GE Healthcare

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

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Imperial College London

Imperial College Healthcare NHS Trust

Julian RF Walters : Disclosures

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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.

Bile Acid Malabsorption: Case History 1 – Ms MH (contd.)

- 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

Fromm & Malavolti, *Clin Gastroenterol 1986; 15:567*

- 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

Gastroenterology 1967; 52(4): 752-7.

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

Hofmann AF.

Dan Med Bull 1973; 20(6): 174-7.

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

Thaysen EH, Pedersen L.

Gut, 1976, **17**, 965-970

Idiopathic bile acid catharsis

E. HESS THAYSEN[1] 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.

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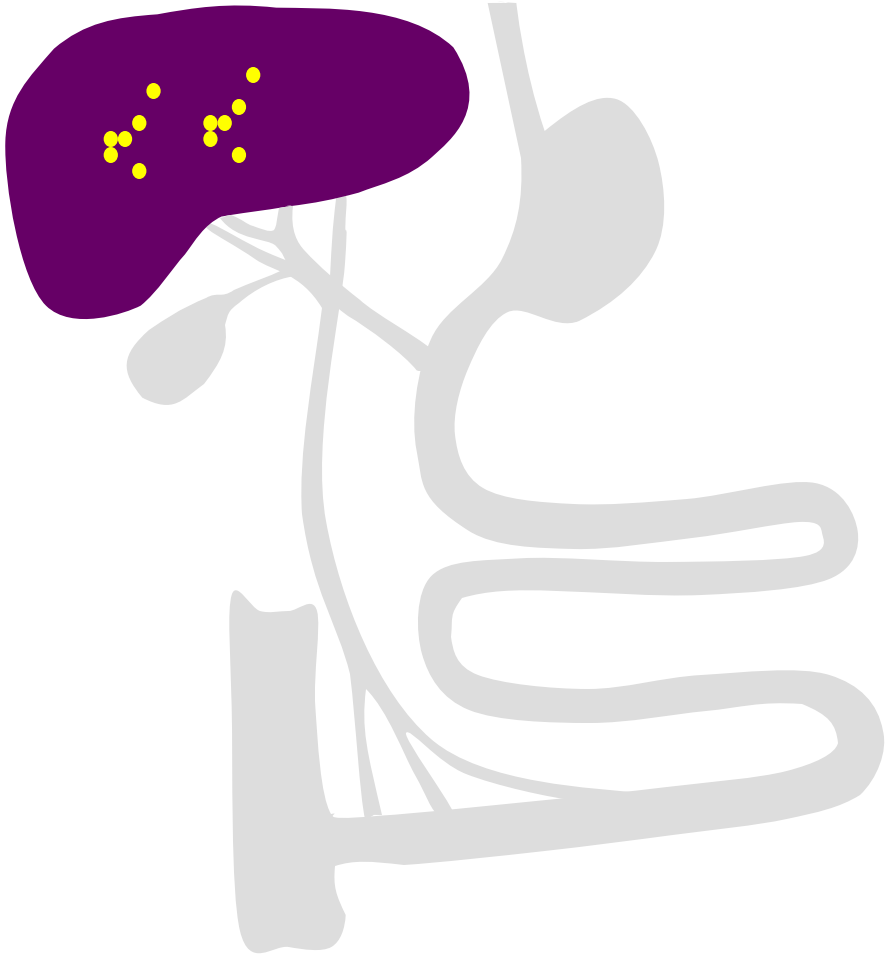
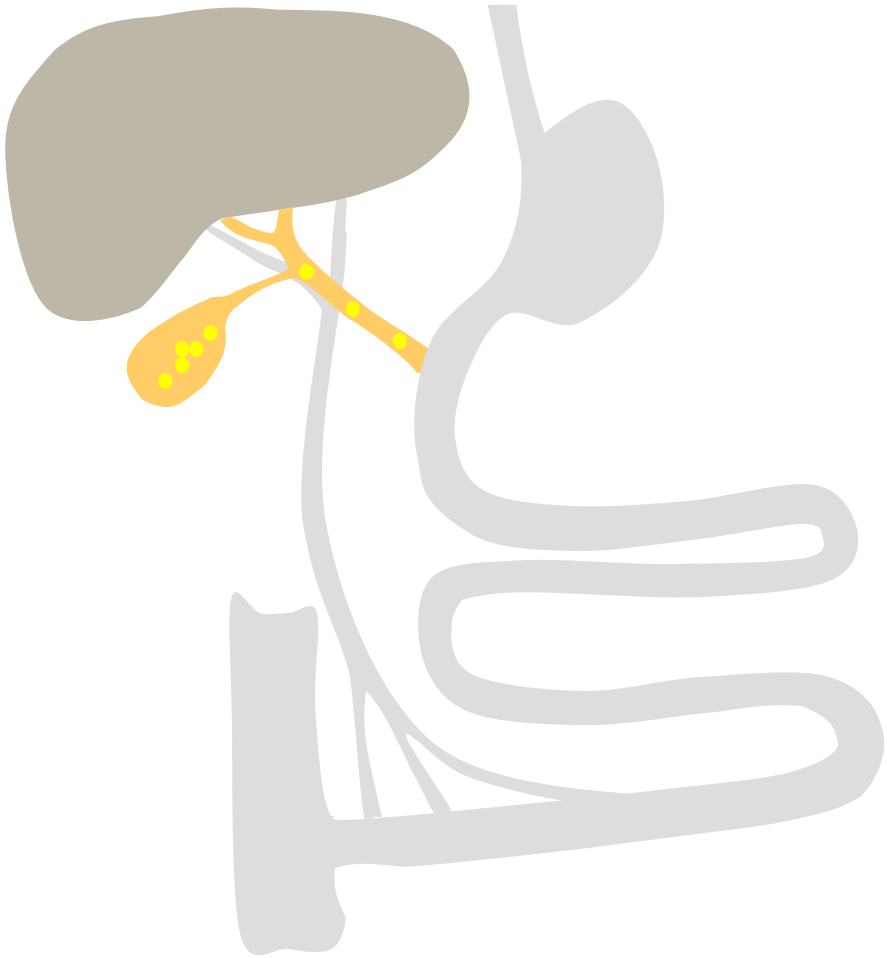
ENTEROHEPATIC CIRCULATION OF BILE ACIDS



Hepatic synthesis from cholesterol by CYP7A1

Conjugated with glycine or taurine

ENTEROHEPATIC CIRCULATION OF BILE ACIDS

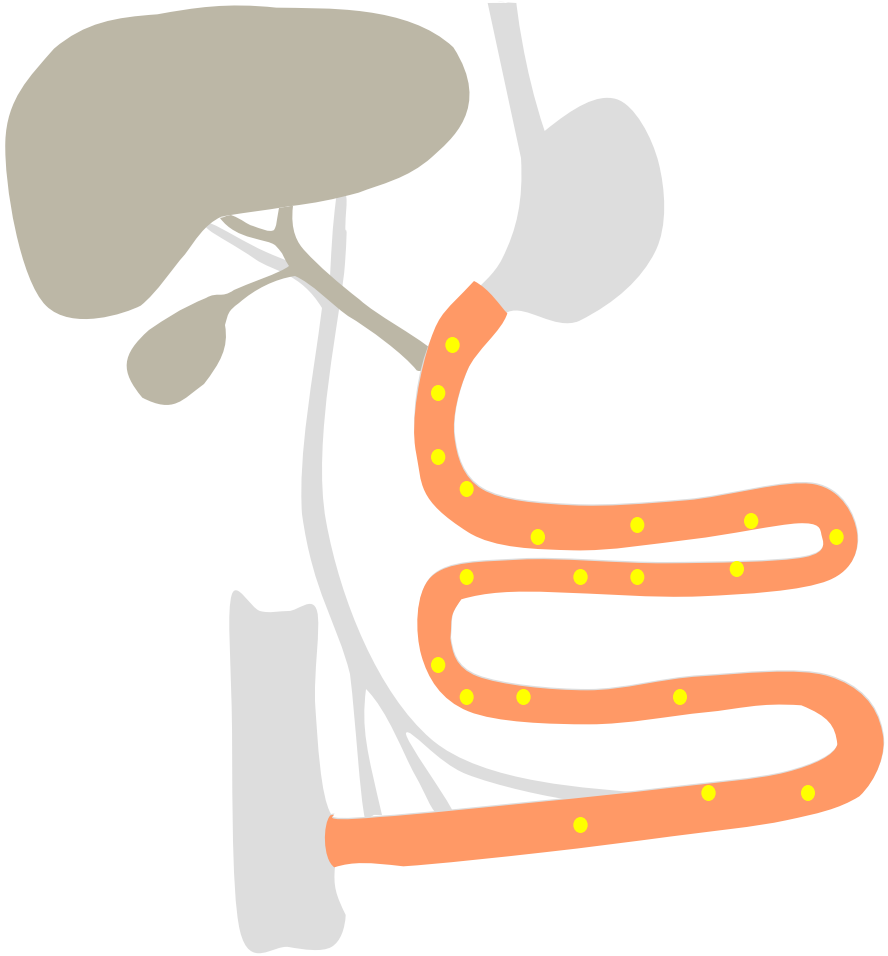


Hepatic synthesis from cholesterol by CYP7A1

Conjugated with glycine or taurine

Secreted via biliary tree into intestine

ENTEROHEPATIC CIRCULATION OF BILE ACIDS



Hepatic synthesis from cholesterol by CYP7A1

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Solubilise lipids in micelles for absorption

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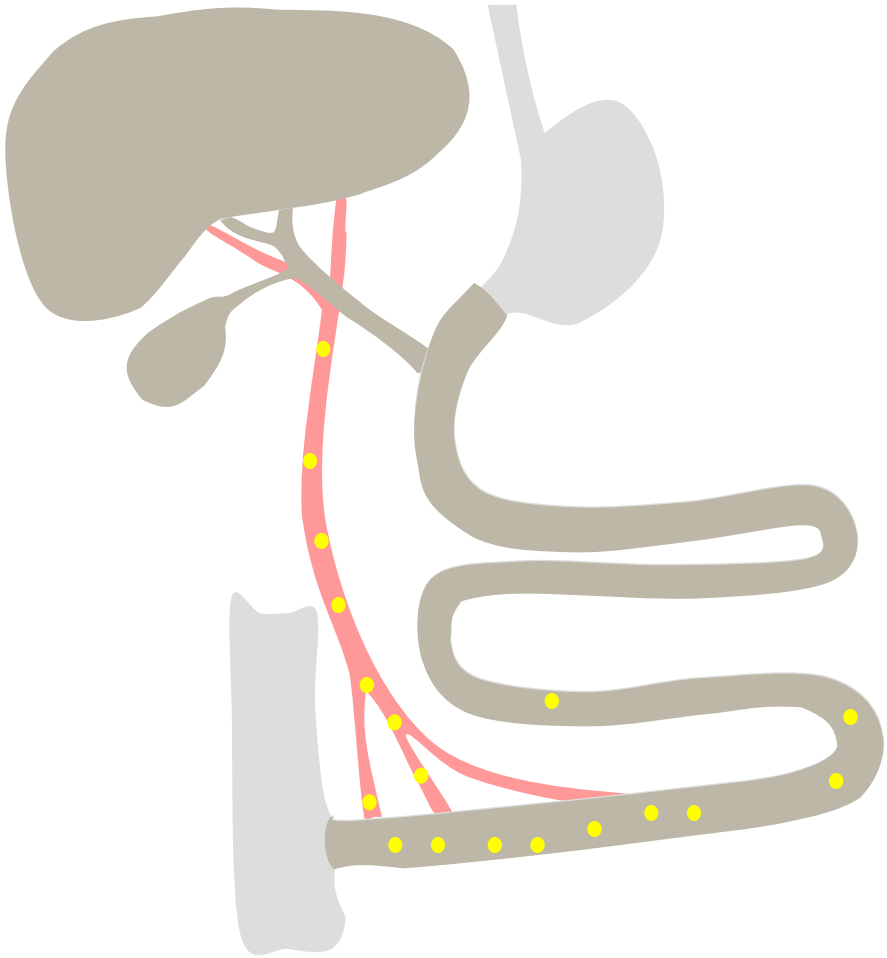


Hepatic synthesis from cholesterol by CYP7A1

Conjugated with glycine or taurine

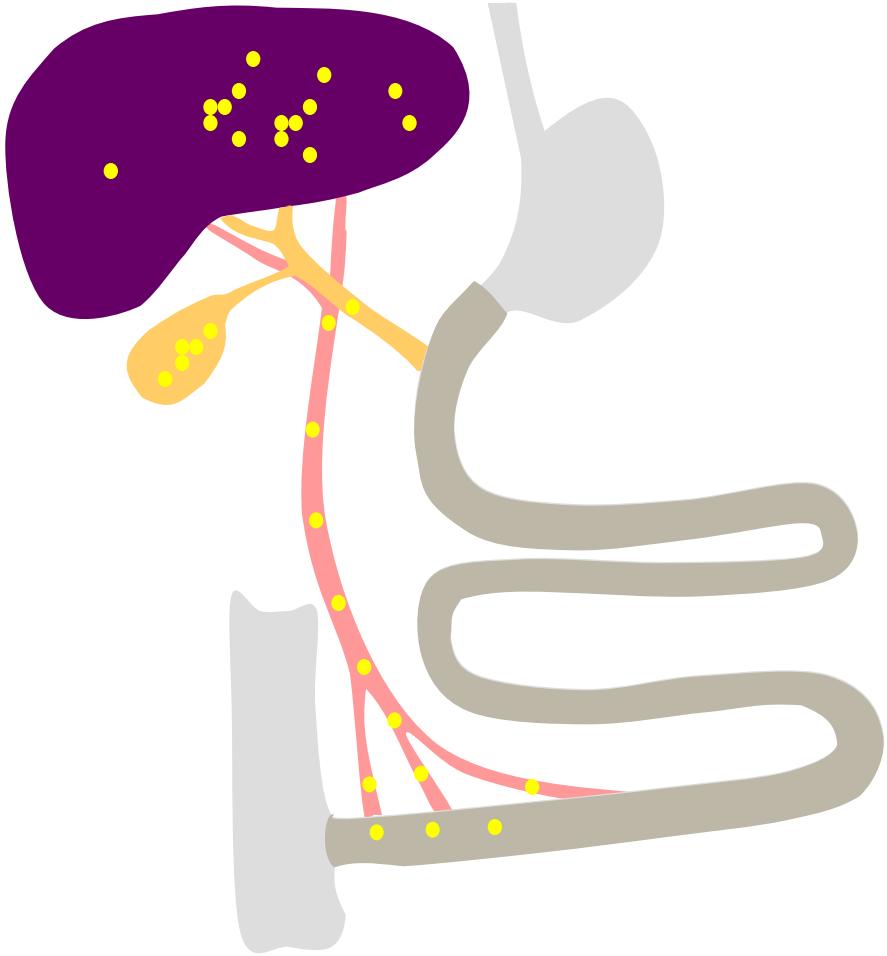
Secreted via biliary tree into intestine

Solubilise lipids in micelles for absorption

Reabsorbed in distal intestine:

- **Active absorption in ileum (conjugated)**

ENTEROHEPATIC CIRCULATION OF BILE ACIDS



Hepatic synthesis from cholesterol by CYP7A1

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Reabsorbed in distal intestine:

- Active absorption in ileum

Reuptake by hepatocytes and resecreted

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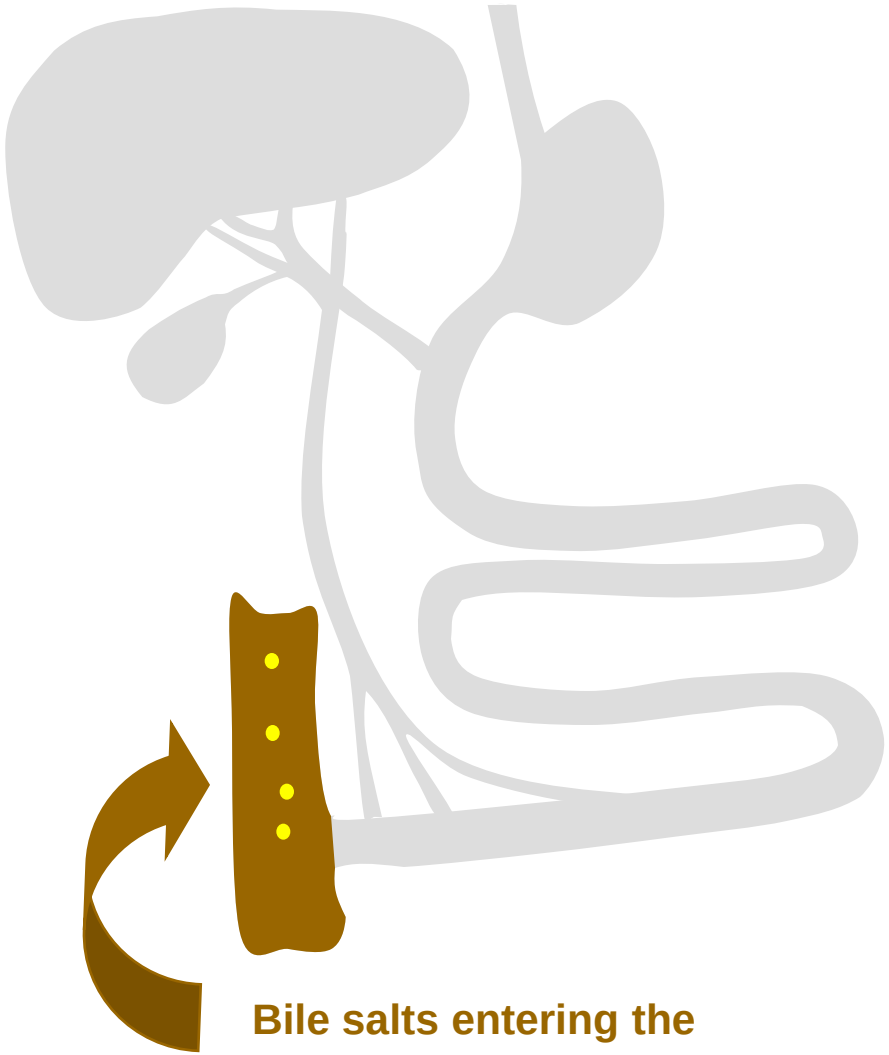

Bile salts entering the colon cause diarrhoea

- 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

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

BA secretion	12 g/d	(30 mmol/d)
BA pool size	2 – 3 g	(5 - 7.5 mmol)
Cycling frequency	4 – 6 x/d	
Amount absorbed / cycle	~ 95%	
Faecal BA loss	< 0.5 g/d	(~ 1 mmol/d)
Average half-life	~ 3 d	

Data from multiple studies reviewed in

Walters & Pattni, *Therapeutic Advances Gastroenterology* 2010; 3: 349

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:1232–1239

Methods for Diagnosis of Bile Acid Malabsorption in Clinical Practice

PRIYA VIJAYVARGIYA,* 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

BAM diagnostic methods	Advantages	Disadvantages
^{14}C glycocholate	May identify small bowel bacterial overgrowth	Radiation exposure, β emission, long half-life Varying normal values Positive breath excretion at 2–4 h does not differentiate BAM from small bowel bacterial overgrowth Laborious test method (stool collection)
^{75}SeHCAT	Gamma emission, short half-life, with decreased radiation to extra-abdominal organs	Not available in U.S.
	Well-defined normal values; level of isotope retention predicts response to bile acid sequestrant	Radiation exposure
	Simple test method: 2 patient visits	
Serum C4	No radiation	Fasting sample, diurnal variation
	Normal values reported in adults	Requires further validation
	Not dependent on age, gender, or cholesterol	False positive in liver disease, treatment with statins, and altered circadian rhythm
	Simple blood test: 1 patient visit	
Fecal BA	No radiation	Variable daily fecal BA excretion, requires at least 48-h sample
	Measures total and individual BAs	Cumbersome method (stool collection)

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

Walters JRF. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. *Expert Rev Gastroenterol Hepatol* 2010; 4: 561-567

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Diagnosis of Bile Acid Malabsorption

- SeHCAT

  Synthetic ^{75}Se radiolabelled bile acid analogue

  Boyd et al. *J Nucl Med* 1981; 22: 720-5

  Detected by gamma-camera

  Limited radiation exposure

  Kinetics similar to taurocholate

  Measure of BA retention

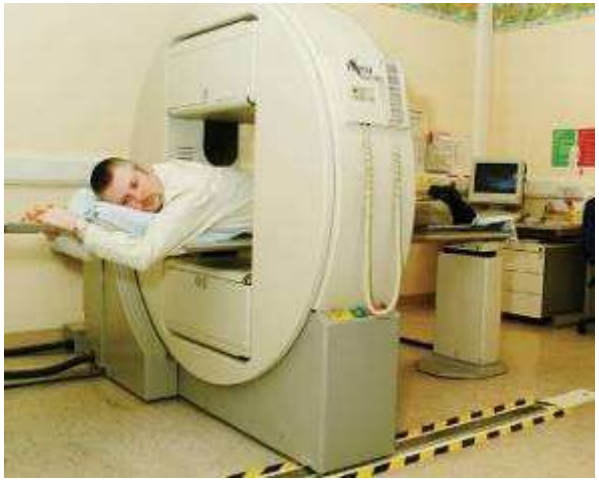
  7 day retention:

  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

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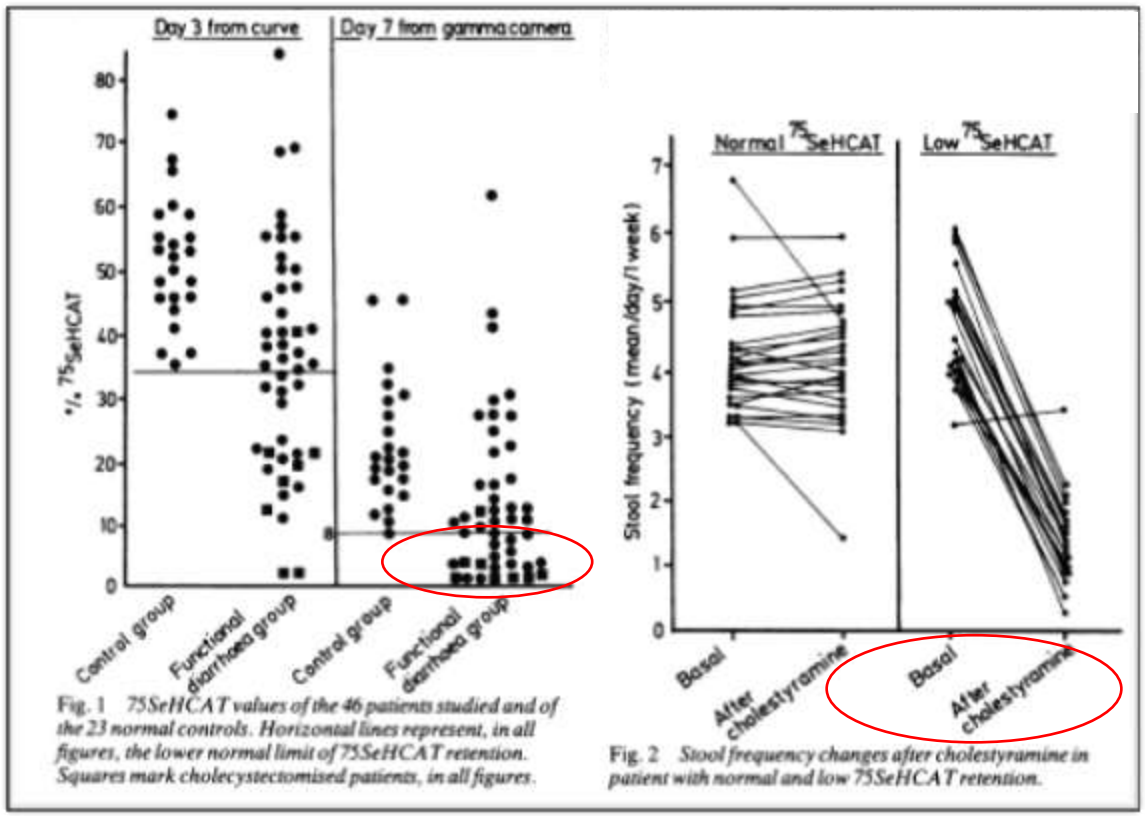
SeHCAT in Diagnosis of Bile Acid Malabsorption & Prediction of Response to Cholestyramine

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

Bile acid malabsorption in persistent diarrhoea

M J Smith, P Cherian, G S Raju, B F Dawson, S Mahon and K D Bardhan

ABSTRACT – We have investigated bile acid malabsorption (BAM), and its response to treatment, in patients seen in this district general hospital with chronic continuous or recurrent diarrhoea.

has commonly been regarded as rare and of limited importance in day-to-day practice in the district general hospital (DGH). The diagnosis has traditionally rested on detecting excess faecal bile acid loss in stool samples, a complex

J R Coll Physicians Lond 2000; 34: 448-451

304 patients

	SeHCAT retention <10%	Response in these to BA sequestrants
Crohn's with resection	36 / 37 97%	60%
Crohn's without resection	24 / 44 54%	40%
Vagotomy / pyloroplasty (+/- cholecystectomy)	15 / 26 58%	64%
Diarrhoea-predominant IBS	65 / 197 33%	70%

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Alimentary Pharmacology & Therapeutics

Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome

L. WEDLAKE*, R. A'HERN†, D. RUSSELL‡, K. THOMAS§, J. R. F. WALTERS¶ & H. J. N. ANDREYEV**

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

doi:10.1111/j.1365-2036.2009.04081.x

Systemic Review of SeHCAT in Chronic Diarrhoea

Wedlake *et al.* Aliment Pharmacol Ther 2009

Table 4. Studies reporting patients with 7d SeHCAT retention <10%

Author (date)	Number of patients tested	Number of positive patients (7dSeHCAT retention <10%)	% BAM-positive patients (confidence interval)
Merrick (1985)	43	5	12 (5–28)
Sciarretta (1986)	13	6	46 (9–61)
Sciarretta (1987)	38	12	32 (18–49)
Williams (1991)	181	39	22 (16–28)
Ford (1992)	74	15	20 (12–31)
Galatola (1992)	98	56	57 (47–67)
Eusufzai (1993)	24	11	46 (26–67)
Sciarretta (1994)	31	18	58 (39–75)
Brydon (1996)	46	13	28 (16–43)
Rudberg (1996)	20	3	15 (3–38)
Sinha (1998)	17	6	35 (14–62)
Smith (2000)	197	65	33 (26–40)
Ung (2000)	36	13	36 (21–54)
Fernandez-Banares (2001)	23	15	65 (43–84)
Muller (2004)	37	15	41 (25–58)
Wildt (2003)	133	21	16 (10–23)
Fernandez-Banares (2007)	62	28	45 (32–58)
Total	1073	339	32 (29–35)

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

Reported SeHCAT value	< 5%	< 10%	< 15%	Total
Number of studies reporting	5	17	7	18
Total number of patients	429	1073	618	1223
Number abnormal	43	339	163	
% abnormal [95% confidence intervals]	10% [7 – 13]	32% [29 – 35]	26% [23 – 30]	
% response to cholestyramine	96%	80%	70%	

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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"

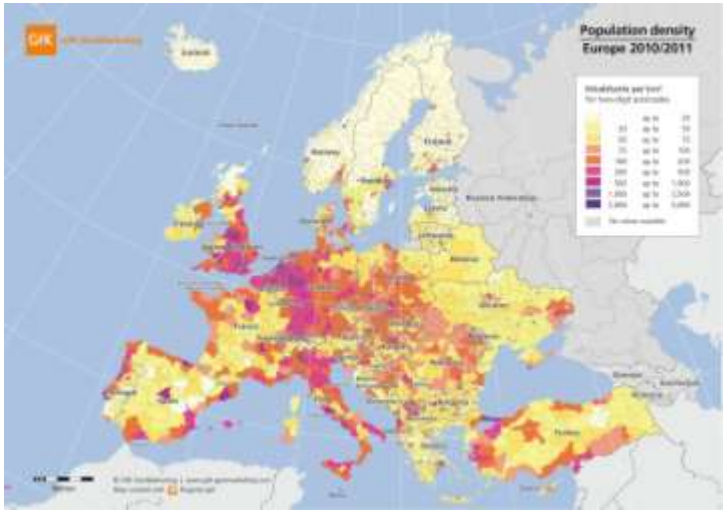
33% of these have diarrhoea-predominant symptoms (D-IBS),

and if approximately 33% have abnormal SeHCAT tests, then …

Adult population prevalence may be about 1%

In Europe Union:

Adult population	**~ 400 million**
1%	**= 4 million**



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Comparisons of the Prevalence of Certain Intestinal Diseases

Disease	Estimated Population Prevalence
Crohn's *	0.1 – 0.2 %
Ulcerative colitis *	0.2 – 0.3 %
Coeliac disease *	0.7 – 1 %
Primary Bile Acid Diarrhoea	**~ 1 %**

* Williams *et al.* Gastroenterology services in the UK. The burden of disease, and the organisation and delivery of services for gastrointestinal and liver disorders: a review of the evidence. Gut. 2007;56 Suppl 1:1-113

Systemic Evaluation of the Causes of Chronic Watery Diarrhoea with Functional Characteristics

Fernández-Bañares et al. Am J Gastro 2007; 102: 2520

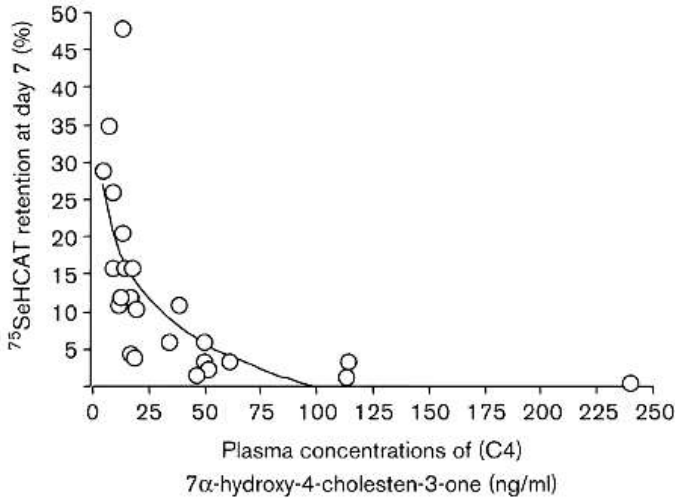
- 62 patients with chronic watery diarrhoea
  - >3 loose stools / d, > 4 weeks
  - HLA-DQ + duodenal biopsy
  - SeHCAT
  - SB follow-through
  - H_2 breath test: lactose, fructose + sorbitol

• 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

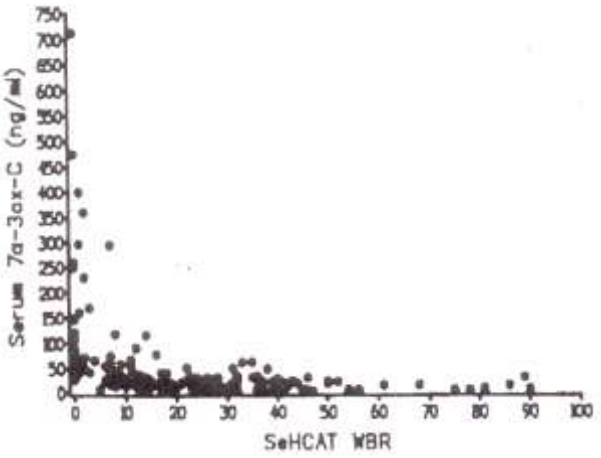
Diagnosis of Bile Acid Diarrhoea

- 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

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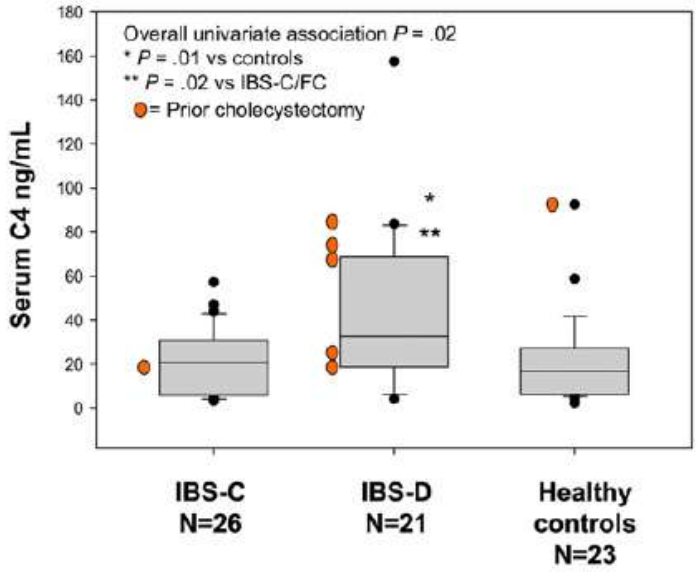
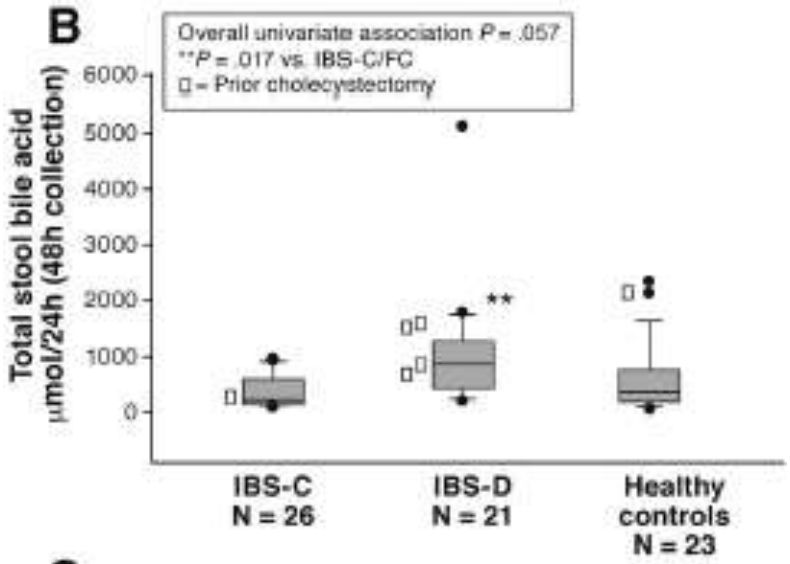
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2012;10:1009–1015

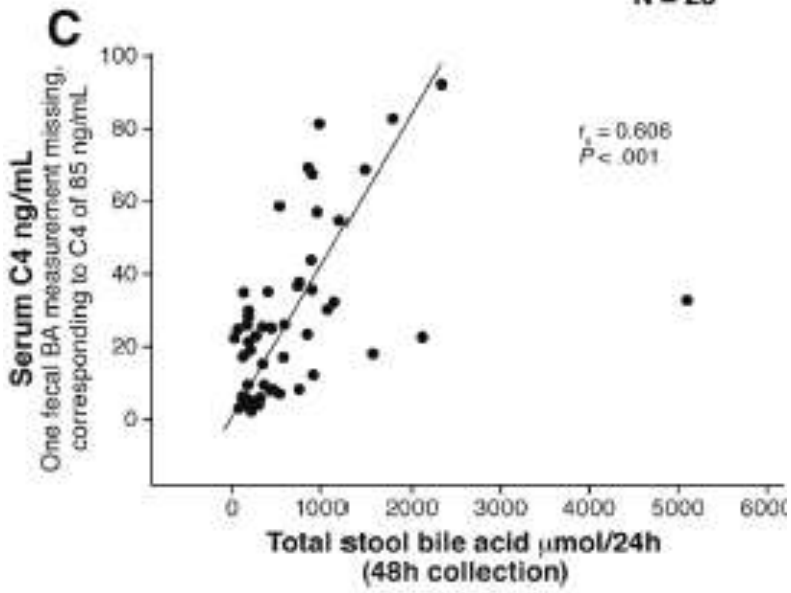
Increased Bile Acid Biosynthesis Is Associated With Irritable Bowel Syndrome With Diarrhea

BANNY S. WONG,* MICHAEL CAMILLERI,* PAULA CARLSON,* SANNA 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, ‡Immunochemical Core Laboratory, Center for Translational Science Activities, and §Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, Minnesota







Pathophysiology of Primary Bile Acid Diarrhoea

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

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

Van Tilburg *Gastro 1990; Gut* 1991; *Sc J Gastro* 1992
Bajor *Eur J Gastro Hep* 2006

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

No Ileal BA Absorption Defect in Primary Bile Acid Diarrhoea

Gut, 1991, 32, 500–503

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 asso ted with diarrhoea that responds to ch styramine was first described in 1973 convincing evidence of the proposed me anism – a defective active ileal bile a transport – has never been substantiat

TABLE III *Active ileal bile acid transport parameters and brush border membrane vesicle (BBMV) yield found in patients with primary bile acid malabsorption (n=10) compared with control subjects (n=132)*

Patient no, sex	*INBAT (pmol/mg prot)*	*INBALTC (pmol/g tissue)*	*BBMV yield (mg prot/g tissue)*
Patients mean (range)	88 (30–136)	158 (85–268)	2·46 (0·67–7·63)
Control mean (range)	63 (1–244)	98 (1–408)	1·69 (0·45–7·61)

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).

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No Ileal BA Absorption Defect in Primary Bile Acid Diarrhoea

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

Means ± SD are shown. * $p < 0.05$

From Van Tilburg *et al. Scand J Gastroenterology Supplement 1992; 194:66-70*

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FGF15 / FGF19 in BA Homeostasis

Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis

Takeshi Inagaki,[1] Mihwa Choi,[1] Antonio Moschetta,[2,7] Li Peng,[1] Carolyn L. Cummins,[2,7] Jeffrey G. McDonald,[3] Guizhen Luo,[8] Stacey A. Jones,[8] Bryan Goodwin,[8] James A. Richardson,[4] Robert D. Gerard,[1,5] Joyce J. Repa,[6] David J. Mangelsdorf,[2,7] and Steven A. Kliewer[1,2,*]

Cell Metab *2005; 2: 217-25*

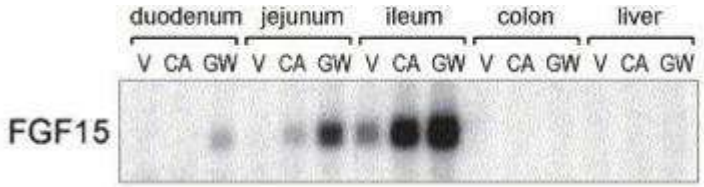
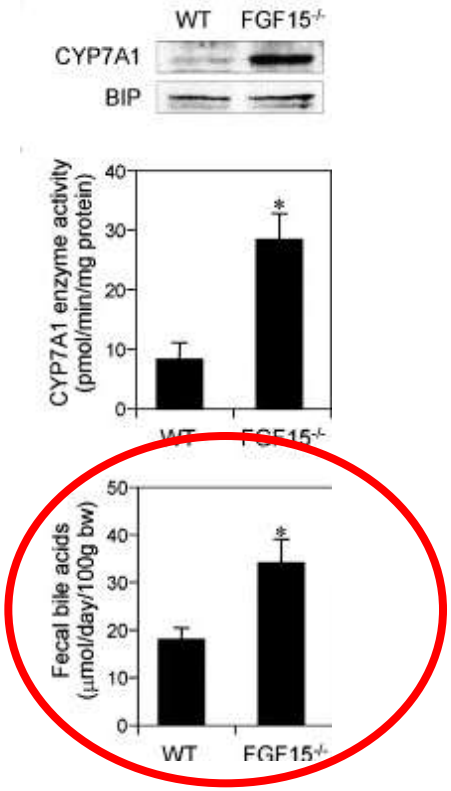


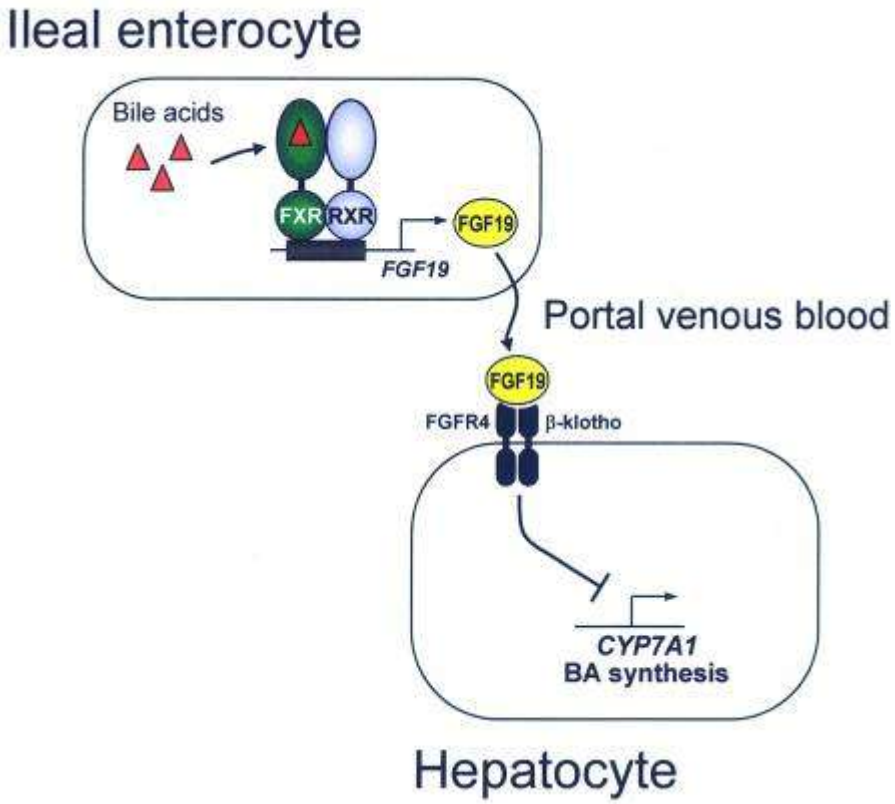
Table 1. Genes regulated by FXR agonist GW4064 in ileum

Average ratio	Unigene accession no.	Gene title
83	Mm.3904	Fibroblast growth factor 15
45	Mm.34209	Small heterodimer partner
11	Mm.140210	Ubiquitin D
4.0	Mm.2893	iNOS
2.8	Mm.175173	RNase A family 4
2.8	Mm.215171	Transient receptor potential cation channel
2.6	Mm.12914	Ubiquitin-specific protease 2
2.3	Mm.202665	Angiogenin
2.3	Mm.21397	Carbonic anhydrase 12
2.2	Mm.1410	IL18
2.1	Mm.142716	Ileal bile acid binding protein

PNAS 2006; 103: 3920–3925



FGF19 is a Negative Regulator of Hepatic Bile Acid Synthesis



FGF19 in humans

FGF15 in mice

Figure from
Inagaki *et al* 2005, modified by
Hofmann, Mangelsdorf, Kliewer 2009

Could defective FGF19 signalling cause primary BA diarrhoea?

Studies of the FGF19/FGFR4/βKlotho System & Diarrhoea

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

Walters. Nat Rev Gastroenterol Hepatol 2014

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CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2009;7:1189–1194

A New Mechanism for Bile Acid Diarrhea: Defective Feedback Inhibition of Bile Acid Biosynthesis

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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 se-

(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.[4] 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

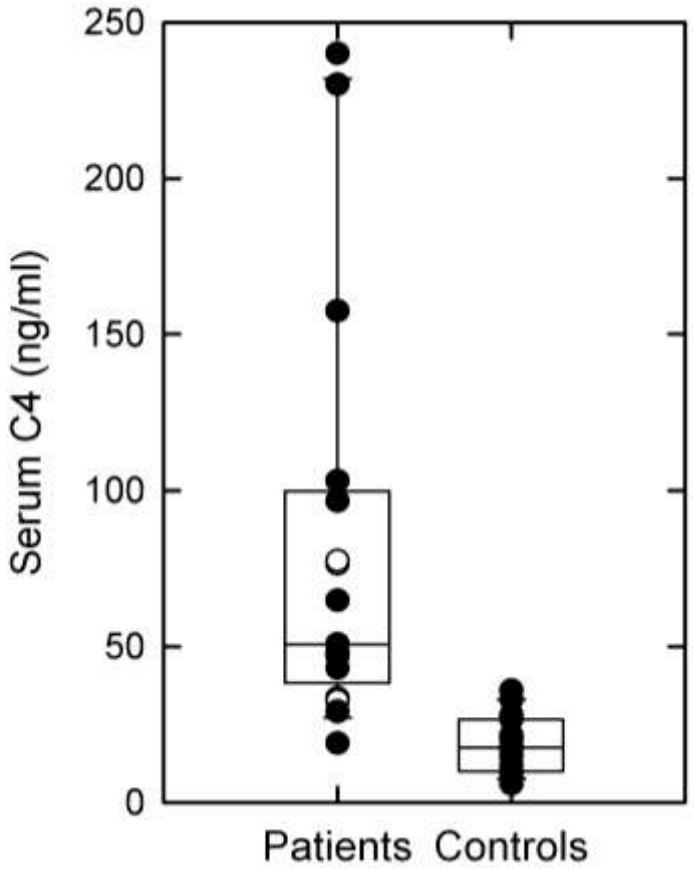
Elsewhere in this issue Julian Walters and his colleagues report a major advance in our understanding of the pathogenesis of chronic diarrhea associated with idiopathic bile acid malabsorption.[1] The story is a fascinating one and unites long-

The elevated concentrations were the result of greatly increased bile acid synthesis.[9–13]

It was quite straightforward to combine these findings and predict the sequence of events in patients undergoing ileal resection.[10] 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.[20] Colesevelam, a more potent bile acid sequestrant, was developed a few years ago, and its off label utility in diarrhea associated with bile acid malab-

Hofmann, Mangelsdorf, Kliewer

Raised 7aOH-4-Cholesten-3-one (C4) in Patients with Chronic Bile Acid Diarrhoea



Walters *et al.* Clin Gastro Hep 2009; 7: 1189

Fasting blood samples from 17 patients and 19 healthy controls

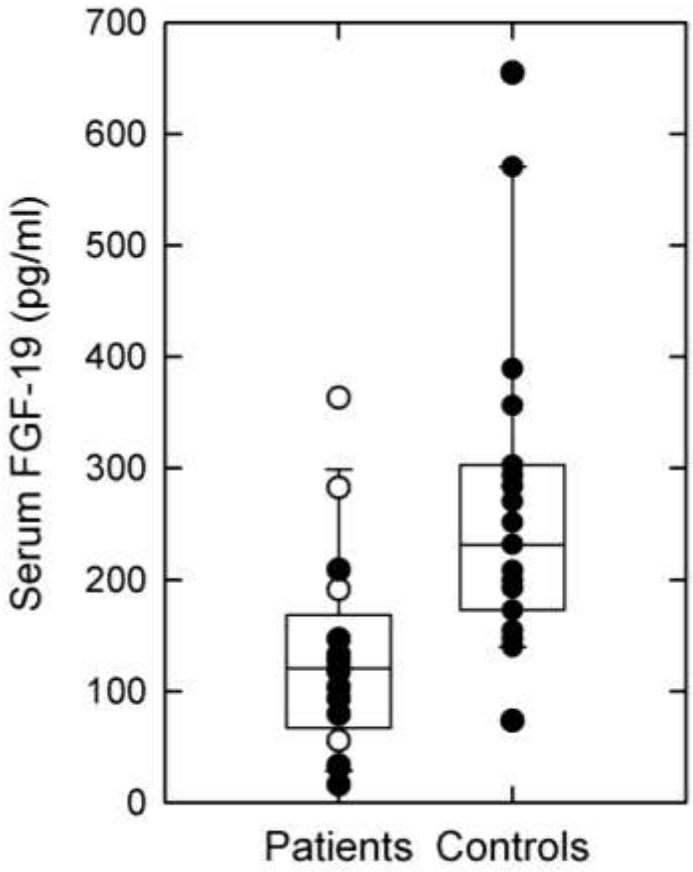
SeHCAT in 13 patients (all < 8%)

Medians & quartiles

***p* < 0.001**

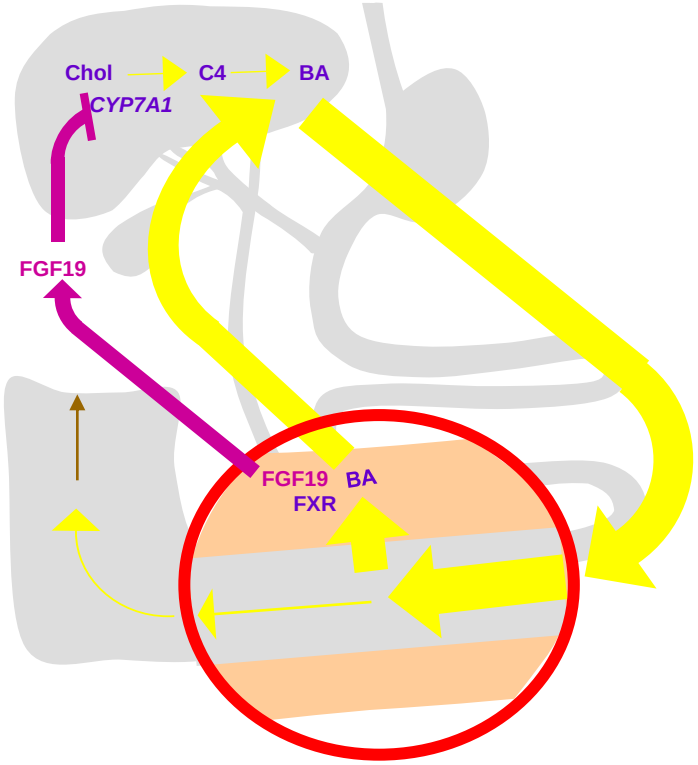
Reduced FGF19 in Patients with Chronic Bile Acid Diarrhoea

Walters *et al.* Clin Gastro Hep 2009; 7: 1189

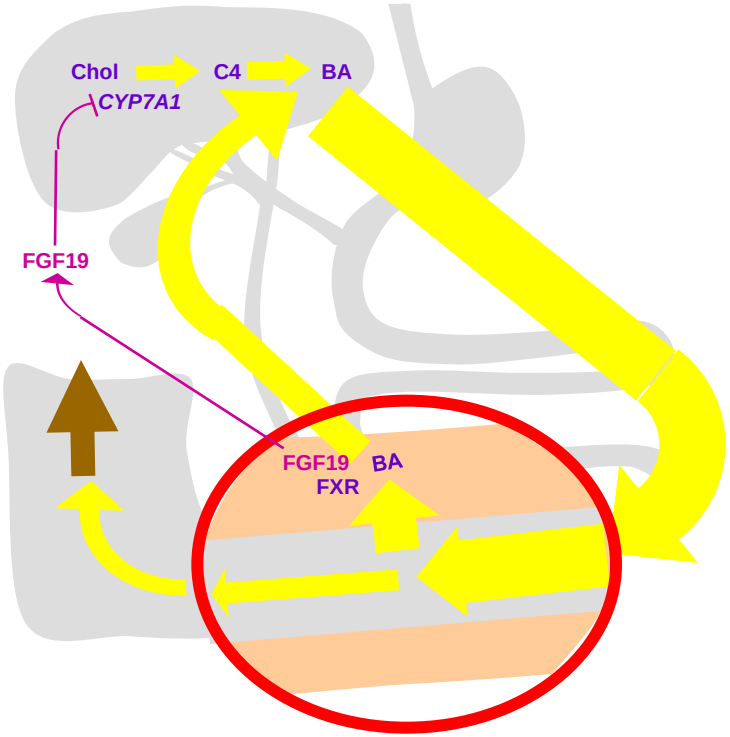


Significantly lower FGF19 in patients
$p < 0.005$

FGF19 & Primary Bile Acid Diarrhoea



Normal



Bile acid diarrhoea:
↓ FGF19
↑ BA synthesis
↑ BA entering colon
↑ Secretory diarrhoea

Walters *et al.* Clin Gastro Hep 2009; 7: 1189

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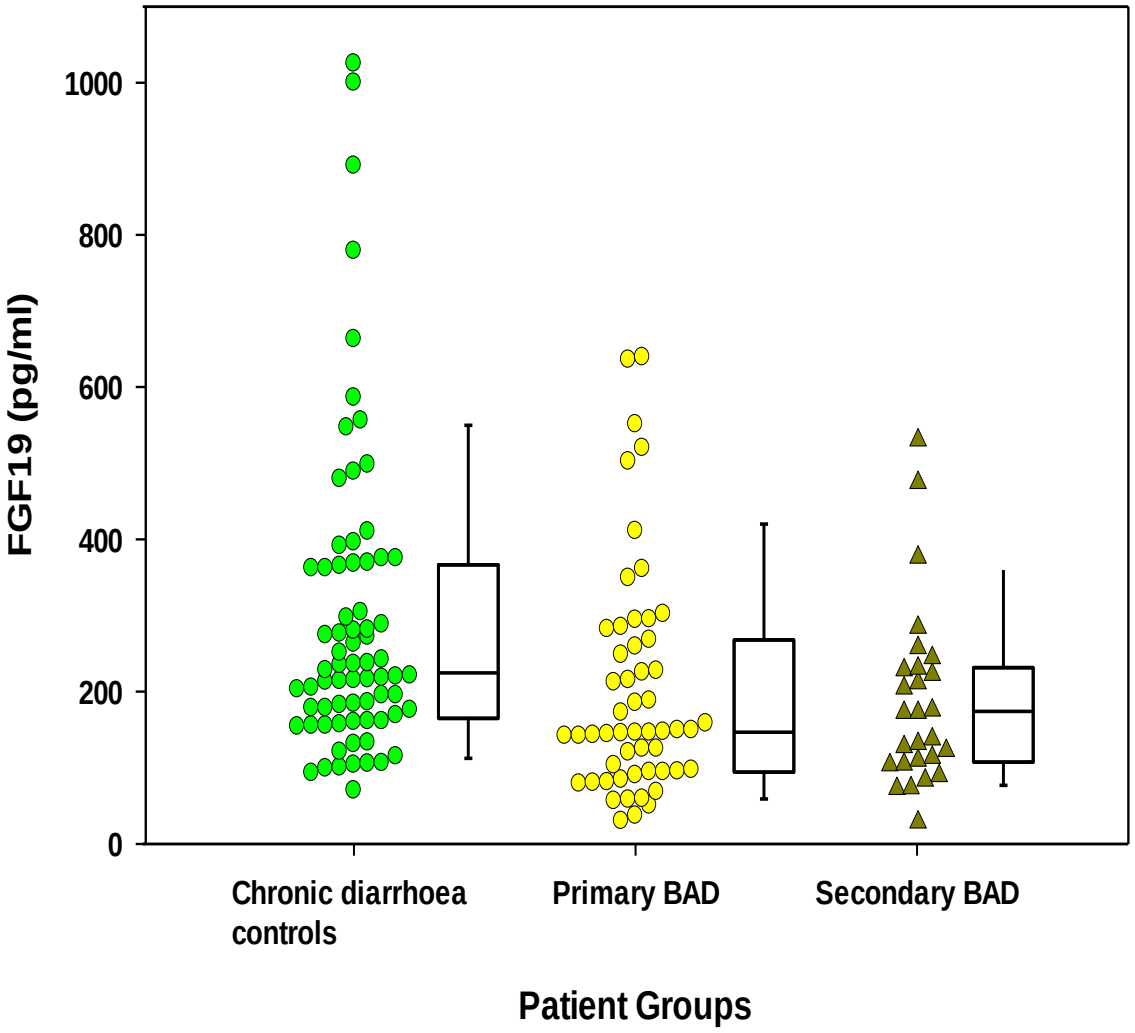
FGF19 in Prospective Groups with Chronic Diarrhoea



Pattni *et al.* APT, 2013; 38: 967–976

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

p **< 0.001**

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Clinical picture in Chronic Diarrhoea Patients with Negative or Positive SeHCAT Values

Pattni *et al.* APT, 2013; 38: 967–976

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

** $p<0.01$; * $p<0.05$
Median and IQR

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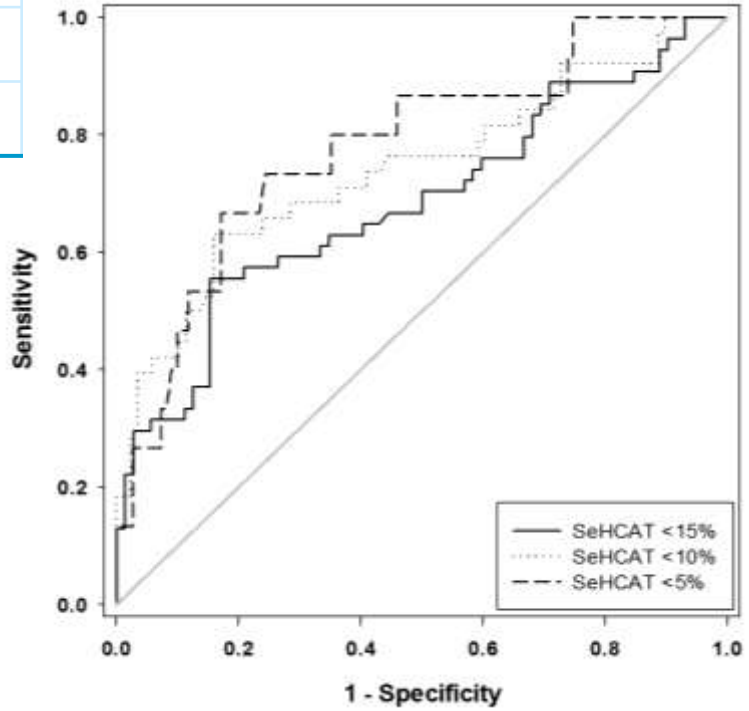
FGF19 & Prediction of SeHCAT – ROC Analysis

Frequency of low FGF19 values in different SeHCAT groups

	SeHCAT value	Total number	FGF19 ≤145pg/ml n	FGF19 ≤145pg/ml %
Normal	>15%	72	11	15%
Primary BAD	10-15%	16	3	19%
	5-10%	23	12	52%
	0-5%	15	10	67%

Pattni *et al.* APT, 2013; 38: 967–976



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FGF19 & Prediction of Response

Pattni *et al.* APT, 2013; 38: 967–976

Response to bile acid sequestrants (Cholestyramine or Colesevelam) in Primary Bile Acid Diarrhoea

	FGF19	
	> 145pg/ml	≤ 145pg/ml
Total	12	16
No response or partial response	6	1
Full response	6	15

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 (Fisher's exact test).

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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

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

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

Walters, Pattni 2010

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

Jacobsen *et al.* BMJ 1985

FGF19 in Different Types of Bile Acid Diarrhoea

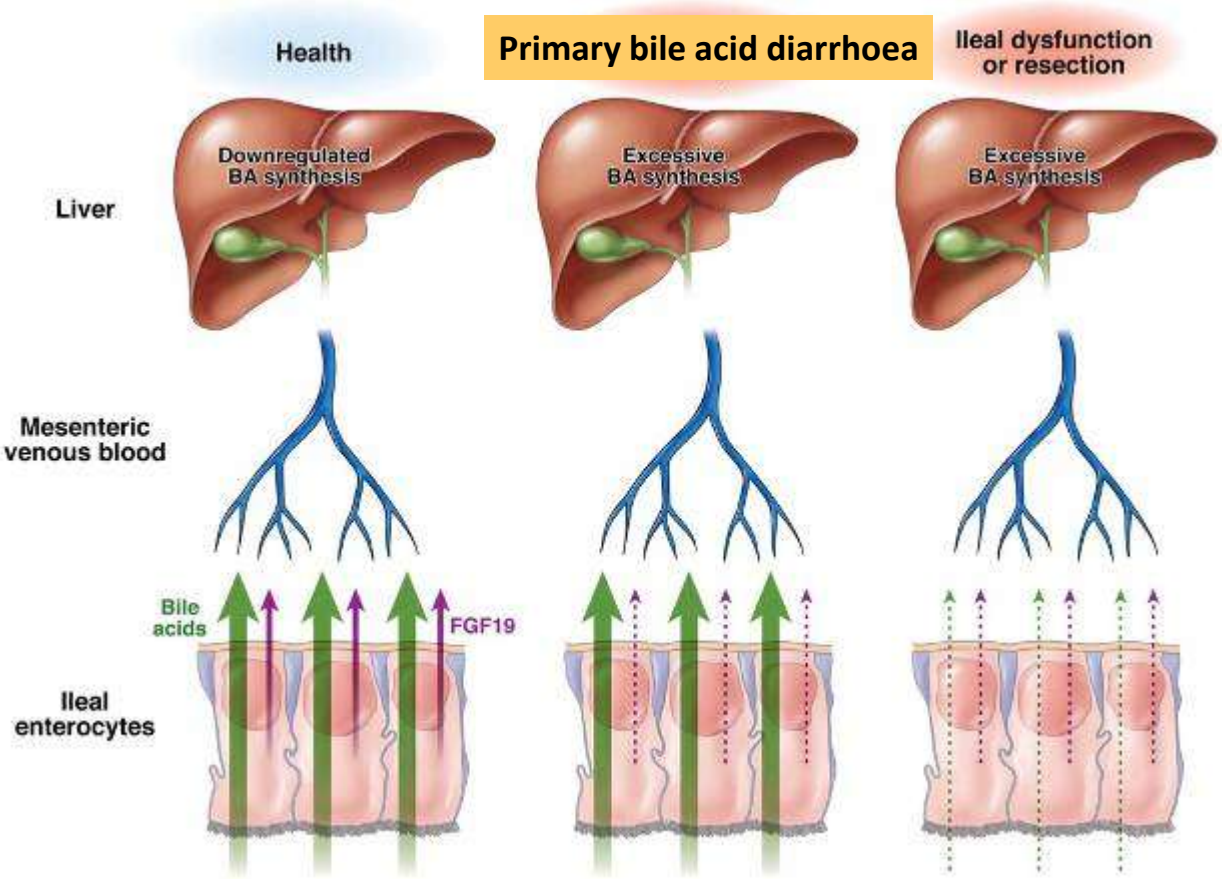


Figure 2

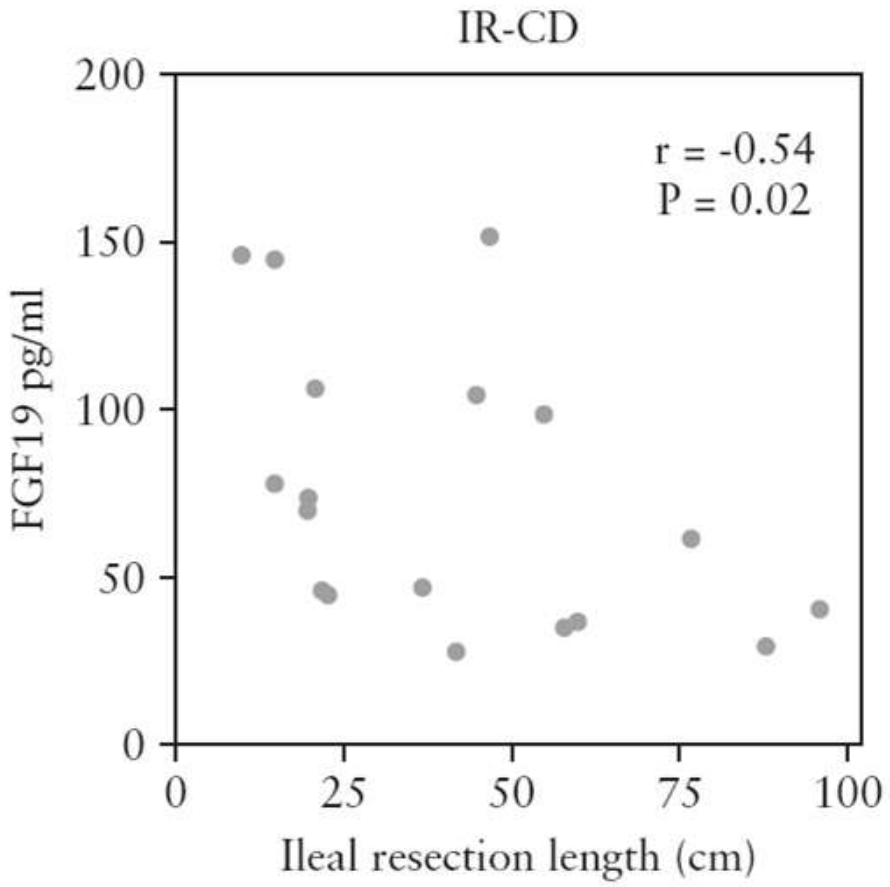
Chronic diarrhea due to excessive bile acid synthesis and not defective ileal transport: a new syndrome of defective FGF19 release.

Hofmann, Mangelsdorf, Kliewer, *Clin Gastroenterol Hepatol*. 2010.;7:1151

FGF19 in patients with Crohn's and Ileal Resection

Nolan et al. J Crohns Colitis 2015

18 patients with documented lengths of ileal resection



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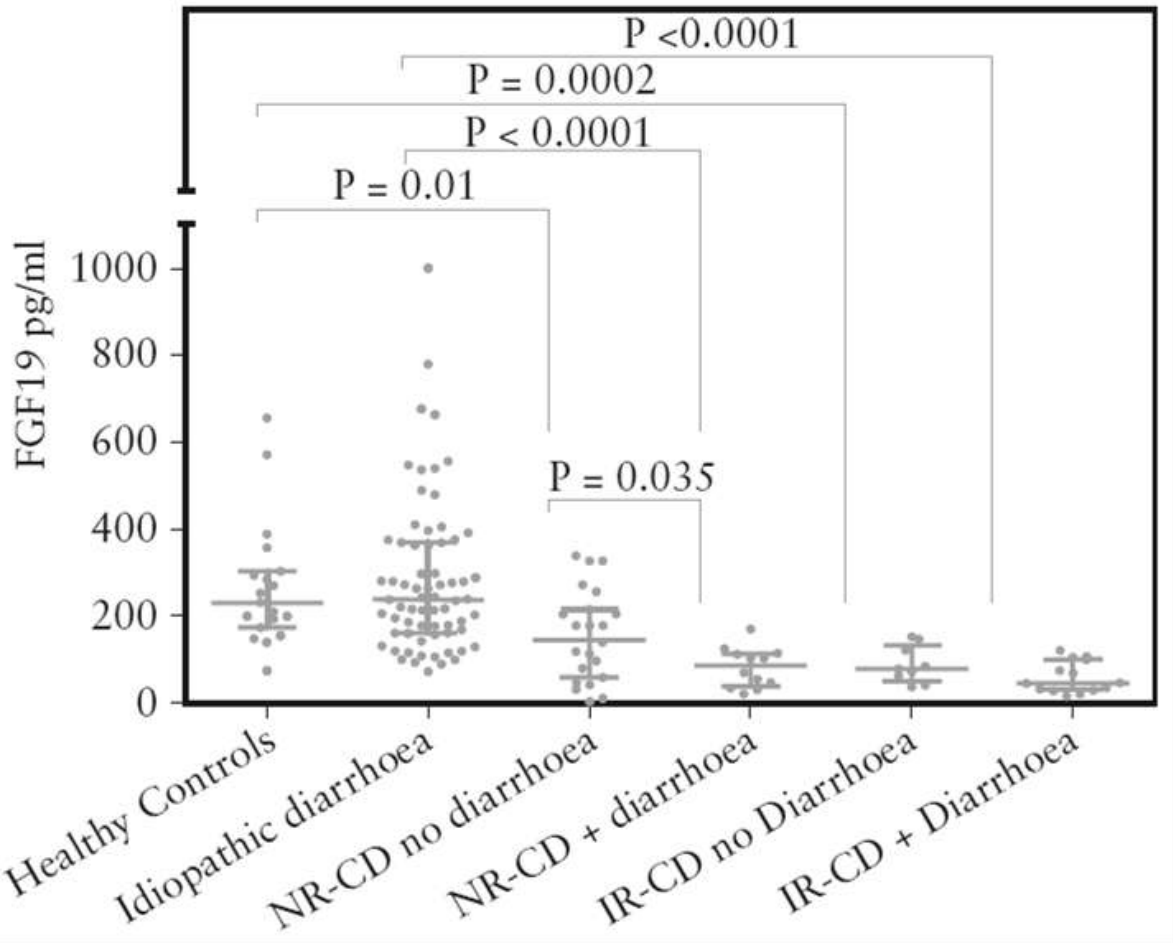
Serum FGF19 in different Crohn's patient groups

Nolan et al. J Crohns Colitis 2015

FGF19 levels lower in patients with Crohn's (CD)

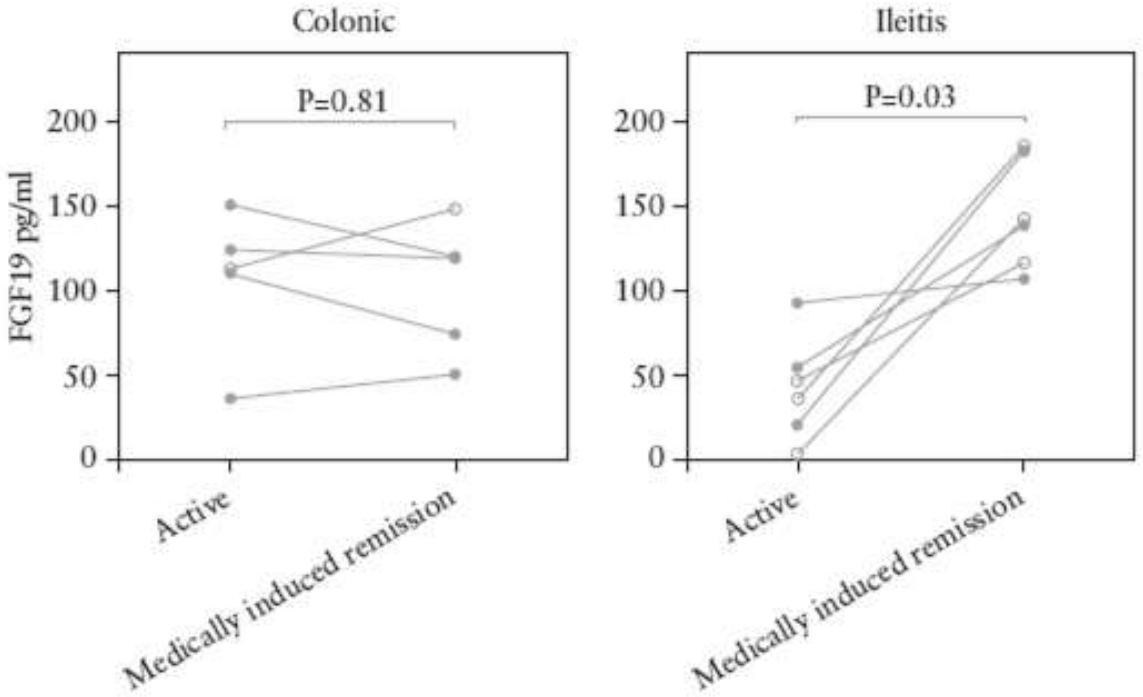
- with no resection (NR)
- diarrhoea
- active disease HBI >4
- ileal resection (IR)

Lowest levels observed in Crohn's with IR and diarrhoea



Serial serum FGF19 in treated Crohn's patients

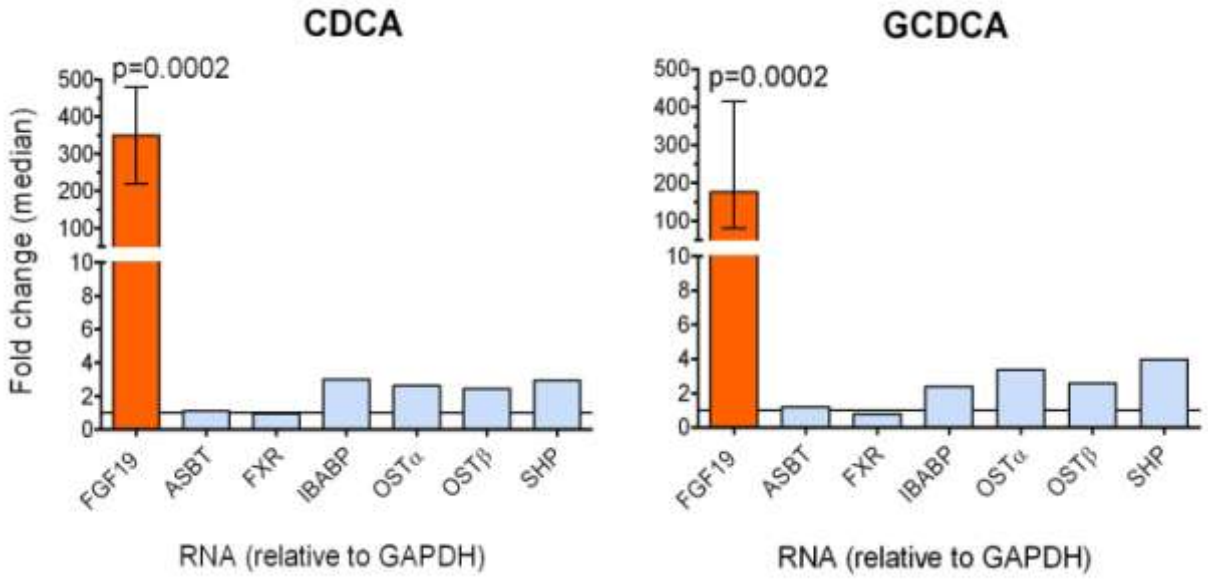
Nolan et al. J Crohns Colitis 2015

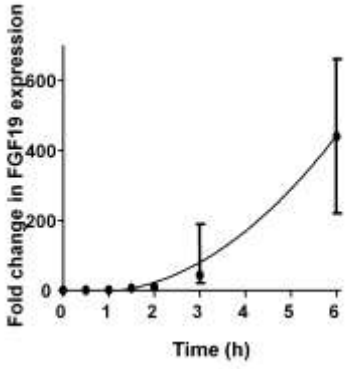


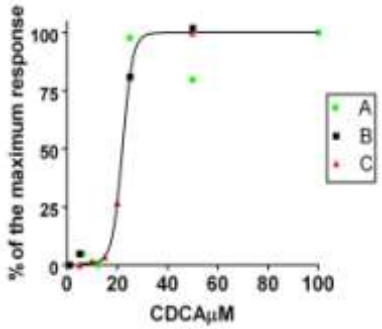
FGF19 levels increased in patients with **ileal** Crohn's treated with steroids or anti-TNFs.

FGF19 expression is highly responsive to BA compared to other BA regulatory genes in human ileum

Zhang, Nolan, Kennie, *et al*. Am J Physiol 2013; 304:G940-8







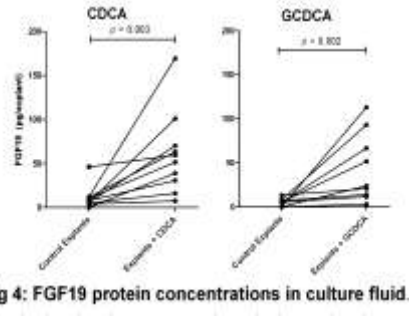


Fig 4: FGF19 protein concentrations in culture fluid.

- Ileal explants
- 6h incubations
- qRT-PCR
- Induction of FGF19 RNA & protein
- FGF19 greater than other transcripts

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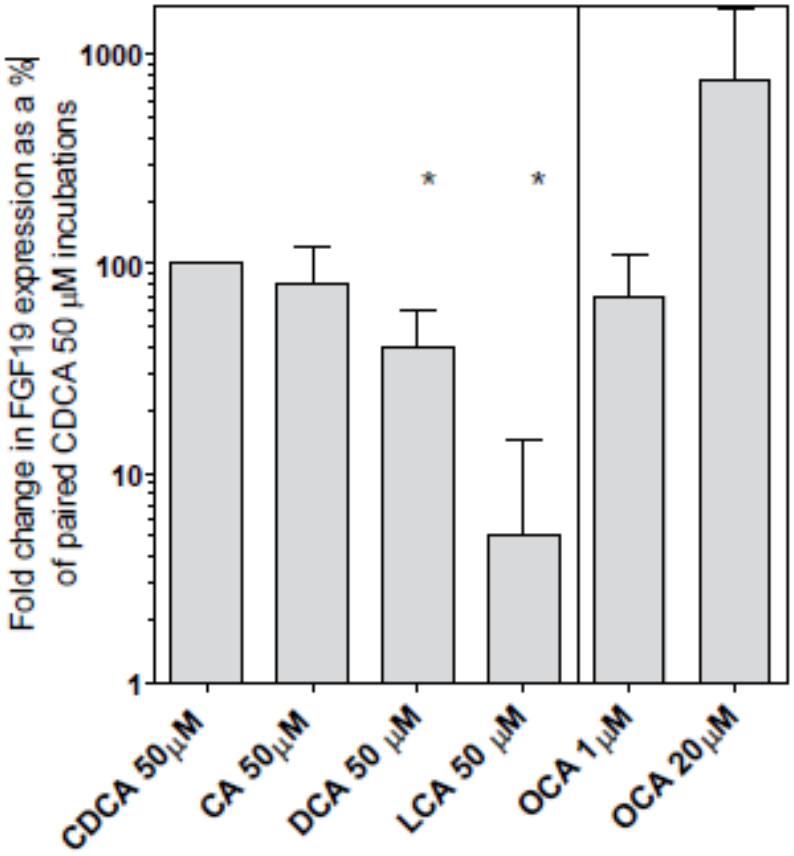
Human ileal FGF19 expression: Stimulation by natural bile acids & obeticholic acid

Zhang, Nolan, Kennie, *et al*. Am J Physiol 2013; 304:G940-8



CDCA = CA > DCA > LCA

OCA 1µM = CDCA 50µM

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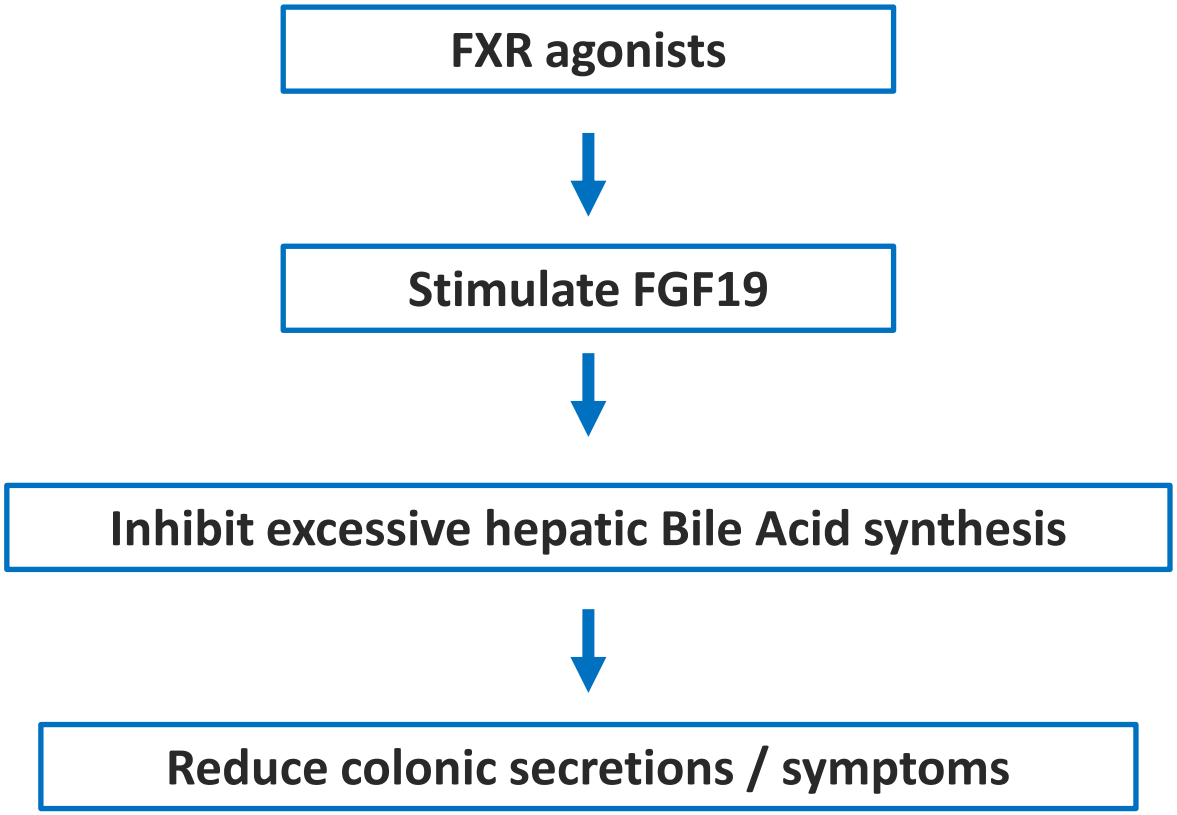
FXR Agonists as Treatment for BAD?



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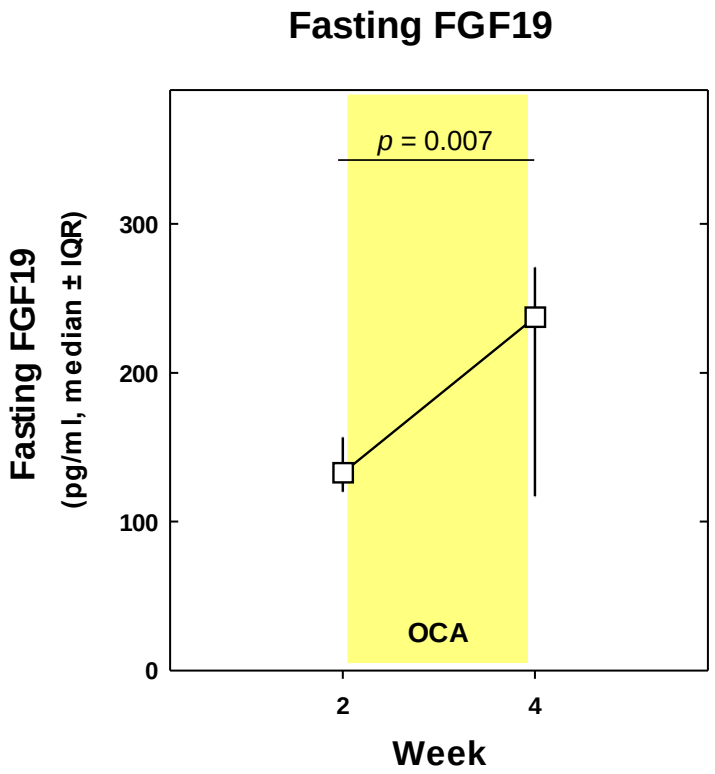
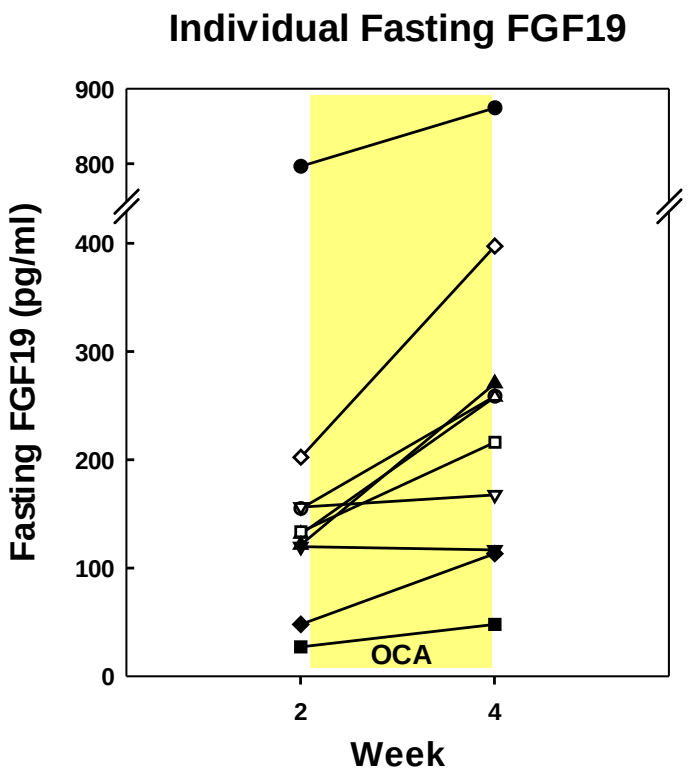
Obeticholic acid (OCA) in Primary BAD: FGF19 results





- 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

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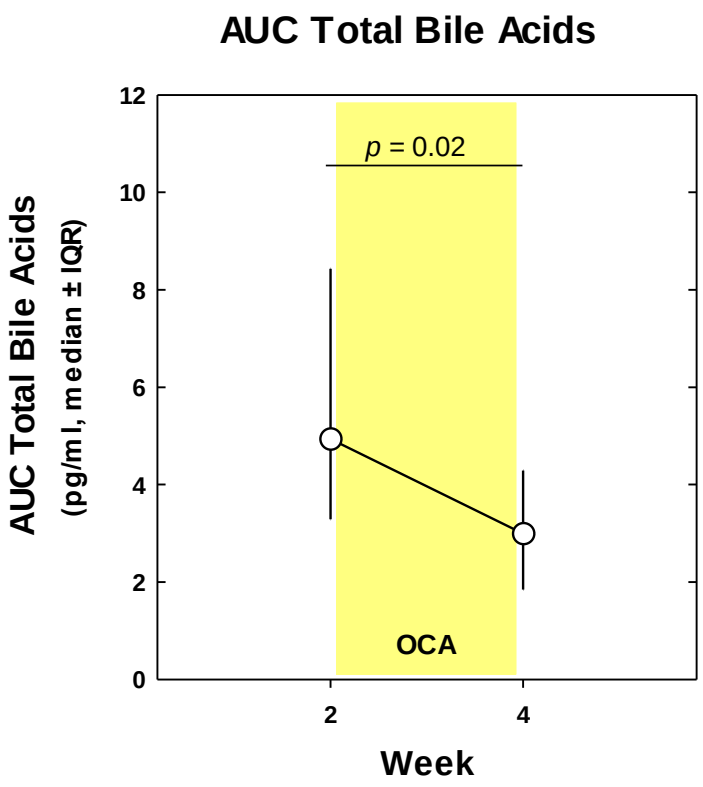
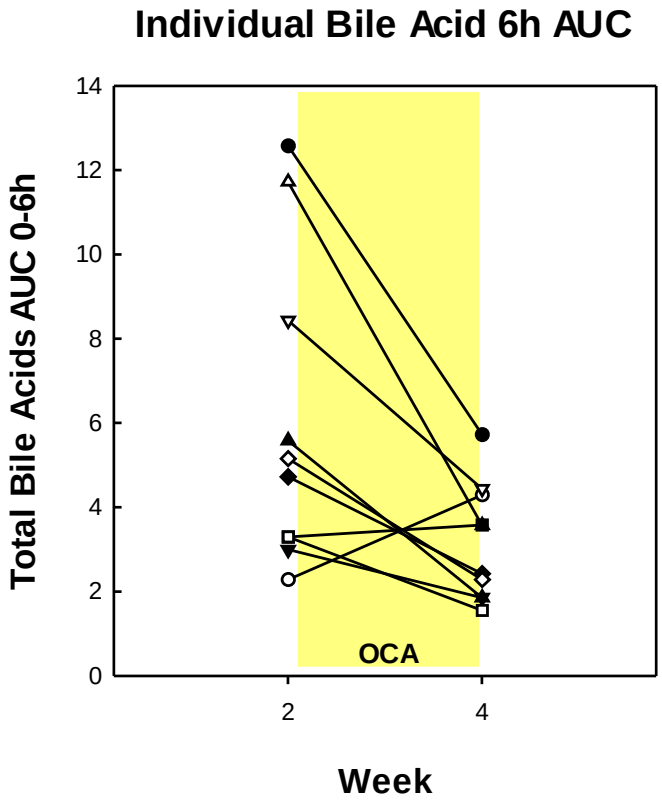
Obeticholic acid (OCA) in Primary BAD: Total Bile Acids Area under the Curve 0 – 6h





- 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

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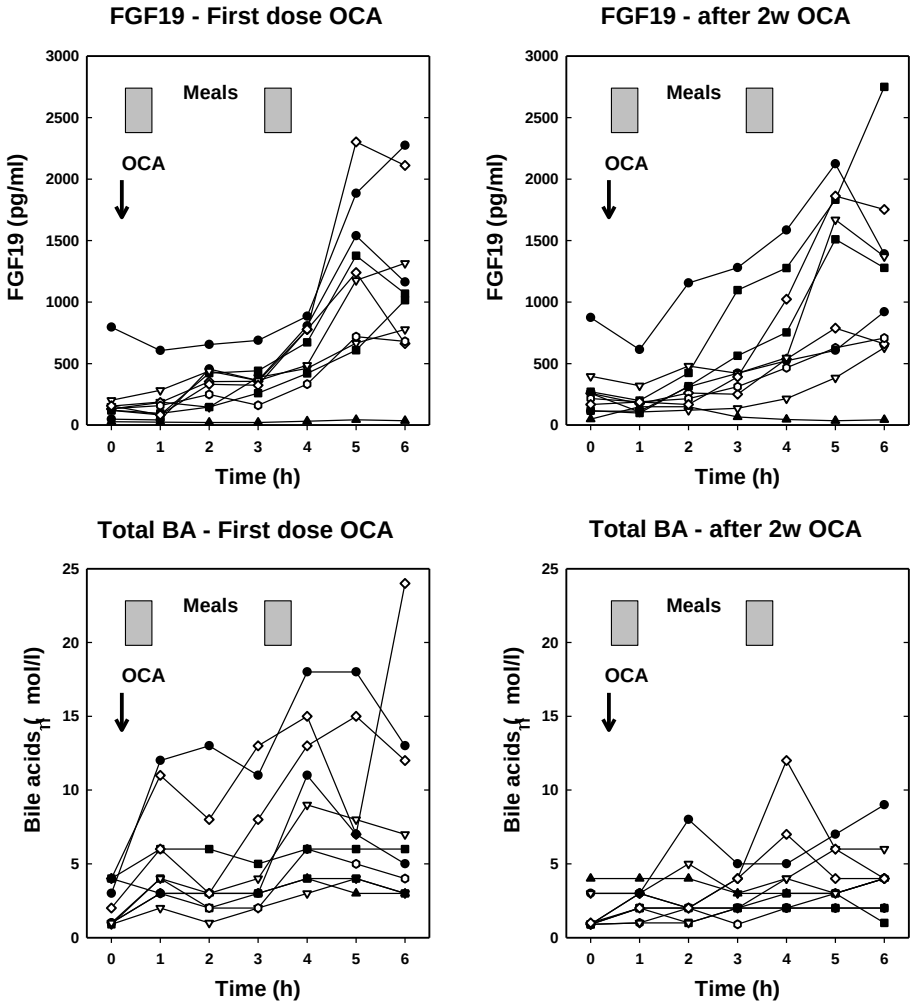
Results: Individual FGF19 and Total Bile Acid Responses



- 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

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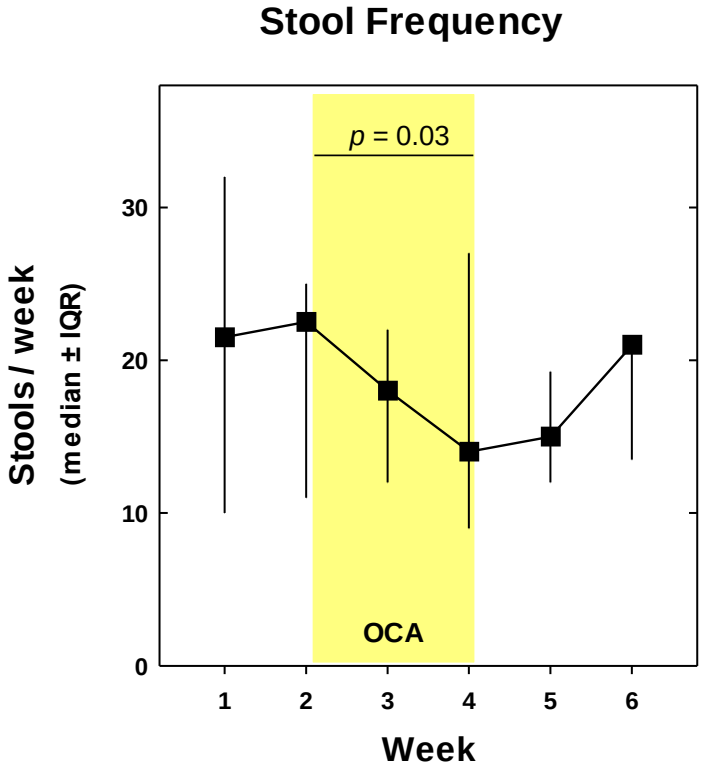
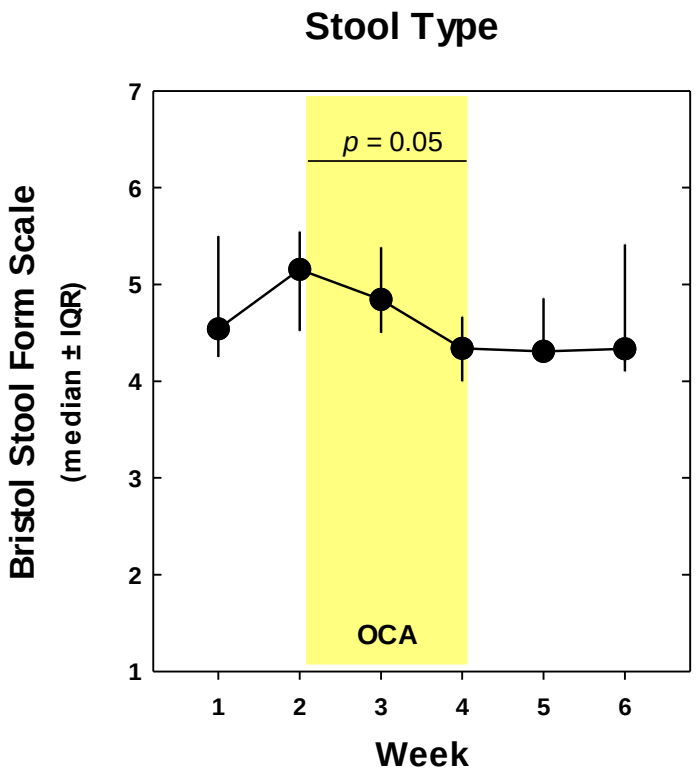
Obeticholic acid (OCA) in Primary BAD: Stool Frequency & Type





- 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

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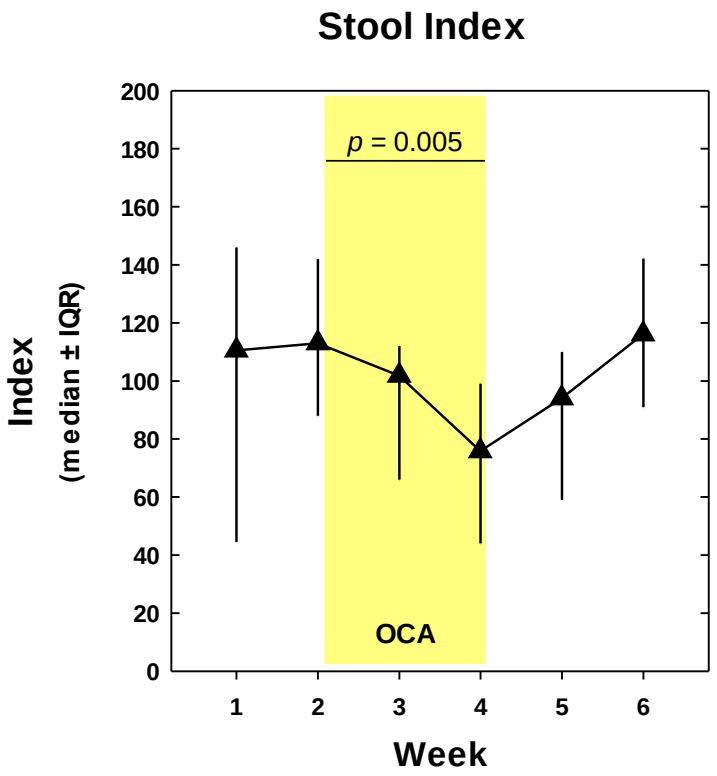
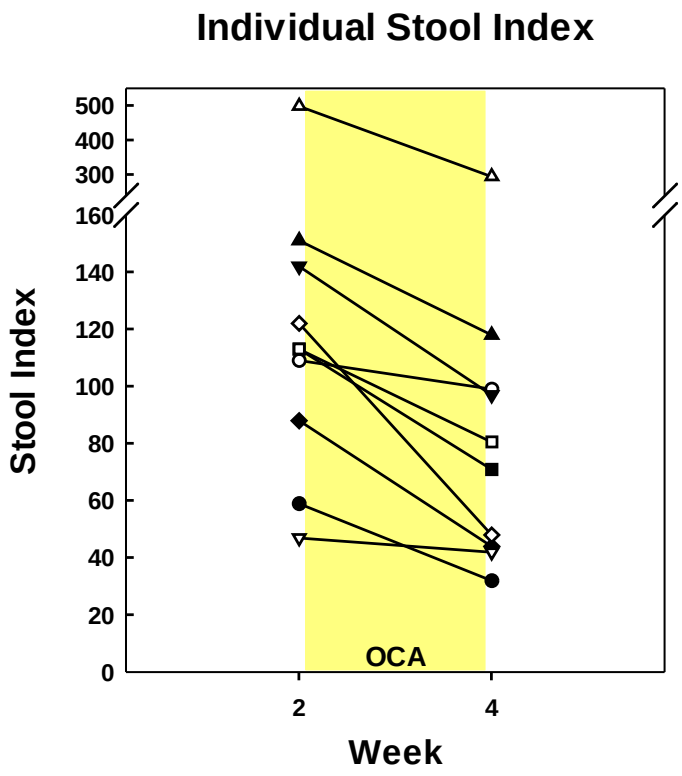
Obeticholic acid (OCA) in Primary BAD: Stool Index





- Stool index = (weekly frequency X average stool form) + loperamide use (mg x 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

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Primary Bile Acid Diarrhoea as an Endocrine Disorder: Pathophysiology

Condition	Primary BA Diarrhoea	Diabetes
Main symptom	**Diarrhoea**	**Polyuria**
Direct cause	**Excess faecal Bile Acids**	**Excess urinary Glucose**
Pathophysiological problem	**Unregulated Bile Acids metabolism**	**Unregulated Glucose metabolism**
Hormone regulating metabolism	**FGF19**	**Insulin**
Defect on feeding	**Impaired production**	**Impaired production (T1D)**
Other causes	**? Impaired receptor function**	**Impaired receptor (T2D)**

Walters JRF. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. *Expert Rev Gastroenterol Hepatol* 2010; 4: 561-567

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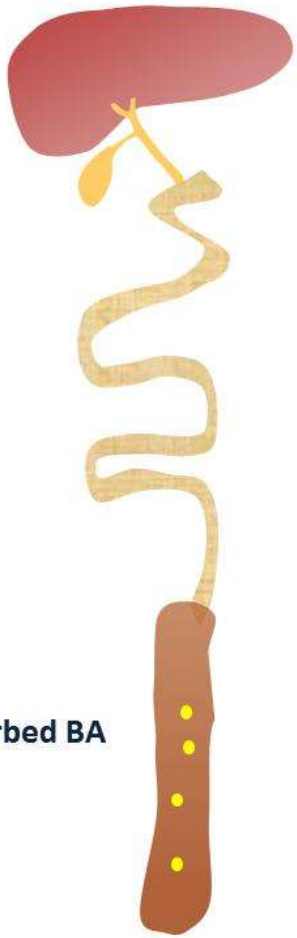
Primary Bile Acid Diarrhoea as an Endocrine Disorder: Diagnostic Strategies

	Primary BA Diarrhoea	Diabetes
Hormone levels	**FGF19**	**Insulin**
Regulated product	**BA; C4**	**Glucose**
Pathophysiological problem	**Excess BA secretion; Faecal BA**	**Hyperglycaemia; Glycosuria**
These vary cyclically after meals as they are dependent on synthesis, absorption and hormone action		
Tests that integrate function over multiple cycles	**SeHCAT**	**HbA1C**

Walters JRF. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. *Expert Rev Gastroenterol Hepatol* 2010; 4: 561-567

Mechanisms affecting the development of Bile Acid Diarrhoea

Tissue	*Physiological process*	*Major factors*	*Other factors*
Liver	**BA synthesis** **BA uptake** **BA conjugation**	**FXR** **FGFR4** **B-Klotho**	Other genes Micro-RNAs
Gallbladder	**BA secretion**	**Recycling rate** **CCK**	FGF19
Duodenum + jejunum	**BA integrity**	**SI bacteria (deconjugation)** **SI motility**	Other dietary factors
Ileum	**BA reuptake**	**Ileal mass** **ASBT , FABP6** **OSTα/OSTβ**	
	FGF19 feedback	**FXR** **FGF19**	Inflammatory cytokines Diet1
Colon	**Effects of unabsorbed BA**	**Bacterial metabolism (to DCA / LCA)** **Anion secretion** **Colonic motility**	Microbiome FXR TGR5
		Overall response	Visceral sensitivity Psychological response



Walters. Nat Rev Gastroenterol Hepatol 2014; 11:426–434

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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

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