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High Prevalence of Idiopathic Bile Acid Diarrhea Among Patients With Diarrhea-predominant Irritable Bowel Syndrome Based on Rome III Criteria

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Running title: Idiopathic bile acid diarrhea in D-IBS

KEY WORDS: PHQ-12; HADS; bile acid reabsorption; synthesis

Abstract:

Background & Aims: Some studies have found that patients with idiopathic bile acid diarrhea (BAD) present with symptoms of diarrhea-predominant irritable bowel syndrome (D-IBS). However, these studies were either retrospective, did not define D-IBS according to current criteria, or included patients with chronic functional diarrhea. We performed a prospective study of the prevalence of idiopathic BAD in consecutive patients fulfilling the Rome III criteria for D-IBS.

Methods: We analyzed data from 118 consecutive adult patients who fulfilled the Rome III criteria for D-IBS (mean age, 41.7 years; 72.9% female), seen at 2 gastroenterology clinics in the UK. We excluded patients with risk factors for BAD (previous history of cholecystectomy, terminal ileal Crohn's disease, terminal ileal resection or right hemicolectomy, pelvic or abdominal radiotherapy, celiac disease, or microscopic colitis). Participants completed questionnaires at baseline (on demographics, hospital anxiety, somatization, and depression, as well as the patient health questionnaire-12 and the short form-36 [SF-36]), and then received the ^{75}selenium homocholic acid taurine retention test. Retention of ^{75}selenium homocholic acid taurine 7 days after administration was used to identify patients with idiopathic BAD (mild BAD, 10%−14.9%; moderate BAD, 5.1%–9.9%; and severe BAD, ≤5%).

Results: Twenty-eight were found to have BAD (23.7% of total), with similar percentages at each study site (25.3% and 20%; *P*=.54). Eight patients had mild BAD (28.6%), 8 had moderate BAD (28.6%), and 12 had severe BAD (42.8%). There was no statistical difference in age or sex, or depression, patient health questionnaire-12, or SF-36 scores, between individuals with vs without BAD. However, patients with BAD had a higher mean body mass index than those without BAD (31.6 vs. 26.4; *P*=.003). Physical activity (based on the SF-36) was significantly lower in subjects with moderate (43.8) or severe BAD (41.7), compared to patients with mild BAD (87.5) (*P*=.046).

Conclusion: Almost 25% of patients presenting with D-IBS have idiopathic BAD; most cases are moderate to severe. Guidelines should advocate testing to exclude BAD before patients are diagnosed with D-IBS.

KEY WORDS: PHQ-12; HADS; bile acid reabsorption; synthesis

Introduction

Guidelines for the management of irritable bowel syndrome (IBS) recommend the use of symptom based criteria to aid clinicians towards making a positive diagnosis without the need to perform extensive investigations.[1] In 1978, Manning *et al* first described six key symptoms commonly seen in individuals ultimately diagnosed with IBS.[2] These were later incorporated by a multinational working party to form the Rome I criteria,[3] and have subsequently been revised on two occasions, to produce the Rome II and, most recently, the Rome III criteria.[4, 5] However, validation of such criteria shows that they perform only modestly in distinguishing IBS from organic diseases.[6] Several studies have reported that gastrointestinal symptoms in organic conditions, such as celiac disease,[7] exocrine pancreatic insufficiency,[8] inflammatory bowel disease,[9] and small bowel bacterial overgrowth,[10] significantly overlap and mimic those of diarrhea-predominant IBS (D-IBS). Most recently, interest has focused on the potential role of bile acids in evoking gastrointestinal symptoms compatible with D-IBS.[11]

Bile acids are synthesised in the liver, stored in the gallbladder, and released into the small bowel, where they aid digestion of lipids. Normally, 95% of bile acids are re-absorbed in the terminal ileum (TI) and re-cycled back to the liver via the enterohepatic circulation. If there is a failure of re-absorption, excess bile acids escape into the colon where they stimulate electrolyte and water secretion, resulting in chronic watery diarrhea.[11] The conditions causing bile acid diarrhea (BAD) can be classified according to the etiology. Type 1 represents failure to absorb bile acids from the TI due to either resection or localised disease (i.e. Crohn's disease). Type 3 incorporates miscellaneous causes such as previous cholecystectomy, fibrosis following abdominal or pelvic radiotherapy, celiac disease or microscopic colitis. Type 2, otherwise known as idiopathic BAD, is where there is no anatomical abnormality or other risk factor apparent.[11] In the latter case, evidence suggests that TI absorption of bile acids is normal or increased,[12] but impaired negative feedback of bile acids on fibroblast growth factor-19 (FGF-19) leads to dysregulation of the enterohepatic circulation and excessive bile acid synthesis.[13]

A relatively simple and highly sensitive method of testing for BAD is via the ^{75}selenium homocholic acid taurine (^{75}SeHCAT) test, where retention of radio-labelled bile acids of less than 10-15% after 7 days is abnormal.[14, 15] The ^{75}SeHCAT retention test is available in the UK, certain European countries, and Canada. However, the test is not available in the USA, where alternate means of detecting BAD can be performed, albeit with difficulty and in selected laboratories only.[16] Measurement of total stool bile acid can be used to diagnose BAD, but stool collections for 48 hours or longer are required to account for variations, which can be demanding and unpopular for both patients and laboratory staff. There have been recent advances in the applicability of measuring serum 7α-hydroxy-4-cholesten-3-one (C4), an intermediary in bile acid synthesis. Elevated C4 represents a surrogate marker for increased bile acid synthesis and increased fecal bile acid loss. The disadvantages to serum C4 are that it requires a fasting sample, can lead to false positives in patients with liver disease, or those on medication that alter bile acid synthesis, such as statins, or in individuals with an altered circadian rhythm.[16] Direct comparisons between the ^{75}SeHCAT retention test and serum C4 demonstrate that low ^{75}SeHCAT values correlate more closely with altered bowel habit, suggesting it is the better method to use for detecting BAD.[17] However, in the current climate, as none of these

tests are routinely available in countries such as the USA, there is interest in the development of a simple, cheap, and readily available biomarker that will help screen for patients that potentially have BAD who can then subsequently be referred on for confirmatory tests. Of these, measurement of serum FGF-19,[18] identification of the primary bile acids cholate and chenodeoxycholate in a single stool sample,[19, 20] or detection of volatile organic compounds in a single urine sample (presumed to be a consequence of dysbiosis secondary to elevated levels of colonic bile acids),[21] have all shown initial promising results, but require further work to validate their clinical applicability.[22]

A systematic review and meta-analysis suggested that idiopathic BAD may be the underlying cause of symptoms in 30% of patients with presumed D-IBS.[23] However, many of the included studies were either retrospective in nature, did not use symptom-based criteria to define D-IBS, or included patients with chronic functional diarrhea. Nevertheless, a recent prospective evaluation has shown that 23% of patients with D-IBS have a ^{75}SeHCAT retention test of <10%, and that colonic bile acid exposure correlates with bowel habit and colonic transit time.[17] Furthermore, in those with BAD, open-label treatment with bile acid sequestrants led to a positive clinical response, thereby supporting the role of bile acids in IBS symptomatology.[17] However, this novel study used the Rome II criteria, which can show differences in agreement when sub-typing against the current Rome III criteria.[24] We now report our experience of testing for idiopathic BAD, using the ^{75}SeHCAT retention test, in a rigorously defined cohort of patients meeting the Rome III criteria for IBS, who would otherwise be labelled as having D-IBS.

Materials and Methods

Participants and setting

This prospective, dual-center, study was carried out at the Royal Hallamshire Hospital (Sheffield, South Yorkshire, UK) and St. James's University Hospital (Leeds, West Yorkshire, UK). Both are located in Northern England and provide secondary care services to a local population of 500 000 and 800 000 people, respectively. On average, each of the general luminal gastroenterology clinics that took part in this study sees 200 new outpatients per Gastroenterologist per year, with diarrhoea and abdominal pain being present in over a quarter of all referrals and accounting for the major workload.[25] Following ethical approval from local research committees, the study was conducted between the time periods of January 2013 to April 2014.

The inclusion criteria were adults who fulfilled the Rome III criteria for D-IBS (Supplementary Table 1).[5] These patients had reported similar symptoms when initially referred by their primary care physician several weeks earlier, suggesting that they were relatively stable in terms of their IBS subtype.[26] We excluded any subjects with known risk factors for BAD, such as a previous history of cholecystectomy, TI Crohn's disease, TI resection or right hemicolectomy, celiac disease, abdominal or pelvic radiotherapy, or microscopic colitis. The latter was via normal colonic biopsies in 84.7% of the cohort, and clinical judgement in those deemed at low risk or who refused colonoscopy.

Baseline Questionnaires and ^{75}SeHCAT retention test

Information concerning baseline questionnaire data is provided in the supplementary materials. The ^{75}SeHCAT retention was performed according to the manufacturers' instructions (GE Healthcare, UK). A 370 KBq capsule of ^{75}SeHCAT was administered with water at day 1. Patients underwent a scan of their abdomen using a gamma camera to obtain baseline counts at 3 hours. A further scan of the abdomen was then performed at day 7 to determine the percentage of ^{75}SeHCAT retention. We used a retention of <15% to define presence of BAD in our primary analysis, but a lower threshold of <10% in a secondary analysis. In our primary analysis the degree of BAD was further classified as severe if retention ≤5%, moderate if 5.1%-9.9%, and mild if 10%-14.9%.

Data Analysis

Statistical analysis was carried out using SPSS version 19.0 software (SPSS Inc, Chicago, USA). Categorical variables were summarized by descriptive statistics, including total numbers and percentages, and compared between those with and without BAD using a Pearson chi-squared test. Continuous variables were summarized by mean and standard deviation (SD), and compared between those with and without BAD using a Student T-test, and across the three categories of BAD severity using a one-way analysis of variance (ANOVA). Statistical significance was set at a p-value of <0.05.

Results

A total of 127 consecutive individuals meeting the Rome III criteria for D-IBS were approached, and 118 (92.9%) participated in the study; 83 individuals from Sheffield and 35 individuals from Leeds. Combined data analysis from both sites revealed the mean age of D-IBS patients to be 41.7 years, with 72.9% (n=86) female, 91.5% (n=108) Caucasian, and a mean-BMI of 27.6. The mean scores for assessments of well-being were as follows; HADS-A was 8.4, HADS-D was 5.03, PHQ-12 was 6.94, SF-36 PCS was 56.1, and SF-36 MCS was 56.7. Subgroup analyses of D-IBS patients, between both recruitment sites, revealed no statistical differences in basic demographics, HADS-A, HADS-D, PHQ-12 somatisation, or SF-36 quality of life scores.

The total prevalence of BAD, using a ^{75}SeHCAT score of <15%, was 23.7% (n=28). The prevalence was statistically similar across both recruitment sites, at 25.3% (n=21/83) in Sheffield and 20.0% (n=7/35) in Leeds (p=0.54). Had we used a lower ^{75}SeHCAT retention test cut-off value of <10% to diagnose BAD, then the total prevalence would have been 16.9% (n=20), with 18.1% (n=15) at Sheffield and 14.3% (n=5) at Leeds (p=0.62).

The characteristics of patients diagnosed with BAD, compared to those without, are reported in Table 1. Individuals with BAD were significantly more likely to have a higher mean BMI than those without BAD (31.6 vs. 26.4, p=0.003). However, other demographic variables or assessments of well-being such as HADS, PHQ-12 or SF-36 did not differ between those with or without BAD.

The breakdown of the 28 patients diagnosed with BAD showed that 8 (28.6%) had mild BAD, 8 (28.6%) had moderate BAD, and 12 (42.8%) had severe BAD. The characteristics of individuals with BAD according to each of the three severities are reported in Table 2. Interestingly, subjects with severe/moderate BAD reported significant role limitations due to their physical health compared to those with mild BAD. However, other variables assessing physical well-being did not differ according to severity of BAD, nor was there any difference in the overall SF-36 PCS. Finally, no difference in baseline demographics, PHQ-12, HADS-A, HADS-D or SF-36 MCS was detected between the various BAD severities.

Discussion

This study has shown that almost one in four individuals presenting to secondary care who fulfill Rome III criteria for D-IBS have evidence of idiopathic BAD. Furthermore, in nearly 70% of cases the severity of BAD fell within the moderate to severe category, and was associated with significant physical role limitations, compared with those with only mild BAD. We also found that individuals with BAD had a significantly higher mean BMI compared with those without BAD. These findings have important implications for the investigation and management of this group of patients.

Strengths of our study include the methodology used. Several previous studies have claimed an association between symptoms that are compatible with D-IBS and idiopathic BAD, yet have been limited by their retrospective design, choice of patients recruited, or use of non-gold standard criteria to define IBS. In contrast, and to our knowledge, we are the first study to evaluate the prevalence of idiopathic BAD in a prospective cohort of consecutive patients fulfilling the Rome III criteria for D-IBS. Furthermore, we also ensured that we did not over-estimate the prevalence of BAD by excluding any individuals who had risk factors associated with type 1 or type 3 BAD. The high participation rate is also a strength, and may reflect the fact that SeHCAT testing was only accessible via this study, and patients were keen to explore this as a potential cause for their symptoms. Finally, we have demonstrated similar results at two independent centers, in secondary care populations. We therefore believe that, having used state of the art definitions and testing modalities, our findings are contemporary and provide compelling evidence that can be generalized to other centers seeing a similar population of patients. In fact, a recent study from the United States identified that 38% of patients with D-IBS were noted to have higher serum C4, and faecal bile acids, compared with healthy volunteers, or patients with constipation-predominant IBS[27] suggesting that, if ^{75}SeHCAT testing were available in the USA, the yield in patients with D-IBS is likely to be similar to ours.

The main limitation of our study is that, despite finding a high prevalence of idiopathic BAD in patients fulfilling the Rome III criteria for D-IBS, we did not assess the clinical response to bile acid sequestrants. Nevertheless, other studies have demonstrated a beneficial response to open treatment, particularly in those with moderate to severe BAD.[17, 23] A systematic review noted that response to colestyramine occurred in 96% of patients with ^{75}SeHCAT retention <5%, 80% with ^{75}SeHCAT retention <10%, and 70% with ^{75}SeHCAT retention <15%.[23] In our study, of those that had BAD, 28.6% were mild, 28.6% moderate and 42.8% severe. This suggests that making a positive diagnosis will be of clinical benefit, and serves as a mandate for randomized placebo-controlled trials of bile acid sequestrants in D-IBS. Another limitation is that we did not assess symptom severity and its relationship with BAD, although a recent study has suggested that perceived symptom severity is not linked to ^{75}SeHCAT retention values.[17] Nevertheless, as a low ^{75}SeHCAT retention test value is characterised by having more frequent stools, and accelerated colonic transit time, future studies in patients presenting with D-IBS type symptoms may wish to explore whether quantifying stool frequency or consistency can be used as a predictive tool to diagnose idiopathic BAD.

The study findings have both major clinical and research implications, as they call into question whether symptom-based criteria can be used as a tool to positively diagnose D-IBS without the need to exclude possible underlying organic pathology. Such uncertainties are already apparent in clinical

practice where healthcare professionals vary greatly in their beliefs as to whether IBS is a diagnosis of exclusion.[28] A survey conducted in the USA amongst primary care physicians, community gastroenterologists and nurse practitioners (collectively referred to as "non-IBS experts") against an internationally recognized panel of IBS key opinion leaders, revealed that non-experts were far more likely to endorse IBS as a diagnosis of exclusion (72% vs. 8%). As a result, non-experts demonstrated an increased utilization of resources, particularly in those presenting with D-IBS.[28] This highlights that, despite decades of expert opinion, clinicians remain concerned about the possibility of a missed organic pathology in patients meeting criteria for IBS. This is reinforced by the fact that celiac disease may account for up to 4% of IBS cases,[7] which subsequently led to a paradigm shift in international guidelines.[1] Similarly, studies elsewhere have shown D-IBS to be associated with other organic pathologies, such as exocrine pancreatic insufficiency, inflammatory bowel disease, and small bowel bacterial overgrowth.[8-10]

Our findings only serve to further heighten this concern by providing clear evidence that idiopathic BAD can masquerade as D-IBS. It is interesting to note that the magnitude of this problem appears far greater than that of celiac disease in suspected IBS. This may be explained by changing referral patterns, with primary care physicians in the UK adhering to recent National Institute of Health and Care Excellence (NICE) guidelines that advocate excluding celiac disease, via serological testing, in patients with suspected IBS. Those who test positive are then likely to be referred directly for endoscopy and duodenal biopsies to confirm the diagnosis, whereas those with negative serology, and therefore suspected IBS, will be referred on to secondary care for further evaluation and treatment of their symptoms.[29, 30] Clearly, patients with positive celiac serology were excluded from this study, but during a similar period of time among 240 consecutive patients referred with chronic diarrhea to the same general luminal gastroenterology clinics, and who were ineligible for the study, as they did not meet the Rome III criteria for IBS, 25 (10.4%) were found to have BAD, compared with only 10 (4.2%) with celiac disease.[31, 32] This suggests that secondary care physicians are now posed with different diagnostic challenges when evaluating patients with suspected D-IBS or chronic diarrhea.

In conclusion, almost one-in-four cases presenting with D-IBS will have idiopathic BAD. In the majority this will be moderate to severe. This suggests that future guidelines should advocate diagnostic testing to exclude BAD before a diagnosis of D-IBS is made.

Table 1: Characteristics of those individuals with BAD compared with those without

	No BAD (n=90)	BAD (n=28)	p value
Mean age (SD)	41.8 (16.5)	41.6 (15.3)	0.96
Female (%)	69 (76.7)	17 (60.7)	0.1
Caucasian (%)	82 (91.1)	26 (92.9)	0.77
Tobacco user (%)	23 (25.6)	9 (32.1)	0.49
Alcohol user (%)	59 (65.6)	19 (67.9)	0.82
Mean BMI (SD)	26.4 (7.37)	31.6 (8.43)	0.003*
Mean HADS-A (SD)	8.59 (4.59)	7.79 (5.57)	0.445
Mean HADS-D (SD)	5.0 (4.02)	5.14 (3.71)	0.87
Mean PHQ-12 (SD)	7.05 (3.86)	6.61 (4.81)	0.62
Physical function (SD)	77.1 (22.0)	72.1 (28.8)	0.40
Role Physical (SD)	53.9 (42.3)	55.4 (44.3)	0.88
Bodily pain (SD)	50 (26.1)	42.1 (22.6)	0.29
General health (SD)	48.7 (22.6)	45 (24.1)	0.46
Vitality (SD)	41.1 (23.4)	46.3 (26.0)	0.33
Social Functioning (SD)	60 (27.6)	62.1 (27.7)	0.73
Role emotional (SD)	61.2 (43.9)	60.7 (48.1)	0.96
Mental health (SD)	61.7 (22.0)	66.3 (24.4)	0.35
SF-36 PCS (SD)	56.9 (24.1)	53.7 (22.3)	0.53
SF-36 MCS (SD)	56.0 (23.9)	58.8 (26.3)	0.6

Table 2: Characteristics of individuals with mild, moderate, and severe BAD

	Mild BAD (n=8) ^{75}**SeHCAT 10%-14.9%**	**Moderate BAD (n=8)** ^{75}**SeHCAT 5.1%-9.9%**	**Severe BAD (n=12)** ^{75}**SeHCAT ≤5%**	**p value**
Mean age (SD)	42.3 (10.1)	37.6 (19.4)	43.8 (15.9)	0.68
Female (%)	4 (50)	5 (62.5)	8 (66.7)	0.67
Caucasian (%)	7 (87.5)	8 (100)	11 (91.7)	0.76
Tobacco user (%)	2 (25)	2 (25)	5 (41.7)	0.41
Alcohol user (%)	4 (50)	8 (100)	7 (58.3)	0.89
Mean BMI (SD)	30.6 (5.52)	29.8 (10.4)	33.3 (9.1)	0.64
Mean HADS-A (SD)	7.38 (5.95)	9.13 (5.6)	7.17 (5.62)	0.736
Mean HADS-D (SD)	3.88 92.17)	5.88 (4.39)	5.5 (4.1)	0.53
Mean PHQ-12 (SD)	5.75 (4.9)	7.75 (4.68)	6.42 (5.1)	0.71
Physical function (SD)	78.1 (37.6)	74.4 (20.9)	66.7 (28.2)	0.68
Role Physical (SD)	87.5 (26.7)	43.8 (49.6)	41.7 (41.7)	0.046*
Bodily pain (SD)	44.1 (22.4)	34.1 (25.5)	46.3 (21.4)	0.50
General health (SD)	53.8 (29)	45.6 (21.3)	38.8 (22.4)	0.41
Vitality (SD)	52.6 (29.2)	41.3 (24.6)	45.4 (26.2)	0.69
Social Functioning (SD)	67.2 (29.3)	51.6 (27.1)	65.6 (28.3)	0.46
Role emotional (SD)	87.5 (34.4)	50 (53.4)	50 (48.2)	0.18
Mental health (SD)	71 (21.7)	60.5 (28.4)	67 (24.7)	0.71
SF-36 PCS (SD)	65.9 (16)	49.5 (25.4)	48.3 (22.3)	0.19
SF-36 MCS (SD)	69.6 (23.8)	50.8 (28.4)	57 (26.3)	0.36

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