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Recent advances in the understanding of bile acid malabsorption

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Abstract

Introduction Bile acid malabsorption (BAM) is a syndrome of chronic watery diarrhoea with excess faecal bile acids. Disruption of the enterohepatic circulation of bile acids following surgical resection is a

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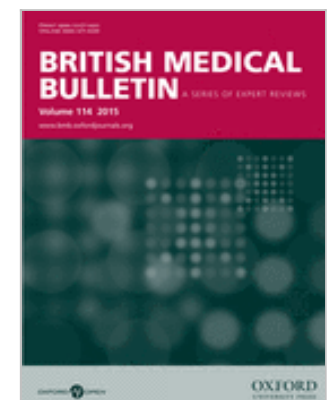
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common cause of BAM. The condition is easily diagnosed by the selenium homocholic acid taurine (SeHCAT) test and responds to bile acid sequestrants. Idiopathic BAM (IBAM, primary bile acid diarrhoea) is the condition where no definitive cause for low SeHCAT retention can be identified.

Sources of data Review of PubMed and major journals.

Areas of agreement Evidence is accumulating that BAM is more prevalent than first thought. Management of chronic diarrhoea involves excluding secondary causes. Treatment of the condition is with bile acid binders.

Areas of controversy SeHCAT testing is not widely performed, limiting awareness of how common this condition can be. The underlying mechanism for IBAM has been unclear.

Growing points Increasing awareness of the condition is important. Alternative mechanisms of IBAM have been suggested which involve an increased bile acid pool size and reduced negative feedback regulation of bile acid synthesis by FGF19. New sequestrants are available.

Areas timely for developing research Further research into the precise mechanism of IBAM is needed. Improvements in the recognition of the condition and optimization of treatment are required.

Key words [bile acid malabsorption](#) ● [diarrhoea](#) ● [SeHCAT](#) ● [mechanisms](#)

Introduction

In patients with bile acid malabsorption (BAM), a larger amount of bile acids than normal spill into the colon, where they stimulate electrolyte and water secretion which results in the typical symptoms of BAM: chronic watery diarrhoea. The concept that bile acids can cause diarrhoea dates back to 1967 when it was first described by Hofmann.¹

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Patients with mild to moderate bile acid malabsorption present solely with watery diarrhoea, while those with severe BAM may also have steatorrhoea. In general, patients respond well to treatment with bile acid sequestrants, such as colestyramine, with significant reduction in bowel frequency and a better quality of life.²

Idiopathic BAM, where there is no obvious cause, occurs in both men and women, mostly between the ages of 30 and 70.³ There is often a long history of diarrhoea, sometimes exceeding 10 years. The diarrhoea is continuous or intermittent, and nocturnal diarrhoea can occur. Mean stool volumes are moderately increased (240–290 g/day), but can be voluminous, up to 900 g/day.⁴

Although the condition is far from life threatening, it can have a significant impact on a patient's lifestyle due to the fact that the increased frequency of bowel motions often dictates the day-to-day functioning, limiting the ability to travel or leave the house.

Bile acid malabsorption has been identified in frequent reports as a possible explanation for persistent chronic diarrhoea, but it has commonly been regarded as rare and of limited importance in clinical practice. It is often far down the list of causes of chronic diarrhoea, and only considered after conditions such as inflammatory bowel disease, colonic cancer, coeliac disease and colonic infections have been excluded.

Investigations to diagnose BAM such as selenium homocholic acid taurine (SeHCAT) tests (see what follows) are not routinely performed at many district general hospitals; the diagnosis is then usually made by a trial of treatment. Overall, this delays diagnosis and treatment and BAM is felt by experts to be an under-recognized cause of chronic diarrhoea. It is often misdiagnosed as diarrhoea-predominant irritable bowel syndrome (IBS). IBS patients are the largest group of patients

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seen in a general gastroenterology clinic. Many studies suggest that 30–50% of patients with previous unexplained chronic diarrhoea have impaired BAM.^{5,6} This could add up to substantial numbers of undiagnosed patients: with a population of 900 million people in the Western world, approximately 90 million people suffer from IBS, of whom 30 million have diarrhoea-predominant IBS. With the above estimates that 30–50% of IBS-D can be diagnosed with idiopathic BAM, this would result in at least 10 million people with this condition in the West.⁷

Bile acid synthesis and the enterohepatic circulation

Bile acids (BA) are synthesized in the liver from cholesterol and in conjugated form are transported into bile ducts. They then accumulate and are stored in the gallbladder where they flow into the duodenum following meal-stimulated gallbladder contraction. After delivery into the intestinal lumen, the vast majority are reabsorbed by the distal ileum into the portal circulation and returned to the liver. Uptake BA by specific transport systems of hepatocytes takes place, and they are secreted again into bile. This process of recycling is called the enterohepatic circulation. A very small percentage of bile salts may be reabsorbed in the proximal small bowel by either passive or carrier mediated transport processes.⁸

Bile formation plays a vital role in intestinal lipid digestion and absorption, cholesterol homeostasis and excretion of lipid soluble xenobiotics (substances naturally present in or added to foods that do not contribute usefully to metabolic function) and heavy metals. The maintenance of hepatic bile formation is essential for normal liver function. Disturbance in BA homeostasis can lead to liver disease, cholesterol gallstones and malabsorption. A number of feedback mechanisms exist in order to sustain sufficient pools of BA.⁹

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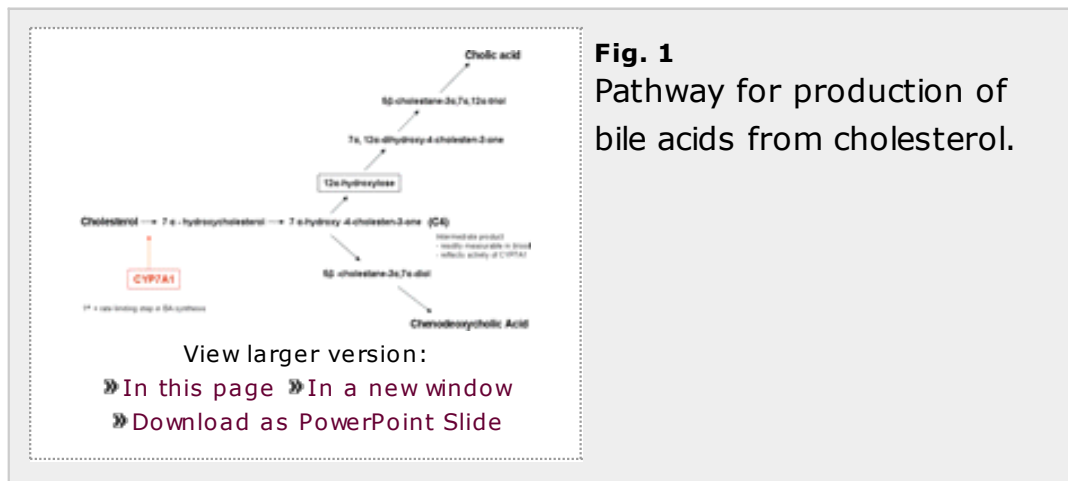
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A small proportion of BAs secreted escapes the intestinal absorption (3–5%) and is irreversibly excreted in the faeces.¹⁰ About 95% of BA's are recycled due to reabsorption in distal ileum by an efficient and well-characterized sodium-dependent apically located bile acid transporter system^{11,12} (see what follows).

Studies by Ung *et al.*¹³ in 2004 to determine active BA absorption in small biopsy specimens, obtained endoscopically or surgically from human intestine, showed that active uptake of BA occurs in the very distal part of ileum and up to 100 cm proximal to ileo-caecal valve.

In humans, daily synthesis to replenish loss is of the order of 600 mg; this allows the maintenance of a pool of 3–5 mmol; the pool cycles 6–10 times in a day. Thus, hepatic secretion amounts to 20–30 mmol per day.¹⁴

Bile acid synthesis occurs via two pathways: the classical pathway (neutral pathway), which utilizes microsomal cholesterol 7 α -hydroxylase (CYP7A1), or by mitochondrial sterol 27-hydroxylase (CYP27A1) of the alternative (acidic pathway).¹⁵ The classical pathway begins with 7 α -hydroxylation of cholesterol catalysed by CYP7A1, which is thought to be the rate limiting step in BA synthesis¹⁰ (Fig. 1).



The classical pathway of BA synthesis occurs exclusively in the liver and gives rise to the two primary BA: cholic acid and chenodeoxycholic acid. The types of the common mammalian BA and their individual kinetics are shown in Table 1.

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Table 1
Names and kinetics of individual bile acids in humans.¹⁷

One of the intermediate products in the bile acid synthesis pathway is 7 α -hydroxy-4-cholesten-3-one (C4). This is readily measurable in peripheral blood samples and its serum concentrations have been shown to accurately reflect the activity of hepatic cholesterol 7 α hydroxylase (CYP7A1), the first enzyme and the rate-limiting step in bile acid synthesis pathway.¹⁶

The newly synthesized primary bile acids are conjugated with glycine or taurine and are readily secreted from the biliary tree into the duodenum following food ingestion. In humans, the majority of biliary bile acids are conjugated to glycine.¹⁷

Conjugation with taurine or glycine increases the hydrophilicity of bile acid and the acidic strength of its side chain. Consequently, this decreases the passive diffusion of BAs across cell membranes during their transit through the biliary tree and small intestine.¹⁸ Conjugation of BAs are therefore only absorbed if a specific membrane carrier is present. The net effect of conjugation is to maintain high luminal micellar concentrations of BAs in order to facilitate lipid digestion and absorption down the length of small intestine.

Regulation of bile acid synthesis



The regulation of bile acids is by a homeostatic mechanism in which bile acids returning to the liver from the distal ileum inhibit their own synthesis (negative feedback). In this regulatory pathway, the returning BAs bind to a nuclear Farnesoid X Receptor (FXR) in the liver, which induces expression of Small Heterodimer Partner (SHP), which in turn inhibits the expression of Liver Receptor Homologue 1 (LRH1); this is an orphan receptor required for CYP7A1 promoter activity and hence transcription of CYP7A1 is suppressed.¹⁹ In addition to this cascade of events, recent studies in mice indicate that intestinal fibroblast growth factor 15 (FGF15) may function as a secretory signal acting on the liver through the hepatic FGF receptor 4 (FGFR4) and leading to suppression of CYP7A1.²⁰ FGF15 and its human orthologue FGF19 has been shown to be expressed in the small intestine and more recently it has been shown that BAs within the liver itself may activate the liver FGF19/FGFR4 signalling pathway to inhibit bile acid synthesis and prevent accumulation of toxic bile acid in the liver.²¹ This may well be a protective adaptation, particularly under conditions of extrahepatic cholestasis.²²

Of interest also is the diurnal regulation of BA production, and the relationship of this with diurnal rhythm changes in FGF19 levels. BA synthesis in humans shows two distinct peaks during the day.²³ Work done by Lundasen *et al.*⁹ showed that FGF19 has a diurnal rhythm with two peaks occurring around 3 and 9 pm. FGF19 peaks in serum with a delay of 90–180 min following the peak of serum BAs. These results support the theory that FGF19 is secreted from the small bowel in response to the postprandial increase in transintestinal BA flux. FGF19-mediated suppression of BA synthesis is reflected by the temporal relationships between FGF19 and C4.

Bile acid malabsorption



Failure of absorption of bile acids by the distal ileum results in spillover of BAs into the colon where they cause loose, watery stools. BAs in the colon, particularly the dihydroxy BAs, chenodeoxycholic and deoxycholic acids, lead to this diarrhoea by various mechanisms including:

- i. inducing secretion of sodium and water, particularly at concentrations above 3 mmol/l²⁴
- ii. increasing colonic motility
- iii. stimulating defaecation
- iv. induce mucus secretion
- v. damage to mucosa increasing mucosal permeability.²⁵

BAM has been divided into three types depending on their aetiology, as shown in Table 2.⁵ The prevalence of sub-groups of BAM can vary; in one study, type 3 BAM represented 51% of all cases of patients positive for SeHCAT over a 5-year period. Cholecystectomy was the commonest cause in this group and represented 24% of cases. Type 1 BAM was seen in 16% of cases of the positive SeHCAT group.²⁶

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Table 2

Classification and aetiology of BAM (types 1–3).

Diagnosis of BAM

SeHCAT

The commonly used test for diagnosis of BAM is the Selenium-homocholeic acid taurine (SeHCAT) test. The Se-labelled bile acid is administered orally and the total body retention is measured with a gamma camera after 7 days. Retention value of less than 10% is

considered abnormal and indicative of BAM.^{27,28} Diarrhoea in patients with greatly reduced SeHCAT retention usually responds to oral colestyramine which binds to bile acids in the gut.⁶ The SeHCAT test is able to evaluate BAM with a sensitivity of 80–90% and specificity of 70–100%. It offers a relatively low radiation dose to the patient (0.26 mSv), equivalent to a plain chest x-ray, compared with a typical CT abdomen (3.0 mSv).²⁹

However, the use of a radioactive test substance and the need for repeated measurements of radioactivity by a highly sensitive counting system restricts the general use of the SeHCAT test. Moreover, the SeHCAT test has not been approved by the drug administration agencies of many countries, including the USA, limiting awareness of how common this condition can be.

Caution should be used in patients with liver disease as this condition may interfere with the SeHCAT results. In addition, the presence of bacterial overgrowth in the small bowel may influence the interpretation of the SeHCAT test.

Faecal bile acids

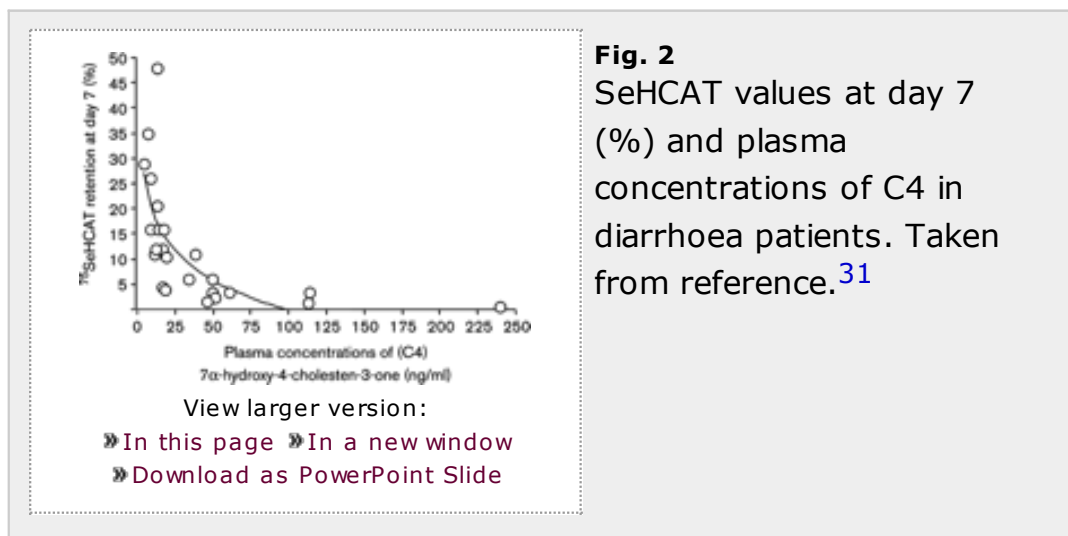
Prior to the established use of SeHCAT in the 1980s, the diagnosis was based upon quantification of faecal bile acids in a 24-h stool collection, where levels exceeding 1.2 mmol/l are considered abnormal.⁴ Some would argue that this is a more accurate measurement of bile acid loss and hence should be the ideal test to perform. The measurements of faecal bile acids, however, are not available in most hospital laboratories and are now only performed in specialized research laboratories. Moreover, the practical aspect of collecting 24 h faecal collection is poorly reproducible and unpleasant for both the patient and laboratory technician.

Trial of treatment

The general approach to the diagnosis of BAM as a cause of chronic diarrhoea in district general hospitals is a trial of a bile acid binder. If the treatment results in amelioration of diarrhoea, the response is seen as an indirect proof of BAM. BAM is a chronic condition and it is therefore important to establish the diagnosis as it requires lifelong treatment.

Cholestenone

Increased activity of hepatic cholesterol 7 α hydroxylase (CYP7A1) results in increased BA synthesis, with a parallel increase in serum levels of the precursor, 7 α -hydroxy-4-cholesten-3-one (C4). In patients with IBAM, BA synthesis has been shown to remain high, which is reflected by elevated levels of C4.^{30,31} Levels of BA synthesis therefore can be determined by measuring C4 using a high pressure liquid chromatography (HPLC) test. The positive predictive value of serum C4 is 74%, but the high negative predictive value of 98% would allow the use of this test for excluding BAM. Studies have shown a significant negative correlation between the SeHCAT retention and C4 (Fig. 2).^{30,31}



The advantages of this test are that only a serum sample from the patient is needed, there is no exposure to radiation, and it is less time-

consuming for the patient. The test, however, is laborious and time-consuming and is not widely available.

Treatment of BAM

The main treatment goal with type 2, idiopathic bile acid diarrhoea, is control of diarrhoea with oral administration of bile acid binders. These mop up free bile acids in the small bowel and prevent the secretory action bile acids on the colonic mucosa. BAM in patients with active inflammation of the terminal ileum in Crohn's disease may improve with glucocorticoids to induce remission.³² The underlying cause should be sought after and treated for patients with type 3 BAM, but they may also require a bile acid binder.

There are currently three bile acid sequestrants available: colestyramine, colestipol, colesevelam. They have been shown to be effective in the control of bile acid-induced diarrhoea. The standard dose for each sequestrant can be titrated up or down in the individual patient depending upon response. In our experience, one sachet of colestyramine taken at night is often sufficient in controlling diarrhoea. Addition of further doses can often lead to overcompensation resulting in constipation. These drugs are not absorbed in the intestine and therefore have no systemic side effects. The added benefit of the use of these drugs is their cholesterol lowering effect.

Colestyramine and colestipol are anion exchange resins that form complexes with organic anions such as bile acids with high affinity.² The main disadvantage of colestyramine is an unpleasant taste, which can lead to intolerability and poor compliance. Colestyramine is generally well tolerated, with constipation being the main side effect. Other side effects include nausea, borborygmi, flatulence, bloating and abdominal pain. They can be present in 30% of patients treated with colestyramine although the extent of severity is difficult to ascertain.²⁶ Both these

medications have multiple drug interactions because of their unspecific affinity for organic anions. Simultaneous use may reduce absorption and serum concentrations of important drugs, such as digoxin, thiazide diuretics, beta-blockers and thyroid hormones. It is recommended therefore that these drugs be administered 2 h before the bile acid binders.³³ Vitamin absorption may also be impaired.

Pooled data from 15 studies^{5,6,26,28,30,34-43} published between 1985 and 2007 suggested a dose-response relationship according to severity of diarrhoea, based upon the retention value of the SeHCAT test, and to treatment with a bile acid binder: response to colestyramine occurred in 96% of patients with <5% retention, 80% at <10% retention and 70% at <15% retention.⁷

Colesevelam is a new bile acid sequestrant that binds bile acids with a higher affinity than colestyramine or colestipol, as it forms a polymeric gel in the gastrointestinal tract. It is available in tablet form and hence bypasses the unpleasant taste of colestyramine and making it more acceptable.⁴⁴ In a recent retrospective study comparing colesevelam to colestyramine, colesevelam appeared to be effective in patients who had failed treatment colestyramine.⁴⁵

Research into mechanisms of IBAM

The pathogenesis of so-called IBAM has not been clearly understood and recent research has focused on uncovering the molecular mechanisms predisposing to this condition. These have to explain an excessive bile acid loss into the colon (which can be treated by bile acid sequestrants), a reduced SeHCAT retention and raised bile acid precursor levels. A number of mechanisms have been proposed:

- i. a defective ileal BA transport system⁴⁶
- ii. a reduced length of the segment capable of functional bile acid

uptake, or a reduced contact time due to a primary increase in small intestinal motility⁴⁷

- iii. an increase in bile acid pool size⁴ due to disordered negative feedback regulation of bile acid synthesis.⁴⁸

We will review the evidence for each of these in turn.

Ileal enterocyte bile acid transport

The transport molecules involved in the uptake of conjugated bile acids in the ileum (Fig. 3) starts with the apical sodium-linked bile salt transporter (ASBT) at the brush-border membrane.⁴⁹ Binding of the potentially toxic bile acids and transport through the cytoplasm is via the ileal bile acid binding protein (IBABP).⁵⁰ Extrusion occurs at the basolateral membrane and is now thought to occur through the organic solute transporter heterodimer α and β subunits (OST α & β).⁵¹

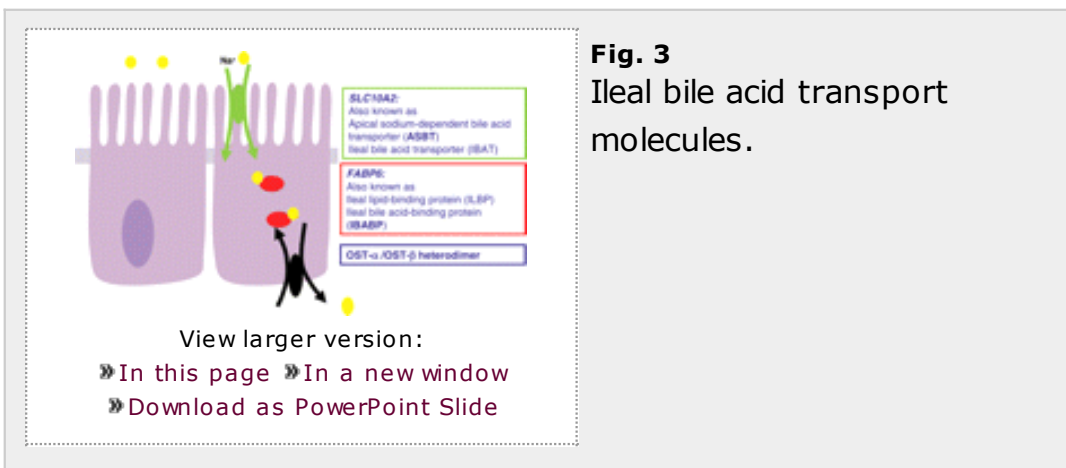


Fig. 3
Ileal bile acid transport molecules.

Originally, it was widely believed that a defective BA transport capacity may be the causative factor of BA diarrhoea. Heubi *et al.*⁵² demonstrated in two brothers an impaired ileal uptake of bile acids. In 1997, Oelkers *et al.*⁴⁶ demonstrated a mutation in the ASBT gene (*SLC10A2*) in this family. This, however, is now known to be a rare

congenital cause of IBAM, as ASBT mutations were not found to be commoner in a series of 13 patients with adult onset bile acid malabsorption than in controls.⁵³ Montagnani *et al.*⁵³ in 2006 studied a family with adult IBAM in three consecutive generations to evaluate whether there was an association of IBAM with inherited mutations affecting the ASBT. It was clearly demonstrated that there was no segregation of the bile acid malabsorption phenotype with polymorphisms in the ASBT gene.⁵⁴

Mutations in IBABP have also been studied and were no more common in patients with IBAM than in controls.⁵⁵ When ileal RNA and cDNA were prepared from patients with chronic diarrhoea and control subjects, no significant difference in mean expression of any of the transporter transcripts was found in IBAM compared with controls. There was, however, evidence to suggest there could be differences in the regulation of expression of OST α by the nuclear bile acid receptor FXR.⁵⁵

However, review of the literature indicates that there may be no overall transport defect in IBAM. Uptake of taurocholate into ileal mucosa biopsies is in fact somewhat higher than in controls.³¹ Transport studies looking at taurocholate uptake into brush border vesicles had also suggested that there was no impairment of bile acid uptake in IBAM; in fact transport was significantly higher.^{56,57} These studies are counter-intuitive for a condition described as 'malabsorption', but they encourage the suggestion that alternative mechanisms need to be considered.

The possible role of rapid small bowel transit in patients with BAM needs consideration. This would result in less time in the terminal ileum and so in reduced reabsorption of bile acids. In one study, there was no correlation between SeHCAT and small bowel transit time detected with hydrogen breath test after lactulose ingestion and with Tc⁹⁹ m-HIDA.³⁵

Rapid small bowel transit was demonstrated however in IBAM⁴⁷ and this was more obvious in women than in men.

An autoimmune phenomena have also been postulated, similar to coeliac disease, with the ileum as a target organ and resultant villous atrophy. This was seen in one study with very small numbers of patients,⁵⁸ but has not been confirmed by other studies; the current definition of idiopathic BAM requires there to be a morphologically normal ileum.

New emerging mechanisms

Recently, a mechanism involving increased bile acid losses as a consequence of defective feedback regulation is gaining momentum. Van Tilburg *et al.*⁴ showed many years ago that the mean BA pool size was larger in patients with primary BAM than controls. This and other results they found are included in Table 3, which shows a doubling of faecal bile acid loss and of the bile acid pool size. These two measurements showed a highly significant correlation. The SeHCAT retention was reduced (roughly equating to a 10% 7-day retention versus 15% in controls). Absorption of bile acids in the ileum may be somewhat increased,⁵⁷ but with greater increases in BA synthesis and secretion, BA spill over into the colon and faeces.

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Table 3

Reported bile acid kinetics and FGF19 in patients with primary bile acid diarrhoea and controls.

High transintestinal and transhepatic BA flux suppress BA synthesis in normal subjects. However, in IBAM, synthesis is increased as shown by the raised values of the BA precursor C4. This has been shown

repeatedly^{30,48} and was thought to compensate for the increased BA loss due to the 'malabsorption'. But with an increased BA pool, this may in fact be the primary disorder.

The feedback regulation of the enterohepatic circulation and hepatic BA synthesis is now thought to be mediated by fibroblast growth factor 19 (FGF19) which is the human homologue of FGF15 in mice. Data have accumulated to indicate this has an important hormonal role in suppressing hepatic bile acid synthesis. In the ileum, FGF19 is a BA responsive gene, transcriptionally activated via FXR, which is synthesized in the absorptive enterocytes.²⁰ Mice with Asbt knock-out have watery diarrhoea which responds to FGF15 treatment,⁵⁹ and so resemble IBAM. Recent data have shown that patients with IBAM have levels of FGF19 which are about 50% of controls, and this level correlates inversely with BA synthesis as measured by C4 (Table 3).⁴⁸

Hence, the disrupted feedback control by FGF19 of BA synthesis results in a cycle of excessive BA production, incomplete absorption and excess faecal loss causing diarrhoea. The precise nature of the defect in the enterocyte that leads to impaired FGF19 secretion is unclear and needs further research. Differing levels of bile acids in the enterocyte might produce different transcriptional signals on the BA/FXR-responsive genes, with greater stimulation of OSTα than FGF19, for instance. Our previous work indicated subtle differences in the relationships of different transcripts in the ileum,⁵⁵ and this will need to be explored further, together with resequencing of the promoter and enhancer regions of the relevant genes. Other studies centred around FGF19 are likely to be the focus of investigation into the mechanism of IBAM for some time.

Conflict of interest: J.R.F.W. has acted as an advisor to GE Healthcare.

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