TITLE

Systematic Review with Meta-analysis: Prevalence of Bile Acid Malabsorption in Irritable Bowel Syndrome with Diarrhoea

RUNNING HEAD

Bile acid malabsorption in IBS-D

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ABSTRACT

BACKGROUND: Irritable bowel syndrome is a widespread disorder with a marked socioeconomic burden. Previous studies support the proposal that a subset of patients with features compatible with diarrhoea predominant IBS (IBS-D) have bile acid malabsorption (BAM).

AIMS: The objective of this study was to perform a systematic review and meta-analysis to assess the prevalence of BAM in patients meeting accepted criteria for IBS-D.

METHODS: MEDLINE and EMBASE were searched up to March 2015. Studies recruiting adults with IBS-D, defined either by the Manning, Kruis, Rome I, II or III criteria and which used 23-seleno-25-homotaurocholic acid (SeHCAT) testing for the assessment of BAM were included. BAM was defined as 7 day SeHCAT retention of <10%. We calculated the rate of BAM and 95% confidence intervals (CI) using a random effects model. The methodological quality of included studies was evaluated using the Quality Assessment for Diagnostic Accuracy Studies (QUADAS-2).

RESULTS: The search strategy identified 6 relevant studies comprising 908 individuals. The rate of BAM ranged from 16.9% to 35.3%, with a crude pooled rate of 29.3%. The pooled rate was 28.1 % (95% CI 22.6-34%). There was significant heterogeneity in effect sizes (Q-test χ^2 = 17.9, p<0.004; I^2 72.1%). The type of diagnostic criteria used or study country did not significantly modify the effect.

CONCLUSIONS: These data provide evidence that in excess of one quarter of patients meeting accepted criteria for IBS-D have BAM. This distinction has implications for the interpretation of previous studies as well as contemporaneous clinical practice and future guideline development.

INTRODUCTION

Irritable bowel syndrome (IBS) is characterised by abdominal pain and alteration in bowel habit in the absence of a structural or biochemical abnormality [1]. IBS is a widespread disorder with a reported global prevalence of >10% and has a marked socioeconomic burden [2, 3]. IBS is also associated with a significant diminution in work productivity and health related quality of life [4]. The pathophysiology of IBS is incompletely understood and to date a clinically applicable biomarker remains elusive [5]. There is marked inter-individual variability in the presentation, natural history and response to treatment of IBS [6], leading to the postulation that, despite internationally accepted classifications, a number of distinct pathophysiological entities may exist [7]. With respect to diarrhoea predominant IBS (IBS-D) two lines of evidence support this proposal. Firstly, >30% of individuals who are exposed to a bacterial gastroenteritis develop chronic symptoms consistent with a diagnosis of IBS-D, termed post-infectious IBS [8, 9]. Secondly, idiopathic bile acid malabsorption (BAM) may account for a proportion of patients with features that are clinically indistinguishable from IBS-D [10].

Synthesized in the liver, bile acids play a pivotal role in the absorption of dietary fats and are excreted into the small intestine via the biliary tree. Within the small intestine, bile acids coalesce with dietary fats to form micelles, of which approximately 95% are actively reabsorbed in the terminal ileum and are returned to the liver via the enterohepatic circulation, with the remainder lost via faecal output [11, 12]. BAM may occur as a sequelae of a defect of bile acid reabsorption in the distal small bowel such that they reach the colon. In the colon, bile acids undergo both

dehyroxylation and deconjugation, where they then exert pro-secretory actions leading to diarrhoea, defaecatory urgency, bloating and abdominal discomfort [13]. Although there is no universally accepted gold standard modality for diagnosing BAM, 23-seleno-25-homotaurocholic acid (SeHCAT) testing is widely used in Europe. Homotaurocholic acid is a synthetic analogue of the naturally occurring conjugated bile acid, taurocholic acid. Following oral administration of a standardized dose of selenium-75-homocholic acid taurine, the retained fraction is assessed using a gamma camera at 1 week, with values of less that 15%, 10% and 5% being considered to represent mild, moderate and severe BAM respectively [14]. Three distinct types of BAM have been described: type 1 – secondary to terminal ileal disease or surgery, type II – primary (or idiopathic) and type III – secondary to previous cholecystectomy, peptic ulcer surgery, coeliac disease or diabetes mellitus [15].

In 2009, Wedlake *et al.* systematically reviewed the literature to evaluate the prevalence of BAM in patients with chronic diarrhoea, identifying 18 studies, containing 1223 patients, and demonstrated that 32% of individuals had BAM, defined as a SeHCAT retention of <10% [10]. However, this review was subject to a number of limitations. Firstly, it only reported the crude pooled rate of BAM, rather than weighted rates. Secondly, it included patients that had 'chronic or recurrent diarrhoea', 'watery diarrhoea', 'diarrhoea of an IBS-D nature", 'or abdominal pain and no recognised organic pathology' rather than utilising accepted definitions [16]. Moreover, since this systemic review, several new reports have been published. The aim of our study was to address these knowledge gaps by performing an updated

systemic review with meta-analysis of the current literature assessing the prevalence of BAM in patients with IBS-D using accepted criteria, reasoning that the prevalence of BAM in those previously diagnosed with IBS-D may be less than previously reported.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

This systematic review and meta-analysis was performed in accordance with PRISMA recommendations [17]. A literature search was performed using MEDLINE (1980 – March 2015) and EMBASE (1980 – March 2015). Studies were searched for using the terms *irritable bowel syndrome*, *functional bowel disorder, functional diarrhoea, chronic diarrhoea, bile acid diarrhoea, primary bile acid diarrhoea,* as medical subject heading (MeSH) and free text terms. These were combined with the set operator "AND" with following terms: *bile acid malabsorption, bile salt malabsorption, SeHCAT, 23-seleno-25-homotaurocholic acid* as free text terms. Publications were restricted to those studying adult populations, defined as greater than 16 years old, with a documented diagnosis of IBS-D according to accepted criteria, i.e. IBS-D based on one of the following accepted international criteria; A) Manning criteria, B) Kruis criteria, C) Rome 1, D) Rome II, or E) Rome III. BAM was defined as SeHCAT retention of <10% at 7 days. The bibliographies of all eligible studies that were identified were also comprehensively searched for studies not identified using the initial search strategy. Furthermore, the abstract books from four conference proceedings (Digestive Disease Week, United European Gastroenterology Week, the British Society of Gastroenterology and the Joint International Neurogastroenterology and Motility meetings) between 1994 -2014 were searched by hand to identify any

potentially eligible studies published in abstract forms. Foreign language papers were translated where required. Where data were missing from the publication, the first and/or senior author was contacted to supply further information. Studies were independently evaluated by two investigators (SMS and ADF) using predesigned eligibility forms; according to the aforementioned eligibility criteria. Disagreements were resolved by consensus.

OUTCOME ASSESSMENT

DATA EXTRACTION

The name of the first author, year of publication, number of subjects, type of internationally accepted definition of IBS-D, study design and outcomes regarding SeHCAT measures were recorded in a standardized fashion utilizing an Excel spreadsheet (Excel for Mac 2011, Microsoft, Redmond, USA).

STUDY METHODOLOGICAL QUALITY

The quality of the studies identified were assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool [18].

DATA SYNTHESIS AND STATISTICAL ANALYSIS

Data were pooled using a random effects model, using DerSimonian-Laird weights [19], as this was considered the most plausible methodology given previously reported heterogeneity [10]. The diversity of study results within a meta-analysis can be evaluated using statistical tests of heterogeneity, the Cochran's Q and I^2 statistic, thereby assessing whether the variation across component studies is due to true heterogeneity or by chance. Cochran's Q is distributed as a chi-square statistic and the I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance with values ranging from 0% to 100%, with 0%

representing no observed heterogeneity and with increasing values indicating increasing heterogeneity. A value less than 25% was chosen to represent low levels of heterogeneity [20]. We aimed to perform the following pre-specified subgroup analyses:- 1) effect modification by diagnostic criteria used, 2) effect modification by county and 3) effect modification by study design. The meta-analysis was performed using Statsdirect (Version V.2.7.2, StatsDirect, Sale, Cheshire, England) and was used for the generation of Forest plots for the stated outcomes.

RESULTS

SEARCH RESULTS

The search strategy returned 3391 citations of which 168 appeared to be relevant. Full texts were subsequently retrieved for detailed assessment. For 2 citations [21, 22], we successfully contacted the senior author to clarify inclusion criteria data. Of the 128 relevant citations, 122 were excluded as they did not meet the inclusion criteria of the systematic review, thus leaving 6 eligible studies of 908 individuals for the IBS-D analysis, *see figure 1.*

INSERT FIGURE 1 HERE

Figure 1 – Flow diagram for the assessment of studies identified in the systematic review.

PREVALENCE OF BILE ACID MALABSORPTION IN IBS-D PATIENTS

There were 6 studies that reported the prevalence of BAM based upon a positive SeHCAT study of 10% at 7 days in patients with IBS-D as defined by accepted criteria. The crude pooled rate of BAM in IBS-D patients was 266/908 (29.3%), with rates varying from 16.9-35.3%, *see table 1*. The pooled rate was 28.1% (95% CI 22.6-34%)

by the random effects model, *see figure 2.* There was significant heterogeneity in effect sizes (Q-test χ^2 = 17.9, p<0.004; I^2 72.1%).

Study Name	Year	Study design*	Total number of patients	Numbers of patients with SeHCAT retention <10% at 7 days	Crude pooled rate	Definition used	Country
Smith *et al.* [23]	2000	P	193	65	33.6%	Rome I	UK
Kurien *et al.* [24]	2011	R	102	36	35.3%	Rome III	UK
Gracie *et al.* [21]	2012	R	143	35	24.5%	Rome III	UK
Dhaliwal *et al.* [22]	2013	P	288	95	33.0%	Rome III	UK
Bajor *et al.* [25]	2014	P	64	15	23.4%	Rome II	Sweden
Aziz *et al.* [26]	2014	P	118	20	16.9%	Rome III	UK
Totals		**4P, 2R**	**908**	**266**	**29.3%**		

*Table 1 – The details of the six studies, which included 908 patients, that met the inclusion criteria, which were included in the meta-analysis. *P=prospective study, R=retrospective study.*

INSERT FIGURE 2 HERE

Figure 2 – A Forest plot of the pooled proportions of BAM in 908 patients with IBS-D. The overall pooled proportion of BAM in patients with IBS-D was 28.1% (95% CI 22.6-34%).

EFFECT MODIFICATION BY DIAGNOSTIC CRITERIA USED

Of the 6 studies that met the inclusion criteria, 4 studies used the Rome III definition, 1 study used Rome II and 1 study used the Rome I. No studies utilised the Kruis criteria. The pooled rate for prospective studies using the Rome III criteria was 25.0%

(95% CI = 11.3 – 41.9%) by the random effects model, *see figure 3.* There was significant heterogeneity in effect sizes (Q-test χ^2 = 11.4, p<0.0001, I^2 91.2%).

INSERT FIGURE 3 HERE

Figure 3 – A Forest plot of the pooled proportions of BAM in prospective studies using the Rome III criteria for IBS-D was 25.0% (95% CI 11.3 - 41.9).

EFFECT MODIFICATION BY COUNTRY

Of the 6 studies that met the inclusion criteria, 5 studies were performed in the UK and 1 in Sweden. The pooled rate in UK studies was 28.7% (95% CI = 22.5 – 35.4%) by the random effects model, *see supplementary material figure A*. There was significant heterogeneity in effect sizes (Q-test χ^2 = 16.9, p=0.002; I^2 76.3%).

EFFECT MODIFICATION BY STUDY DESIGN

Of the 6 studies, 4 were prospective. The pooled rate was 27.2% (95% CI = 19.7% - to 35.4%) by the random effects model, *see supplementary material figure B.* There was significant heterogeneity in effect sizes (Q-test χ^2 = 14.5, p=0.002; I^2 79.4%).

STUDY METHODOLOGICAL QUALITY ASSESSMENT

The methodological quality of the included studies is summarised in *table 2*. The overall quality of the included studies was high. The subject selection method may have introduced high bias in two studies, as the index standard, in this case the Rome criteria, was applied retrospectively. Four out of the six studies identified were performed in tertiary care centres, which may therefore limit the external validity, especially towards primary and general secondary care populations.

	Risk of Bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow & timing	Patient selection	Index test	Reference standard
Smith *et al.* [23]	+	+	+	+	+	+	+
Kurien *et al.* [24]	?	+	−	+	?	+	?
Gracie *et al.* [21]	?	+	−	+	+	+	?
Dhaliwal *et al.* [22]	?	+	+	+	+	+	+
Bajor *et al.* [25]	+	+	+	+	?	+	+
Aziz *et al.* [26]	+	+	+	+	?	+	+

Table 2 - Quality Assessment for Diagnostic Accuracy Studies (QUADAS)-2 evaluation of each study included in the meta-analysis assessing the prevalence of BAM in patients with IBS-D.

DISCUSSION

In excess of 28% of patients meeting internationally accepted criteria for IBS-D, have SeHCAT results consistent with BAM. This effect size was not modified by either country in which the study was undertaken or the particularly iteration of international guidelines that was used to make the diagnosis of IBS-D. These results have a number of important implications across the field, particularly with respect to clinical practice, diagnostic criteria development and research.

IBS is a common disorder worldwide, and whilst the exact prevalence varies according to the wording of questions used to define the disorder, it is most commonly reported to be in the order of 5-10% [27]. The relative balance of diarrhoea versus constipation varies considerably dependent on the geographical location,

complicated by the observation that patients can change from one subtype to another over time [6]. The reported population prevalence of IBS-D is approximately 4% [2]. Therefore based on a UK population of 64.1 million [28], it is possible to extrapolate that potentially 2.5 million individuals have IBS-D. A similar prevalence rate of IBS-D has been reported in a large longitudinal cohort study from the USA [29]. By comparison, 2.3 million people live with coronary heart disease in the UK [30]. Although it is difficult to accurately estimate the community based population prevalence based upon data derived from secondary/tertiary care centres, potentially in excess of 700,000 individuals in the UK have BAM, albeit with symptoms consistent with, and/or a diagnosis of, IBS-D. In reality however, this figure may be further skewed given that we excluded those with type 1/3 BAM and those studies reporting patients with functional diarrhoea. Nonetheless, it is entirely plausible that BAM is a prevalent, yet probably under-recognized, disorder in the general population. The question as to why BAM is under diagnosed remains an enigmatic one and is almost certainly multifactorial. For example, failure of BAM *ab initio* to enter the differential diagnosis [31], negative perceptions concerning tolerability of traditional bile-acid sequestrants and a paucity of guidance regarding optimal treatment regimens may play a pivotal role. A number of therapeutic options are available including colestyramine, colesevalam, colestipol, aluminium hydroxide and obeticholic acid [32]. Wilcox *et* al. reported that colesystramine and colestipol are efficacious treatments albeit limited by their tolerability and hence bioavailability [33]. Whilst newer agents such as colesevalam and obeticholic acid having a promising role, to date there are no randomised controlled or comparison trials establishing their efficacy in type 2 BAM. However, in a small double blind

placebo controlled trial, colesevalam has been shown to be efficacious in BAM related to Crohn's disease [34]. Nevertheless, significant knowledge gaps remain as to the long-term effectiveness and tolerability of the current therapeutic armamentarium.

The clinical performance of internationally accepted criteria including the Rome criteria, the most widely accepted current standard for diagnosing functional gastrointestinal (GI) disorders, remains limited [35, 36]. For instance, a diverse array of GI disorders such as coeliac disease [37], inflammatory bowel disease [38] and small bowel bacterial overgrowth [39] may fulfill such criteria for the diagnosis of IBS-D. Whilst there has been particular emphasis placed upon the attractiveness of making a positive diagnosis of IBS in primary care, without resorting to investigations, by advisory bodies [40], the evidence suggests otherwise. Hungin *et al.* demonstrated in a recent systematic review that primary care physicians tend to use additional testing to confirm the diagnosis, arguably as a consequence of the current criteria not having the required sensitivity and specificity to ameliorate concerns regarding diagnostic uncertainty [41]. Given the sub-optimal characteristics of current symptom-based diagnostic criteria, various quantitative biomarkers have been investigated. Recently, Camilleri *et al*. reported that total faecal bile acids, in conjunction with the measurement of colonic transit, were of utility in discriminating between health and the IBS state, as well as subtypes of IBS [42]. In this study, faecal bile acids were elevated in patients with IBS-D, although 15.6% had undergone a previous cholecystectomy and BAM was not screened for. Therefore, such biomarkers may be delineating the presence of BAM rather than IBS *per se* considering that faecal bile

acids may be elevated in the former [43]. Future guidelines could adopt an alternative stratagem where patients with IBS-D like symptoms undergo a "test and treat" approach for BAM, analogous to that widely utilised for dyspepsia [44]. However, such an approach is likely to be limited by the cost and availability of SeHCAT testing, as it is currently only available in 30-40% of GI centres in the UK. A diagnostics consultation document from the National Institute of Health and Care excellence concluded that presently there is insufficient evidence regarding the cost effectiveness of using SeHCAT in IBS-D, although further research is warranted [45]. Nevertheless the lack of availability of SeHCAT testing, particularly in the USA, prompts the use of an empirical trial of bile acid sequestrants as a surrogate diagnostic measure. This lack of availability of such testing should not discourage healthcare providers from the use of such a pragmatic empirical trial of therapy, although this is often limited by an individual's tolerability of bile acid sequestrants.

Our findings have important ramifications for a) the interpretation of existing data and b) the design of future studies. With respect to the former, many studies have evaluated both pathophysiological and therapeutic aspects of IBS-D. To date, the overwhelming majority of such studies have not actively sought to exclude BAM as a differential diagnosis and therefore the homogeneity of study populations becomes limited. Therefore such data are skewed and thus the interpretation of the true effect of the observation/therapeutic intervention becomes more challenging to interpret given this confounder. Therefore future studies could be markedly improved by actively screening for BAM as part of the inclusion criteria, thereby improving the homogeneity of participants.

This study is not without significant limitations. There was significant heterogeneity seen in all of the analyses, which was not explained by our subgroup analyses. On account of the strict set of inclusion criteria, the number of studies yielded from the literature search was relatively small and therefore did not permit formal assessment of publication bias. Two of the studies identified applied the Rome criteria retrospectively, which could potentially introduce a degree of ascertainment bias although Vanner and colleagues suggest that there is only a marginal difference in positive predicted value between retrospective and prospective application of the Rome criteria [46]. Moreover, all the studies reported herein are either from secondary or tertiary care centres and thus the applicability to community populations, as mentioned earlier, remains speculative. Similarly, other concerns regarding generalizability focus on the fact that we chose to use <10% SeHCAT retention at 7 days as our cut off for delineating BAM. We chose this particular cut off for two reasons. Firstly, in order to report a more conservative estimate of prevalence rates in comparison to using <15% and secondly to provide a more clinically applicable result, as the probability of a positive therapeutic response to bile acid sequestrants is negatively associated with retention rates [47]. We also chose to use SeHCAT testing as the reference standard for diagnosing BAM, although hitherto the diagnostic accuracy of SeHCAT has only been evaluated by response to treatment with bile acid sequestrants, and therefore maybe liable to assessment bias due to lack of blinding both in investigators and patients [47]. Furthermore, the lack of availability of SeHCAT testing outside Europe has limited the geographical spread from which studies could have been undertaken. As a consequence, the generalizability to other IBS-D

populations around the world is purely conjectural, although there is little objective evidence to suggest that prevalence rates of BAM would be significantly different elsewhere.

In conclusion, our results demonstrate that in excess of 1 in 4 patients meeting internationally accepted criteria for IBS-D have BAM. Considering the marked socioeconomic burden of IBS-D, in conjunction with the efficacy of bile acid sequestrants in treating BAM, such a distinction has meaningful implications for contemporaneous clinical practice, future guideline development and research.

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CONFLICT OF INTEREST/STUDY SUPPORT

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ACF - supervised the study, conducted the meta-analysis and revised the manuscript for important intellectual content.
QA - supervised the study, conducted the meta-analysis and revised the manuscript for important intellectual content.
ADF - performed the methodological assessment and revised the manuscript for important intellectual content.

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