>
<td>Animal</td>
<td>Ito</td>
<td>2005</td>
<td>βKlotho -/-</td>
<td>Increased fecal bile acids &amp; bile acid pool size</td>
</tr>
<tr>
<td>Animal</td>
<td>Jung</td>
<td>2007</td>
<td>Asbt -/-</td>
<td>FXR agonist &amp; FGF15 expression improved bile acid kinetics</td>
</tr>
<tr>
<td>Animal</td>
<td>Pai</td>
<td>2012</td>
<td>FGF19 antibodies</td>
<td>Neutralising antibodies produced severe diarrhoea in monkeys</td>
</tr>
<tr>
<td>Human</td>
<td>Walters</td>
<td>2009</td>
<td>Serum FGF19</td>
<td>Low FGF19 in PBAD patients compared to healthy controls.</td>
</tr>
<tr>
<td>Human</td>
<td>Wong</td>
<td>2011</td>
<td>FGFR4/βKlotho</td>
<td>Genotypes affect colonic function</td>
</tr>
<tr>
<td>Human</td>
<td>Pattni</td>
<td>2012</td>
<td>Serum FGF19</td>
<td>Low FGF19 and raised C4 correlated.</td>
</tr>
<tr>
<td>Human</td>
<td>Pattni</td>
<td>2013</td>
<td>Serum FGF19</td>
<td>Low FGF19 in prospective study of chronic diarrhoea. Associations with SeHCAT and therapeutic response.</td>
</tr>
</tbody>
</table>

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Walters. Nat Rev Gastroenterol Hepatol 2014
A New Mechanism for Bile Acid Diarrhea: Defective Feedback Inhibition of Bile Acid Biosynthesis

JULIAN R. F. WALTERS,* ALI M. TASLEEM,* OMER S. OMER,* W. GORDON BRYDON,** TRACY DEW,† and CAREL W. LE ROUX‡

Departments of *Gastroenterology and ‡Metabolic Medicine, Imperial College, London; †Clinical Chemistry, Western General Hospital, Edinburgh; and ‡Clinical Biochemistry, King’s College Hospital, London, United Kingdom

See Editorial on page 1151.

BACKGROUND & AIMS: Primary (idiopathic) bile acid malabsorption (BAM) is a common, yet underrecognized, chronic diarrheal syndrome. Diagnosis is difficult without steatorrhea (12 g) in 24 hours. This indicates the importance of absorption and resecretion, with recycling estimated to average 4–6 times a day, depending in part on diet.‡ Surgical resection of the terminal ileum, or inflammation as in Crohn’s disease is well recognized as producing the condition known as secondary bile acid malabsorption (or type 1 BAM), with clear impairment of

Editorials

Chronic Diarrhea Due to Excessive Bile Acid Synthesis and not Defective Ileal Transport: A New Syndrome of Defective Fibroblast Growth Factor 19 Release

Elsewhere in this issue Julian Walters and his colleagues report a major advance in our understanding of the pathogenesis of chronic diarrhea associated with idiopathic bile acid malabsorption. The story is a fascinating one and unites long-standing and unexpected discoveries in physiology, biochemistry, and cell biology. The elevated concentrations were the result of greatly increased bile acid synthesis.

It was quite straightforward to combine these findings and predict the course of events in patients undergoing ileal resection. Defective bile acid absorption led to increased hepatic synthesis. In this new steady state, increased bile acids passed into the colon and induced secretion, manifest clinically as diarrhea. If diarrhea were caused by bile acid–induced secretion in the colon, it should respond to a bile acid sequestrant. Indeed, cholestyramine was shown to be effective for the treatment of diarrhea in a small clinical study. In a more potent bile acid sequestrant, was developed a few years ago, and its off-label utility in diarrhea associated with bile acid malab-
Raised 7aOH-4-Cholesten-3-one (C4) in Patients with Chronic Bile Acid Diarrhoea

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 Diarrhoea


Significantly lower FGF19 in patients
p < 0.005
FGF19 & Primary Bile Acid Diarrhoea

FGF19 in Prospective Groups with Chronic Diarrhoea

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

\[ p < 0.001 \]

Pattini et al. APT, 2013; 38: 967–976
Clinical picture in Chronic Diarrhoea Patients with Negative or Positive SeHCAT Values

<table>
<thead>
<tr>
<th></th>
<th>Diarrhoea controls (SeHCAT &gt; 15%)</th>
<th>Primary BAD (SeHCAT &lt; 15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>72</td>
<td>54</td>
</tr>
<tr>
<td>Age</td>
<td>45 (31-59)</td>
<td>47 (34-57)</td>
</tr>
<tr>
<td>F:M ratio</td>
<td>1.9 : 1</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>BMI</td>
<td>24 (21-29)</td>
<td>27 (23-32) **</td>
</tr>
<tr>
<td>Bowel movements (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>per day</td>
<td>5 (3-6)</td>
<td>6 (4-8) **</td>
</tr>
<tr>
<td>per night</td>
<td>0 (0-0)</td>
<td>0 (0-1) *</td>
</tr>
<tr>
<td>Duration of diarrhoea (months)</td>
<td>18 (6-60)</td>
<td>24 (12-114)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>30%</td>
<td>31%</td>
</tr>
<tr>
<td>Urgency</td>
<td>83%</td>
<td>92%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>58%</td>
<td>59%</td>
</tr>
<tr>
<td>Bloating</td>
<td>61%</td>
<td>73%</td>
</tr>
</tbody>
</table>

** p<0.01; * p<0.05
Median and IQR
## FGF19 & Prediction of SeHCAT – ROC Analysis

### Frequency of low FGF19 values in different SeHCAT groups

<table>
<thead>
<tr>
<th>SeHCAT value</th>
<th>Total number</th>
<th>FGF19 ≤145pg/ml</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;15%</td>
<td>72</td>
<td>11</td>
</tr>
<tr>
<td>Primary BAD</td>
<td>10-15%</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5-10%</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>0-5%</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Pattni et al. APT, 2013; 38: 967–976
Response to bile acid sequestrants (Cholestyramine or Colesevelam) in Primary Bile Acid Diarrhoea

<table>
<thead>
<tr>
<th></th>
<th>FGF19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 145pg/ml</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12</td>
</tr>
<tr>
<td><strong>No response or partial response</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Full response</strong></td>
<td>6</td>
</tr>
</tbody>
</table>

Response data were available on 28 patients with primary BA diarrhoea and SeHCAT retention < 15%. Patients with a full response had a frequency of bowel movements of less than 3/day.

\[ P = 0.02 \text{ (Fisher's exact test).} \]
Current Treatment of Bile Acid Diarrhoea

- Bile acid sequestrants are effective treatments
  - Bind Bile Salts in intestine
  - Cholestyramine (Questran) & Colestipol (Colestid) – powders
  - Colesevelam (Cholestagel, Wellchol) – tablets

- Therapeutic problems
  - Poor long-term compliance
  - Bloating may worsen
  - Sequestrants can bind other drugs / vitamins
  - Optimal dosing regimes uncertain
  - Therapeutic trials not necessarily successful

- Possible solutions
  - Titration to individual needs
  - Try alternative sequestrants
  - ? with food or between meals
  - Entero-coated cholestyramine

Hofmann, Poley 1969; Westergaard 2007
Wedlake et al, Clin Therap 2009

Walters, Pattini 2010

Jacobsen et al. BMJ 1985
Figure 2
Chronic diarrhea due to excessive bile acid synthesis and not defective ileal transport: a new syndrome of defective FGF19 release.
FGF19 in patients with Crohn’s and Ileal Resection

Nolan et al. J Crohns Colitis 2015

18 patients with documented lengths of ileal resection
Serum FGF19 in different Crohn’s patient groups

FGF19 levels lower in patients with Crohn’s (CD)
- with no resection (NR)
- diarrhoea
- active disease HBI >4
- ileal resection (IR)

Lowest levels observed in Crohn’s with IR and diarrhoea

Nolan et al. J Crohns Colitis 2015
Serial serum FGF19 in treated Crohn’s patients

Nolan et al. J Crohns Colitis 2015

FGF19 levels increased in patients with ileal Crohn’s treated with steroids or anti-TNFs.
FGF19 expression is highly responsive to BA compared to other BA regulatory genes in human ileum


Ileal explants
6h incubations
qRT-PCR
Induction of FGF19 RNA & protein
FGF19 greater than other transcripts
Human ileal FGF19 expression: Stimulation by natural bile acids & obeticholic acid


CDCA = CA > DCA > LCA

OCA 1µM = CDCA 50µM
FXR Agonists as Treatment for BAD?

FXR agonists

Stimulate FGF19

Inhibit excessive hepatic Bile Acid synthesis

Reduce colonic secretions / symptoms
Obeticholic acid (OCA) in Primary BAD: FGF19 results

- OCA increased median fasting FGF19 from 133 to 237 pg/ml, (p=0.007).
- Most patients had an increase of >60% in fasting FGF19.

Walters JRF, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015; 41: 54-64
Obeticholic acid (OCA) in Primary BAD:
Total Bile Acids Area under the Curve 0 – 6h

Postprandial BA AUC was lower after the 2 w OCA treatment (from 4.9 to 3.0 units, p=0.02).

Walters JRF, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015; 41: 54-64
Results: Individual FGF19 and Total Bile Acid Responses

- Considerable variation
- Fasting FGF19 increased
- FGF19 AUC unchanged
- Fasting total BA non-significant reduction
- Total BA AUC reduced

Walters JRF, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015; 41: 54-64
Obeticholic acid (OCA) in Primary BAD: Stool Frequency & Type

Clinical improvements were found in all patients, including in stool frequency (from 23 to 14/wk, p=0.02), BSFS (from 5.15 to 4.34, p=0.05).

Walters JRF, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015; 41: 54-64
Obeticholic acid (OCA) in Primary BAD: Stool Index

- **Stool index** = (weekly frequency × average stool form) + loperamide use (mg × 3)
- **Change in median from 113 to 76, p=0.005.**

Walters JRF, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015; 41: 54-64
Primary Bile Acid Diarrhoea as an Endocrine Disorder: Pathophysiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary BA Diarrhoea</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main symptom</td>
<td>Diarrhoea</td>
<td>Polyuria</td>
</tr>
<tr>
<td>Direct cause</td>
<td>Excess faecal Bile Acids</td>
<td>Excess urinary Glucose</td>
</tr>
<tr>
<td>Pathophysiological problem</td>
<td>Unregulated Bile Acids metabolism</td>
<td>Unregulated Glucose metabolism</td>
</tr>
<tr>
<td>Hormone regulating metabolism</td>
<td>FGF19</td>
<td>Insulin</td>
</tr>
<tr>
<td>Defect on feeding</td>
<td>Impaired production</td>
<td>Impaired production (T1D)</td>
</tr>
<tr>
<td>Other causes</td>
<td>? Impaired receptor function</td>
<td>Impaired receptor (T2D)</td>
</tr>
</tbody>
</table>

Primary Bile Acid Diarrhoea as an Endocrine Disorder: Diagnostic Strategies

<table>
<thead>
<tr>
<th>Primary BA Diarrhoea</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone levels</td>
<td>FGF19</td>
</tr>
<tr>
<td>Regulated product</td>
<td>BA; C4</td>
</tr>
<tr>
<td>Pathophysiological problem</td>
<td>Excess BA secretion; Faecal BA</td>
</tr>
</tbody>
</table>

These vary cyclically after meals as they are dependent on synthesis, absorption and hormone action

<table>
<thead>
<tr>
<th>Tests that integrate function over multiple cycles</th>
<th>SeHCAT</th>
<th>HbA1C</th>
</tr>
</thead>
</table>

# Mechanisms affecting the development of Bile Acid Diarrhoea

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Physiological process</th>
<th>Major factors</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>BA synthesis</td>
<td>FXR</td>
<td>Other genes</td>
</tr>
<tr>
<td></td>
<td>BA uptake</td>
<td>FGFR4, B-Klotho</td>
<td>Micro-RNAs</td>
</tr>
<tr>
<td></td>
<td>BA conjugation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>BA secretion</td>
<td>Recycling rate</td>
<td>FGF19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCK</td>
<td></td>
</tr>
<tr>
<td>Duodenum +</td>
<td>BA integrity</td>
<td>SI bacteria (deconjugation)</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td></td>
<td>SI motility</td>
<td>Other dietary factors</td>
</tr>
<tr>
<td>Ileum</td>
<td>BA reuptake</td>
<td>Ileal mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASBT, FABP6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OSTα/OSTβ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FGF19 feedback</td>
<td>FXR</td>
<td>Inflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FGF19</td>
<td>Diet1</td>
</tr>
<tr>
<td>Colon</td>
<td>Effects of unabsorbed BA</td>
<td>Bacterial metabolism (to DCA/LCA)</td>
<td>Microbiome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anion secretion</td>
<td>FXR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic motility</td>
<td>TGR5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall response</td>
<td>Visceral sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Psychological response</td>
</tr>
</tbody>
</table>
Bile Acid Diarrhoea and FGF19: new views on diagnosis, pathogenesis and therapy

- Clinical features of BA diarrhoea & malabsorption
- Diagnosis
- Causes: Malabsorption / overproduction
- Regulation of Bile Acid synthesis by FGF19
- Approaches to treatment: current and future