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TOPIC HIGHLIGHT

2015 Advances in irritable bowel syndrome

Food, fibre, bile acids and the pelvic floor: An integrated low risk low cost approach to managing irritable bowel syndrome

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Abstract

Patients presenting with abdominal pain and diarrhea are often labelled as suffering from irritable bowel syndrome, and medications may be used often without success. Advances in the understanding of the causes of the symptoms (including pelvic floor weakness and incontinence, bile salt malabsorption and food intolerance) mean that effective, safe and well tolerated treatments are now available.

Key words: Bile acids; Pelvic floor; Food intolerance; Irritable bowel syndrome; Diarrhoea

Core tip: Decreasing the dietary intake of poorly absorbed carbohydrates and/or using bile acid binders can greatly decrease symptoms of diarrhoea. Pelvic floor weakness with urgency and incontinence may masquerade as diarrhoea and can be managed with soluble fibre supplements and bile acid binders in many cases.

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INTRODUCTION

Patients with functional gastrointestinal disorders dominate the waiting rooms of general practitioners and gastroenterologists alike, and the financial burden of looking after them is considerable[1,2]. When faced with a condition that is of high prevalence, appreciable morbidity but without associated mortality,

low cost well-tolerated treatment options are sorely required. Evolving pharmacotherapies, whilst promising come at significant financial cost[1]. Precise history taking to define dietary indiscretions and adjust intake, particularly of poorly absorbed carbohydrates (FODMAPS) has gained increasing acceptance and is now validated by randomised controlled studies[2]. Some cases of diarrhoea labelled as irritable bowel syndrome with predominant diarrhoea (IBS-D) may, on further questioning represent evolving urgency and incontinence in the context of pelvic floor dysfunction[3,4]. Simple measures again including dietary modification, fibre supplementation and also instructions about toilet habits are effective treatments for many, and supported by clinical studies[5,6]. Finally, for the patient with refractory diarrhoea, manipulation of the bile acid pool with the empirical use of sequestrants such as cholestyramine may be useful, although more studies are needed[7]. Unifying these three broad subject areas (namely the role of dietary intake, the pelvic floor and bile acids in functional symptoms) is a growing awareness of their profound impact on gastrointestinal physiology, the lack of available or reliable investigations, but the simplicity, low cost and low risk of empirical treatment. This opinion-based review considers the rationale and evidence behind these management strategies and presents a pragmatic and cost effective approach to treatment.

FOOD INTOLERANCE AND FUNCTIONAL GI SYMPTOMS

Patients with IBS frequently attribute certain foods as a precipitant to their symptoms. Several recent, high quality reviews have comprehensively outlined this area. Notably, some of the commonest implicated foods are coffee and hot spices (which remain relatively unstudied) but also peas and cabbage (which would be encompassed by the acronym FODMAP). An awareness of these trigger foods obviously opens the door to simple avoidance, a process that obviously requires the patient to accept treatment as opposed to investigation and cure as the goal.

The Low FODMAP approach to the treatment of gastrointestinal symptoms is now well studied and the efficacy is established by a number of studies, albeit usually involving small numbers of patients but notably including randomised and placebo controlled methodologies. The underlying rationale to this approach is that poorly absorbed carbohydrates may exert an osmotic effect in the small bowel (leading to water retention and diarrhoea) and may be fermented in the colon (leading to distension and a feeling of bloating). This is supported by a study of patients with intestinal stoma, where the diet decreased stomal output, and by a separate MRI study of patients with intact gastrointestinal tracts demonstrating both increased small intestinal water content and colonic distension[8,9]. Interestingly, improvements in global satisfaction with gastrointestinal functioning, including constipation as well as diarrhoea are reported by patients, and this strategy has been studied in all subtypes of irritable bowel syndrome[2]. Theoretically however, the removal of osmotically active molecules should worsen constipation.

Investigation of carbohydrate absorption or "malabsorption" utilizing hydrogen breath test (HBT) is proposed to assist in the appropriate selection of individuals likely to respond to dietary restriction of these substrates. However, healthy individuals vary markedly in their ability to absorb carbohydrates such as fructose (commonly tested with HBT), and the reliability of the HBT (including test - retest data) has been brought into question[10,11]. The results of HBT have never been used in a research setting to ascertain a response to dietary modification, with the major studies empirically reducing FODMAP intake. Thus HBT's cannot be recommended as part of the management of patients modifying their FODMAP intake.

Resources are readily and affordably available to help patients manage their IBS symptoms *via* the low FODMAP approach. Applications for smart phones and tablets, websites and cookbooks enable many to self-administer the diet. It is recommended however that a supervised process of graded reintroduction occur to minimise the stringency of the modification, given the evolving evidence that intestinal microbiota are altered, and the potential that products of colonic fermentation (such as short chain fatty acids *e.g.,* butyrate) that would otherwise be produced in a routine diet may be reduced and are physiologically important (this is yet to be demonstrated)[12].

Dietary protein and dietary fat intolerance occur but are less well understood and interventions remain ineffective or unstudied. The protein receiving greatest attention from scientists, patients and the popular press is gluten. The phenomenon of gluten intolerance is controversial and conflicting research abounds[13,14]. Outside of patients with established coeliac disease, many with normal coeliac serology and normal duodenal biopsy following gluten loading (the gold standard) avidly ascribe symptoms to the ingestion of gluten, and attest to improvements on a gluten free diet. It is possible that carbohydrate components of the wheat (fructans) that are poorly absorbed and thus considered FODMAPS are responsible for the symptoms[13]. Alternatively, additives in bread and baking techniques may be the cause of this modern epidemic[15]. Many clinicians speak of patients that can tolerate bread in France or Italy, only to experience symptoms on returning home, a fact that may be secondary to an increased utilisation of fast - rise bread making techniques in countries such as the United Kingdom.

It is likely that dietary fat also is responsible for

Table 1 Types of bile acid malabsorption

Type 1	Examples
	Terminal ileitis (*e.g.*, Crohn's disease)
	Following resection of terminal ileum
Type 2	No definable underlying abnormality
	(this would apply to idiopathic chronic diarrhoea with a response to bile acid sequestrants and/or abnormal SeHCAT)
Type 3	Post cholecystectomy
	Post vagotomy
	Coeliac disease

symptoms in patients with IBS, and that modification may improve symptom control, however this remains unstudied in the context of practical clinical dietary studies. An interventional laboratory based study demonstrated increased rectal sensitivity to balloon inflation induced by duodenal lipid infusion, which provides a compelling argument that lipids are important in IBS, given that sensitivity to rectal balloon distension has been proposed as a surrogate marker for the visceral hypersensitivity that underpins the pathophysiology of IBS[16]. Pancreatic insufficiency and a positive response to pancreatic enzyme replacement has been described in patients with IBS-D, although the evidence for this approach is currently scant[17]. If further research is supportive, then the use of pancreatic enzymes, along with the other measures proposed herewith could in addition offer a low cost, readily available treatment option.

Bile acids and diarrhoea

Clinicians first learnt that bile salts caused diarrhoea by observing patients with Crohn's disease that had undergone ileal resection. Pioneering work by Hoffman *et al*[18], demonstrated increased colonic bile acid exposure, increased stool weight and water content that was reversible when cholestyramine was administered. Similarly diarrhoea induced by cholecystectomy may respond to cholestyramine[19]. In routine clinical practise, we manage many patients that have urgency, abdominal pain, diarrhoea and even occasional incontinence years after cholecystectomy that has passed unrecognised by other practitioners. Typically these patients respond to cholestyramine. In recent years, the proposition that anatomically normal individuals may have measurable abnormalities in bile salt recirculation has gained acceptance[20]. The proposed subtypes of bile acid malabsorption (BAM) are presented in Table 1.

BAM may be a more appropriate diagnosis in at least 25% of patients with IBS-D, and treatment with a bile acid binder may improve the symptoms of many patients with unexplained diarrhoea with (or perhaps more controversially) without BAM demonstrated by selenium homocholic acid taurine (SeHCAT)[21]. In the future, the use of BAS may not be limited simply to treating diarrhoea, and have been trialled for patients with incontinence, anorectal pain post haemorrhoidectomy and for gastritis post cholecystectomy[22-24].

Bile salts are excreted from the liver and are involved in the solubilisation and lipolysis of ingested lipids, thus facilitating absorption in the small intestine[25]. The conjugation within the liver of the bile acids to glycine and choline to produce chenodeoxycholic acid and cholic acid allows them to remain in an ionised form that resists passive absorption. Rather, 95% of excreted bile acids are absorbed *via* the apical Na^+ dependent transporter in the ileum. The process whereby bile acids are produced in the liver, stored in the gallbladder, released into the duodenum and absorbed in the terminal ileum is termed the enterohepatic circulation of bile acids[26] (Figure 1).

The regulation of bile acid production and recirculation involves a negative feedback loop where the receptor farnesoid X (FXR) in the ileum and liver senses the recirculated bile and, *via* secondary mechanisms involving gene transcription and production of the inhibitory fibroblast growth factor-19 (FGF-19), leads to decreased bile acid synthesis from cholesterol (a more detailed discussion can be found elsewhere as listed)[20].

The delivery of excess amounts of the bile acids chenodeoxycholic acid and deoxycholic acids to the colon results in excess salt and water excretion, colonic contractions and thus potentially diarrhoea whilst a deficiency may have the opposite effect and cause constipation[27]. These observations arguably should place interventions related to bile acid delivery to the colon at the forefront of considerations when treating these symptoms (see below).

The suggestion that many patients with IBS-D have BAM means that a large number of current patients have an undiagnosed, undefined and untreated entity. The alternative view is that modulation of bile acid recirculation with bile acids sequestrants will alter intestinal transit in most patients, with the results of investigations to delineate physiological variation instead arbitrary, untested and not useful. From a theoretical standpoint, excess conjugated bile acid delivery to the colon could be secondary to: (1) Excessive bile salt production; (2) Inefficient bile salt resorption (due to abnormalities of active transport mechanisms in the ileum or rapid transit precluding adequate absorption); (3) Excessive colonic salt and water production, or colonic motility in contact with a "normal" amount of bile salts; and (4) Abnormal bile salts.

The preferred explanation for bile salt diarrhoea, is in fact, excessive production of bile salts due to a failure of the negative feedback loop, as a consequence of inadequate FGF-19 production[28]. An enlarged bile acid pool thus causes diarrhoea, and supposedly would cause an abnormal SeHCAT test[7,29]. Expansion of the bile acid pool in those with clinical BAM has been previously demonstrated. Conflicting

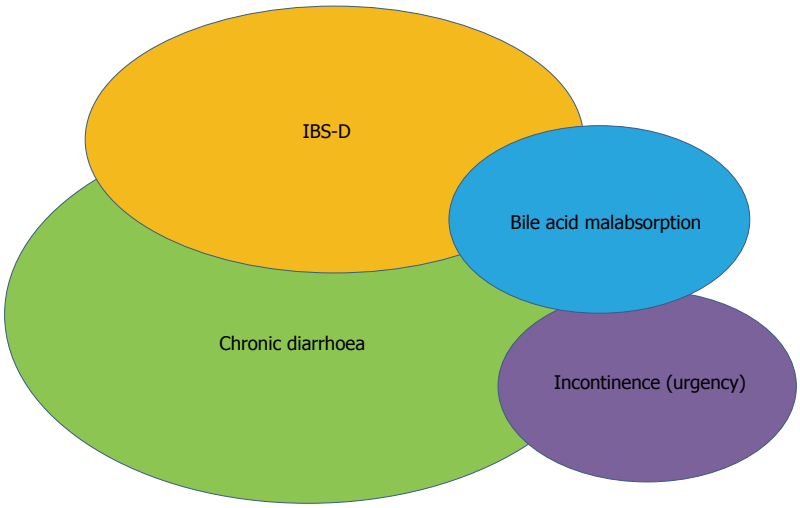

Figure 1 Overlapping entities presenting as loose motions and abdominal discomfort. Note that patients with incontinence and urgency often report abdominal pain, as do those with loose motions and a positive SeHCAT. IBS-D: Irritable bowel syndrome-diarrhea.

data emerge when attempting to correlate SeHCAT values and FGF-19, with a recent study failing to demonstrate a difference between healthy controls and those with IBS-D[28]. Earlier research however has linked low FGF-19, elevated plasma 7 alpha-hydroxyl-4-cholesten-3-one (C-4 - a surrogate marker of the hepatic biosynthesis of bile) and BAM[25].

Inefficient bile acid absorption is thought to be rare, with abnormalities of genes coding the ileal apical bile acid transporter thought to be uncommon, phenotypically rare and limited to well defined familial cases[30]. Rapid small intestinal transit may explain BAM, although this theory is only weakly supported by evidence and the high efficiency of the apical BA would make this hypothesis less likely[31]. The notion that the SeHCAT may instead reflect alterations in small intestinal transit is also disputed with contradictory evidence[32].

The response of the animal colon and importantly human colon to bile acids has only been studied in several small experiments, and further more definitive enquiry seems technically difficult and unlikely to occur. However it seems plausible that significant differences between individuals when exposed to the same concentration of bile salts could occur. Variations in the constituents of bile salts have not been studied in this context.

INVESTIGATION

Selenium homocholic-acid taurine (SeHCAT) is a radiopharmaceutical that is licensed for the investigation of BAM, and demonstrates behaviour identical to endogenous bile acids once being absorbed in the ileum after oral ingestion[7]. The severity of the BAM (or loss) is defined when measured by a gamma camera at 7 d and is defined by the percentage remaining *in-situ* (cut off commonly < 5% defining severe malabsorption, and 15% mild). SeHCAT is the only widely available measure of enterohepatic bile salt recirculation, and as such is used as to define the entity of BAM. There is no comparable test commonly available, and no gold standard definition of BAM. The flaw is this approach is that normal values have never been clearly established, that the reliability of the test (including test-retest characteristics) remains unknown, and that the definition of an abnormal result varies. A health technology review commissioned by the National Health Service (NHS) in 2013 concluded that before SeHCAT can be recommended as a reliable and cost effective measure, studies that include treatment of all patients regardless of SeHCAT result are needed[33]. The majority of those performed to date have simply compared patients with variable levels of BAM, with retention of selenium isotopes of < 5%, < 10% or < 15 % respectively most often reported. In fact in a recent systematic review of the area, the efficacy of patients treated with cholestyramine did not differ between those with various levels of BAM defined by SeHCAT[21].

Several alternative tests are available that hold future promise in defining BAM, but require further validation. Serum C-4 is a surrogate measure of bile acid production, whilst FGF-19 is produced by enterocytes and hepatocytes and is integral to the negative feedback loop regulating bile acid production[34]. Studies have variably demonstrated a correlation between these seromarkers and the SeHCAT, and clinically with symptoms of BAM[20]. Measurement of stool bile acids *via* spectroscopic techniques is feasible but costly.

TREATMENT

In countries such as the United States and in Australasia, SeHCAT is either not available or available in a limited capacity. This means that empirical treatment with bile acid binders such as cholestyramine

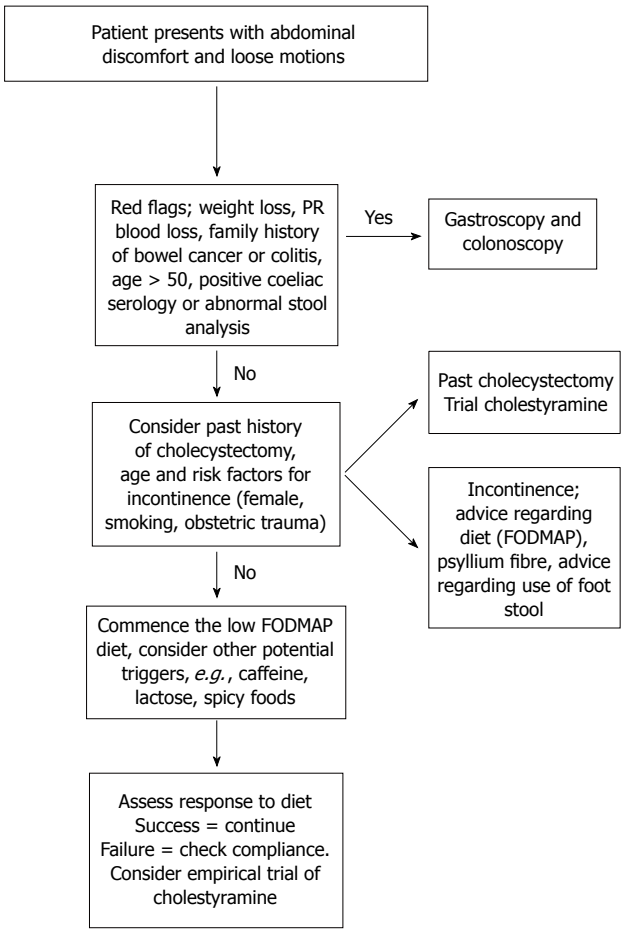

Figure 2 Proposed management algorithm for patients with loose motions ± abdominal pain.

is the only rational and available approach, whereby a response to treatment defines the entity. There is much to commend this approach given the current concerns with the validity of measures for BAM, although in the context of an aim to improve, tailor and streamline the treatment of patients with functional GI conditions this is questionable.

There is little doubt in our minds, based on the available evidence and our own clinical experience, the bile acid sequestrants have a potent effect on gastrointestinal physiology and thus ameliorate symptoms of diarrhoea in many patients. Some degree of caution should be exercised before widespread empirical therapy can be proposed first line in those with diarrhoea however. We thus propose this treatment in those who have not responded to dietary therapy (Figure 2). The ability of cholestyramine to ameliorate symptoms of IBS-D in a patient with a normal SeHCAT is unknown, and even when there is a clearly defined abnormality on SeHCAT, open studies (as opposed to placebo controlled) only have been undertaken. Cholestyramine is not always well tolerated, with 20%-30% of patients ceasing this medication as a result, describing unpleasant taste, constipation (ironically) or abdominal discomfort[21]. Newly developed medications such as colesevelam, and a colonic release colestyramine may improve palatability and limit side effects, however limited availability and high cost limit these options currently[35]. Finally, malabsorption of fat soluble vitamins has been described, suggesting that monitoring with blood tests (*e.g.,* INR and vitamin D) and supplementation where necessary (*e.g.,* multivitamins) is needed[36,37].

Defecatory disorders

Disorders of defecation are a common cause of gastrointestinal symptoms[4]. Awareness of and training in these issues is arguably suboptimal within the field of gastroenterology[38]. Several recent comprehensive position papers and reviews have emphasised the importance of considering these conditions early in the management of patients with altered bowel habit[39,40].

Incontinence and urgency

Faecal incontinence, defined as the unintentional passage of faeces or flatus encompasses a range of severities, and is a common and socially debilitating problem, affecting 5%-15% of adults, with some but not all studies demonstrating a female gender predominance[41]. Other risk factors for faecal incontinence include cigarette smoking, multiparity, advancing age and cholecystectomy. Demonstrable deficits in anal sphincter integrity (*e.g.,* at endoanal ultrasound) are particularly prevalent in multiparous women, sphincter atrophy common in smokers and pudental nerve injury is a factor in some cases[6].

A full, detailed knowledge of the investigations available to diagnose FI is not practically required for most gastroenterologists (and indeed is the domain of colorectal surgeons in many regions of the world). An awareness of the spectrum of the problem (that may be described by patients as "diarrhoea" until questioned further) and the good response to conservative treatments in 25%-50% is however vitally important[41]. A range of incontinence scoring systems have been proposed, and it is notable that included in some definitions is an inability to defer defecation for 15 or more minutes, (hence urgency is included) and the use of anti-diarrhoeals[42]. In clinical practise we are referred many patients who are mildly incontinent but have had the diagnosis missed or labelled as diarrhoea. Urgency and lower abdominal discomfort is often a feature. Obviously, exclusion of other conditions or precipitants (that may affect particularly women in their 5th and 6th decade- the age when incontinence has a peak onset in adults) including microscopic colitis and BAM type 3 is also essential.

Conservative therapies including dietary advice (eliminating the ingestion of poorly absorbed carbohydrates), use of bulk forming laxatives (in particular psyllium), instruction concerning the most efficient

posture to defecate (with the feet elevated at least 10 cm from the floor to open up the anorectal angle) and possibly pharmacotherapy (loperamide is most frequent, but interestingly cholestyramine has been trialled and found to be effective in an open labelled study, as has clonidine) have in combination demonstrated efficacy[24,43]. Failure of these simple measures mandates referral for physiological and anatomical investigations including anorectal manometry and endoanal ultrasound.

CONCLUSION

The symptoms of abdominal pain and diarrhoea are common causes of morbidity. Simple low risk high efficacy treatments are available. Dietary modification of poorly absorbed carbohydrates is a strategy now supported by randomised controlled trial evidence. Incontinence with pelvic floor weakness (often misdiagnosed as diarrhoea) is effectively managed conservatively in many. Evolving evidence suggests widespread use of empirical bile acid sequestrants may be appropriate in unexplained diarrhoea unresponsive to dietary modification.

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