



Brief report: length of ileal resection correlates with severity of bile acid malabsorption in Crohn's disease

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Abstract

Purpose Bile acid malabsorption (BAM) is a common cause of diarrhoea in Crohn's disease (CD) patients with ileal resection. BAM is usually diagnosed by selenium-labelled homotaurocholic acid test (75SeHCAT) but its availability is limited. Consequently, a large proportion of patients either remain undiagnosed or subject to empirical therapy. There is a paucity of studies examining the correlation between length of ileal resection and severity of BAM, which will be of use to clinicians with no recourse to diagnostic testing for BAM.

Methods We tested the correlation between length of resected ileum and percentage retention on 75SeHCAT of all CD patients with a prior surgical resection who underwent 75SeHCAT testing. Response to treatment with bile salt sequestrant and 75SeHCAT retention values was tested using Fisher's exact test.

Results A total of 91 patients were identified with a median age of 47 (IQR 21–80). The median length of resected ileum was 24 cm (range 15–165 cm) with a median of 1 resection (range 1–4). Overall, 88 patients (97%) had 75SeHCAT retention values of < 10% and 85 (93%) had retention of < 5%. There was a modest correlation between 75SeHCAT retention and length of ileal resection (Spearman's rho = 0.392, $P = 0.0001$). Data on response to treatment was available for 57 (63%) patients, of who 38 (67%) responded to bile salt sequestrant. There was no difference in 75SeHCAT retention values between responders and non-responders.

Conclusions There was a modest correlation between length of ileal resection and severity of BAM as defined by 75SeHCAT retention values. Response to bile salt sequestrant therapy was not dependent on 75SeHCAT retention values.

Keywords Inflammatory bowel disease · Crohn's disease · Ileal resection · Bile acid malabsorption

Introduction

A significant proportion of patients with ileal Crohn's disease (CD) undergo surgical resection at some point during their disease course [1]. Bile acid malabsorption (BAM) is a common complication of ileal resection and causes diarrhoea, hyperoxaluria with renal stone formation [2] and pigment gallstone formation [3]. Despite its potential to cause problems, the identification and treatment of BAM is

suboptimal. A recent survey of gastroenterologists showed heterogeneity among both the type of assays and their availability to diagnose BAM [4]. Current methods to diagnose BAM include faecal bile acid (BA) determination, labelled BA retention tests such as the 75Se-homotaurocholic acid test (75SeHCAT), determination of plasma metabolites of the BA biosynthetic pathway such as plasma levels of lathosterol, 7 α -hydroxycholesterol, or 7 α -hydroxycholest-4-en-3-one (C4) and the measurement of the levels of plasma FGF [5]. 75SeHCAT is often the most widely used and considered the "gold standard" diagnostic marker with a high sensitivity (80–90%) and specificity (70–100%) for diagnosing BAM [6]. However, it is not widely available mainly because of cost and logistical reasons, and it has never been approved for use in some countries, including the USA [7].

The lack of widely available diagnostic assays for BAM means that clinicians often empirically treat patients with

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symptoms of diarrhoea following ileal resection even though many patients have normal enterohepatic circulation despite ileal resection [4]. Thus, studies examining the correlation between length of resection and severity of BAM are likely beneficial to clinicians who do not have access to testing for BAM. Previous studies in this area have been limited as BAM was diagnosed using serum C4 [4], a less reliable marker of BAM, due to its diurnal variation [8] and methodological demands [9]. We sought to examine the correlation between length of ileal resection and severity of BAM, as assessed by ⁷⁵SeHCAT testing.

Methods

We conducted a retrospective study of Crohn's disease patients attending a specialist IBD clinic in the UK. The diagnosis of Crohn's disease was established using conventional clinical, endoscopic and radiological criteria. Patients who had a previous resection and had a subsequent ⁷⁵SeHCAT scan were eligible for inclusion. The need for ⁷⁵SeHCAT scan was determined by the treating clinician and the test was performed using a standard protocol as described previously [10] and the percentage of radiolabelled bile salt retention was recorded. The following details were subsequently extracted from the case notes: disease duration, disease location and maximal extent, smoking status, concurrent medications, details of previous surgery, length of resected ileum from histopathology report, details of bile salt sequestrant therapy and response to therapy. Response to bile salt sequestrant therapy was defined as a reduction in stool frequency following treatment.

Statistical analysis

Patient demographics are summarised as median (IQR) for continuous variables and frequency (%) for categorical variables. Spearman's rank correlation coefficients (Spearman's rho) were calculated to assess correlation between continuous variables (length and number of ileal resections versus percentage of radiolabelled bile salt retention). Mann-Whitney test was used to determine relationship between percentage of radiolabelled bile salt retention and response to therapy. All analysis was performed using Stata v15 software (State Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

A total of 91 patients were included, with a median age of 47 (inter-quartile range, IQR 21–80). The baseline characteristics of the included subjects including disease and treatment details are summarised in Table 1. Most patients (88/90) had

Table 1 Baseline characteristics of included subjects

	Number (%)	Median (range)
Age, median (range)		47 (21, 80)
CRP		
< 5	66 (73)	
≥ 5	12 (13)	
Missing	13 (14)	
Disease location		
Ileal	39 (39.8)	
Ileocolonic	48 (48.9)	
Colonic	5 (5.1)	
Ileal with perianal involvement	4 (4.1)	
Colonic with perianal involvement	2 (2.0)	
Medications		
Thiopurines	58 (64)	
Biologics	33 (36)	
Colesevelam	27 (30)	
Questran	39 (43)	
Colesevelam and Questran	2 (2)	
Missing	23 (25)	
Smoking status		
Yes	20 (22)	
No	59 (65)	
Missing	12 (13)	
Number of previous resections		
1	63 (69)	
2	19 (21)	
3	6 (7)	
4	3 (3)	

BAM as defined by a ⁷⁵SeHCAT retention of < 10% and 85 patients (94.4%) had severe BAM with a retention of < 5%.

Correlation between length/number of ileal resection and severity of BAM

There was a modest, negative relationship between length of ileal resection and percentage retention on ⁷⁵SeHCAT scan (Fig. 1) ($r_s = -0.392$, $P = 0.0001$). There was a highly significant difference in ⁷⁵SeHCAT retention between patients with moderate (< 50 cm, median (range) 0.03% (0, 49.8), $n = 78$) and extensive resection (> 50 cm, median (range) 0.01 (0, 0.1)%, $n = 12$; $P = 0.0064$) There was no correlation between number of resections and severity of BAM ($r_s = -0.1142$, $P = 0.2837$).

Correlation between severity of BAM and response to therapy

Of the 91 patients, 68 (75%) patients were on sequestrant therapy and 57 (63%) had data on response to therapy

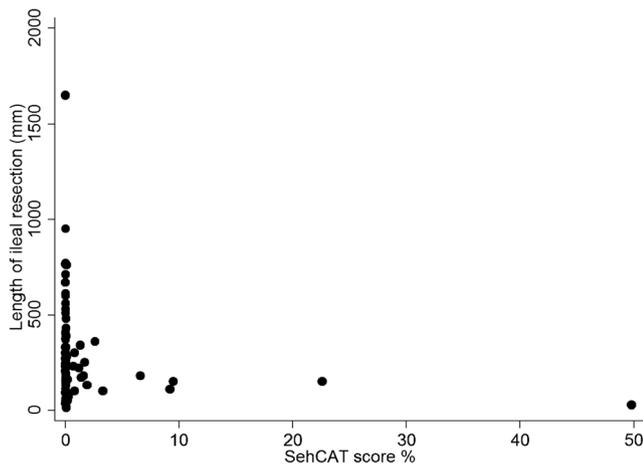


Fig. 1 Correlation between length of ileal resection and severity of BAM as defined by % retention on 75SeHCAT scan

(Table 2). Thirty-eight patients (67%) responded to therapy and 19 (33%) failed to respond. There was no difference in the 75SeHCAT retention values of responders (median (range) = 0.02 (0, 6.6)%) compared to non-responders (median (range) = 0.01 (0, 1.3), $P = 0.9309$).

Discussion

In this study, we report a modest correlation between length of resected ileum and severity of BAM. Our findings are broadly comparable to previously reported studies with some notable differences. Firstly, our findings of a high prevalence of bile salt diarrhoea in resected patients are consistent with previously reported studies [4, 11]. This is likely due to selection of patients with a high a priori probability of BAM for 75SeHCAT testing. We did note a significant difference in severity of BAM in patients undergoing less extensive compared to more extensive ileal resection. This is similar to the findings reported

by Lenicek et al. [4] despite the different methods used to diagnose BAM by the two studies. In our study, even patients with minimal ileal resection (< 10 cm) had severe BAM. This is not entirely unexpected as active uptake of BA is confined to the distal ileum and previous studies have shown that resections as low as 30 cm is associated with increased faecal BA loss [12].

We did not note a correlation between degree of 75SeHCAT retention and response to bile salt sequestrant therapy. Previous studies have shown that patients with severe BAM are more likely to respond to treatment in unexplained chronic diarrhoea [13], collagenous colitis [14] as well as Crohn's disease [4, 11]. The differences in findings are likely explained by several factors: firstly, we had insufficient number of patients with mild to moderate BAM to allow meaningful comparisons across the two groups. Moreover, due to the retrospective nature of the study, we were unable to obtain response data in a third of our patients. Finally, we were unable to establish factors such as adherence to treatment, which may have influenced response to treatment.

Our study has several important strengths and limitations. We used the more sensitive 75SeHCAT to assess severity of BAM, unlike previous studies, which used serum C4. The need for 75SeHCAT testing was determined by the testing clinician and we were unable to establish a true prevalence of BAM in this population. It has been previously noted that patients have evidence of BAM on biochemical testing despite a lack of symptoms [4]. Due to the retrospective nature of the study, we were unable to obtain treatment response data in a structured manner. This may have resulted in a false-negative result between severity of retention and treatment response unlike previous studies. Future studies should be performed to establish the true prevalence of BAM in patients undergoing ileal resection and use systematic approaches to measure response to sequestrant therapy.

In conclusion, we show that there is a modest correlation between length of ileal resection and severity of BAM. Patients with less extensive resection but suggestive symptoms of BAM should be tested and treated with bile salt sequestrant therapy.

Table 2 Correlation between severity of BAM and response to bile salt sequestrant therapy

% retention on 75SeHCAT	Response: number (% within SeHCAT category)			
	No	Yes	Missing	Total
≤ 5%	19 (22.4)	37 (43.5)	29 (34.1)	85
> 5–10%	0 (0)	1 (33)	2 (67)	3
> 10–15%	–	–	–	–
> 15%	0 (0)	0 (0)	2 (100)	2
Missing			1 (100)	1
Total	19 (21%)	38 (42%)	34 (37%)	91

Author contributions TS, YP, JR and NM were involved in data collection. SD conducted the data analysis. All authors were involved in drafting and final revision of the manuscript.

Compliance with ethical standards

Conflict of interest TS, SD, YP, JR and NM have no conflicts of interest. SS has received speaker fee from MSD, Actavis, Abbvie, Dr. Falk pharmaceuticals, Shire and received educational grant from MSD, Abbvie, Actavis and is an advisory board member for Abbvie, Dr. Falk pharmaceuticals, Janssen and Vifor pharmaceuticals.

References

1. Goldberg PA, Wright JP, Gerber M, Claassen R (1993) Incidence of surgical resection for Crohn's disease. *Dis Colon Rectum* 36(8):736–739
2. Chadwick VS, Modha K, Dowling RH (1973) Mechanism for hyperoxaluria in patients with ileal dysfunction. *N Engl J Med* 289(4):172–176. <https://doi.org/10.1056/NEJM197307262890402>
3. Vitek L, Carey MC (2012) New pathophysiological concepts underlying pathogenesis of pigment gallstones. *Clin Res Hepatol Gastroenterol* 36(2):122–129. <https://doi.org/10.1016/j.clinre.2011.08.010>
4. Lenicek M, Duricova D, Komarek V, Gabrysova B, Lukas M, Smerhovsky Z, Vitek L (2011) Bile acid malabsorption in inflammatory bowel disease: assessment by serum markers. *Inflamm Bowel Dis* 17(6):1322–1327. <https://doi.org/10.1002/ibd.21502>
5. Vijayvargiya P, Camilleri M, Shin A, Saenger A (2013) Methods for diagnosis of bile acid malabsorption in clinical practice. *Clin Gastroenterol Hepatol* 11(10):1232–1239. <https://doi.org/10.1016/j.cgh.2013.04.029>
6. Wilcox C, Turner J, Green J (2014) Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. *Aliment Pharmacol Ther* 39(9):923–939. <https://doi.org/10.1111/apt.12684>
7. Camilleri M (2014) Advances in understanding of bile acid diarrhea. *Expert Rev Gastroenterol Hepatol* 8(1):49–61. <https://doi.org/10.1586/17474124.2014.851599>
8. Kovar J, Lenicek M, Zimolova M, Vitek L, Jirsa M, Pitha J (2010) Regulation of diurnal variation of cholesterol 7 α -hydroxylase (CYP7A1) activity in healthy subjects. *Physiol Res* 59(2):233–238
9. Lenicek M, Juklova M, Zelenka J, Kovar J, Lukas M, Bortlik M, Vitek L (2008) Improved HPLC analysis of serum 7 α -hydroxycholest-4-en-3-one, a marker of bile acid malabsorption. *Clin Chem* 54(6):1087–1088. <https://doi.org/10.1373/clinchem.2007.100107>
10. Merrick MV, Eastwood MA, Ford MJ (1985) Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention. *Br Med J (Clin Res Ed)* 290(6469):665–668
11. Nyhlin H, Merrick MV, Eastwood MA (1994) Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. *Gut* 35(1):90–93
12. Aldini R, Roda A, Festi D, Sama C, Mazzella G, Bazzoli F, Morselli AM, Roda E, Barbara L (1982) Bile acid malabsorption and bile acid diarrhea in intestinal resection. *Dig Dis Sci* 27(6):495–502
13. Williams AJ, Merrick MV, Eastwood MA (1991) Idiopathic bile acid malabsorption—a review of clinical presentation, diagnosis, and response to treatment. *Gut* 32(9):1004–1006
14. Eusufzai S, Axelson M, Angelin B, Einarsson K (1993) Serum 7 α -hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. *Gut* 34(5):698–701