ORIGINAL ARTICLE

Bile Acid Malabsorption in Patients with Neuroendocrine Tumors

Lehar Khanna[1] · Thorvardur R. Halfdanarson[2] · Mohamad B. Sonbol[2] · Rachel Eiring[2] · Teresa Prond[2] ·
Michael Camilleri[1]

Abstract

Background Chronic diarrhea in patients with neuroendocrine tumors (NET) may be caused by bioactive products of NET, bile acid malabsorption (BAM), ileal resection (IR) or steatorrhea.

Aim To quantitate BA and fat malabsorption in NET with diarrhea.

Methods Part of evaluation in medical oncology clinical practice, 67 patients [42F, 25 M; median age 64.0 y (17.0 IQR)] with well-differentiated NET and diarrhea underwent clinically indicated measurements of 48-h fecal BA [(FBA), fecal weight (normal < 400 g/48 h), fecal fat (normal < 7 g/day) in $n = 52$] and fasting serum 7αC4 (marker of hepatic BA synthesis, $n = 30$) between 01/2018 and 11/2020. IR had been performed in 45 patients. BAM diagnosis was based on FBA criteria: elevated total FBA (> 2337 μmol/48 h) or > 10% primary FBA or combination > 4% primary FBA plus > 1000 μmol total FBA/48 h. We also measured fecal elastase (for pancreatic insufficiency) in 13 patients.

Results BAM was present in 48/52 (92%) patients with NET. There were significant correlations between total FBA and 48-h fecal weight ($R_s = 0.645$, $P < 0.001$). Mean length of IR was 47 cm; in patients with IR < 25 cm, total FBA was elevated in 85% and primary FBA > 10% in 69%. In 22 patients with no IR, 13/15 tested (87%) had BAM. Among 6 patients with pancreatic NET and no IR, 80% had BAM. Fecal fat was ≥ 15 g/day in 18/42 (43%). In 4/17 (24%) with IR < 25 cm and 8/19 (42%) patients with IR > 25 cm fecal fat was 44.0 (40.5) and 38.0 (38.0)g/day, respectively.

Conclusion A majority of patients with NET and diarrhea had BAM, even with < 25 cm or no IR.

Keywords Steatorrhea · Somatostatin · Pancreas · Primary

Introduction

Chronic diarrhea is very frequent in patients with gastro-enteropancreatic neuroendocrine tumors, which hyper-secrete serotonin and other vasoactive peptides such as histamine, prostaglandins, kallikrein, neurokinin, and tachykinins. When diarrhea occurs, about 80% of patients have hepatic metastases which increase the mass of tumor tissue synthesizing the mediator of hormonal diarrhea. The Carcinoid Syndrome Control Collaborative [1] has drawn attention to the fact that diarrhea may develop in response to other hormonal syndromes associated with neuroendocrine tumors, surgical complications, medical comorbidities, medications, or food sensitivities. In addition, the Collaborative proposed an algorithm for management based on clinical evaluation, differentiation between secretory and osmotic (non-secretory) diarrhea based on the absence of a stool osmotic gap [Osmolar gap (mOsm/kg) = 290 − 2(stool [Na +] + [K +])] and positive identification of neuroendocrine tumor diarrheal syndromes (such as gastrinoma or VIPoma), identification of maldigestion, inflammation or malabsorption. Malabsorption may be the result of resection of the intestinal or pancreatic neuroendocrine tumors or coincidental small intestinal or pancreatic disease.

When no reversible cause is identified, treatment paradigms for diarrhea range from surgical debulking to liver-directed therapies to treatment with somatostatin analogs,

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✉ Michael Camilleri
camilleri.michael@mayo.edu

1 Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905, USA

2 Division of Medical Oncology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905, USA

nonspecific anti-diarrheal agents as well as a tryptophan hydroxylase inhibitor [2]. Somatostatin analogs for diarrhea with neuroendocrine tumor may cause steatorrhea secondary to drug-induced exocrine pancreatic insufficiency, potentially complicating the etiology of the diarrhea. Patients with neuroendocrine tumors (NET) are commonly referred for evaluation of refractory diarrhea which significantly impacts the quality of life of the patients in addition to indirect costs related to work productivity losses [3], but clinical experience has shown that the etiology of the diarrhea is not the neuroendocrine syndrome itself, but either bile acid malabsorption or steatorrhea. Identification of either bile acid malabsorption or steatorrhea in patients with NET provides an opportunity to enhance the management of the diarrhea (for example by administration of bile acid sequestrants or pancreatic enzyme supplementation respectively), as well as reduction of NET-related healthcare expenditures through preventive treatment and appropriate management of the associated diarrhea which has been shown to increase the healthcare costs in patients with NET [4, 5]. Therefore, there is an opportunity to impact the screening of patients with diarrhea associated with NET. However, the prevalence of these alternative causes of diarrhea in a large cohort of patients with NET has not been described.

The primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized from cholesterol and conjugated in the liver and are actively and efficiently (~90%) reabsorbed in the ileum through the apical sodium bile acid transporter (ASBT, also called ileal bile acid transporter or IBAT). The bile acids and the enteroendocrine hormone, fibroblast growth factor-19 (FGF-19), produced in ileal enterocytes are transported via the portal circulation to the hepatocytes to decrease synthesis of bile acids, with reduced production of an intermediate by-product called 7α-hydroxy-4-cholesten-3-one (7αC4) [6]. The circulating level of 7αC4 is an indirect marker of the rate of bile acid synthesis in hepatocytes and is directly correlated with fecal bile acid excretion [7]. The human colon reabsorbs, by diffusion, at least 50% of the mass of bile acids reaching the colon [8]; hence, about 5% of the bile acids is normally lost each day in stool.

Given the propensity for NET to occur in the ileocolonic region and the frequent requirement of surgical resection, bile acid malabsorption is recognized as a complication that may lead to diarrhea, and screening or treatment of bile acid malabsorption is recommended in several recent reviews [2, 9, 10]. Prior literature has not addressed the relationship between NET with limited or no ileal resections and the potential for bile acid malabsorption as the cause of diarrhea [1, 11, 12].

Bile acid malabsorption may result in diarrhea due to stimulation of secretory mechanisms (as reviewed elsewhere) [13] or stimulation of colonic motility including high amplitude colonic contractions [14], with stimulation of TGR5 (G protein coupled bile acid receptor 1) [15]. Bile acid diarrhea type III has also been associated with chronic pancreatic insufficiency, small intestinal mucosal diseases, or bacterial overgrowth [16]. Evidence of a motor component of carcinoid diarrhea has been well documented [17].

Recent research has validated biochemical measurements for the diagnosis of bile acid malabsorption; these are fasting serum 7αC4 (a marker of hepatocyte bile acid synthesis) and total fecal bile acid excretion and fecal primary bile acid (CA plus CDCA) excretion over 48 h [18]. These tests are available through reference laboratories and may be simplified by combining fasting serum 7αC4 and the percent of primary fecal bile acids in a random stool sample [19].

The aim of our study was to quantitate bile acid excretion and synthesis, stool weight and fat malabsorption in patients with NET and diarrhea in tertiary referral practice.

Methods

Participants and Medical Record Review

We reviewed the electronic medical records of 67 patients with well-differentiated NET, age 18–85 years, who underwent clinically indicated 48-h fecal bile acid and fat tests (from 01/2018 to 11/2020). Demographics (age, gender, BMI), fecal weight, comorbidity and specifically extent of ileal resection, prior cholecystectomy, pancreatic surgery, presence of hepatic metastases, biochemical markers of neuroendocrine tumors (such as serum chromogranin and 24-h urine 5-HIAA), and fecal bile acid and fat measurements were collected from the medical records.

Measurement of Fecal Bile Acids and Fecal Fat

Since the ^{75}SeHCAT retention test is not available in the United States, the diagnosis of bile acid diarrhea is based on either fecal bile acid excretion or measurement of fasting 7αC4.

Patients completed a 4-day, 100-g fat diet, with a 48-h stool collection for total and individual fecal bile acids. The same 48-h stool collection can also be used to estimate fecal fat excretion, and the protocol used is standard in clinical practice for the diagnosis of fat malabsorption (van der Kamer test, see below). Using high performance liquid chromatography (HPLC)/tandem mass spectrometry (MS), we have adapted a method used with serum samples for fecal bile acid measurement [20]. The method for stool processing, homogenization, methanol extraction, and purification on C18 column prior to HPLC/MS measurement is detailed elsewhere [7]. Increased fecal bile acid excretion, indicative of bile acid malabsorption, was defined

as: elevated total fecal bile acids (> 2337 μmol total bile acids/48 h) or elevated primary fecal bile acids (> 10% primary bile acids) or the combination of > 4% primary bile acids plus > 1000 μmol total bile acids/48 h [21]. Fecal weight over 48 h was recorded by the same laboratory that performed the fecal bile acid and fat measurements. Normal fecal weight is 400 g/48 h.

Fecal fat was measured in the Department of Laboratory Medicine and Pathology at Mayo Clinic using an adaptation of the van der Kamer test using an aliquot from the 48-hour stool collection. Total fecal fat in the 48-hour collection was divided by 2 and reported as g/24 h. The upper limit of normal for fecal fat is 7 g/day. In addition to identifying patients with steatorrhea based on fecal fat greater than 7 g/day, we also assessed when the patients passed more than 15 g fat/day in stool, given the evidence that induction of watery diarrhea with an osmotic laxative in healthy volunteers may result in up to 15 g fecal fat/day [22].

Other Measurements

Fecal elastase was measured on a separate random stool sample in order to screen for pancreatic exocrine insufficiency in 13 patients in whom this diagnosis was entertained clinically. Fasting serum 7αC4 marker of hepatic bile acid synthesis [23] was measured in samples collected before 10:00 a.m. (to avoid known diurnal variation) and assayed by HPLC/MS. Levels of 7αC4 > 52.5 ng/mL are suggestive of bile acid diarrhea.

Serum chromogranin A was available at multiple times in these patients; the measurement included in this analysis corresponded to the sample acquired closest to the time of the 48-h stool collection for bile acids and fat.

Statistical Analysis

We compared results of continuous variables (total and primary fecal bile acids and serum 7αC4) in patients with ileal resection with or without cholecystectomy using 2-sample Mann–Whitney rank sum test. Other results tabulated were based on descriptive statistical analysis using median (IQR) unless otherwise stated.

Results

Clinical Features of Patients with Neuroendocrine Tumors

Demographics as well as length of ileal resection (which was documented precisely in the medical records in 36/45 patients), presence of hepatic metastases, and markers of NET, specifically serum chromogranin A and plasma, and

24-h urine 5-HIAA are summarized in Table 1. The vast majority of patients (43%) had evidence of hepatic metastatic disease, and the biochemical markers of NET were elevated; for example, for the entire group of 56 patients with measurements of serum chromogranin, almost 50% had levels greater than the upper limit of normal of 93 ng/mL. Evidence of diarrhea was documented by fecal weight over 48 h of 82% for the entire group and 88% for those with ileal resection having fecal weight > 400 g/48 h. In the 22 patients without ileal resection, the percentage with fecal weight > 400 g/48 h was 66.67%.

Three patients were receiving telotristat and 23 were receiving somatostatin analogs (18 octreotide and 5 lanreotide).

Bile Acid Measurements and Relationship with Fecal Weight in Patients with Neuroendocrine Tumors

This information is also summarized in Tables 1 and 2, which also provide the normal values for the different biochemical parameters and illustrate the high prevalence of abnormal tests reflecting bile acid synthesis and fecal excretion (as summarized below). Bile acid malabsorption was present in 48/52 patients. There were significant correlations between total fecal bile acids and 48-h stool weight in the overall 51 patients with or without ileal resection ($R_s = 0.645$, $P < 0.001$), and in the 36 patients with ileal resection ($R_s = 0.621$; $P < 0.0001$) (Fig. 1, left panels). There were weaker (significant) correlations between primary fecal bile acids and fecal weight in the entire group of 51 patients ($R_s = 0.30$, $P = 0.0324$) and the 36 patients with ileal resection ($R_s = 0.336$, $P = 0.0452$) (Fig. 1, right panels).

Impact of Length of Ileal Resection and Cholecystectomy on Bile Acid Malabsorption in Neuroendocrine Tumors

The mean length of ileal resection (in 45/67 patients) was 47 cm; the median length of ileal resection was 33 [55 cm (IQR)] in those with cholecystectomy, and 26 [72 cm (IQR)] without cholecystectomy ($P = 0.985$). There were no significant differences in bile acid parameters between patients with ileal resection and prior history of cholecystectomy or lack of cholecystectomy (Table 1: total fecal bile acid $P = 0.462$, primary fecal bile acids $P = 0.973$ or serum 7αC4 $P = 0.806$). Similarly, there were no significant differences in 24-h fecal fat ($P = 1.0$) and total fecal weight per 48 h ($P = 0.315$).

In patients with ileal resection < 25 cm, total fecal bile acid was elevated in 11/13 (85%) and primary fecal bile acids > 10% in 9/13 (69%), and these were also associated with elevated fecal weight in 12/13 patients (Fig. 2).

Table 1 Clinical features of patients with neuroendocrine tumors who had undergone fecal bile acid measurements

Characteristics	All patients with available data (Total N=67)		Patients without ileal resection (n=22)		All patients with ileum resection (n=45)							
					Patients with any ileum resection (N=45)		Patients with ileum resection <25 cm (N=17)		Patients with cholecystectomy (N=35)		Patients without cholecystectomy (N=10)	
	N	Median (IQR)	N	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Females	42		15		27		11		22		5	
Males	25		7		18		6		13		5	
Age, years	67	64.0 (53.0,70.0)	22	60.5 (46.0,73.2)	45	64.0 (56.0,69.0)	17	59.0 (49.5,68.0)	35	64.0 (54.0,69.0)	10	66.0 (57.5,72.2)
Length ileum resection, cm	36*	32.5 (14.6,69.2)			36	32.5 (14.6,69.2)	17	14.5 (8.7,18.0)	28	33.0 (14.6,69.2)	8	26.5 (12.9,85.2)
Serum chromogranin A, ng/ml	56	88.5 (47.5,228.2)	16	75.0 (49.2,210.7)	40	93.5 (47.0,307.2)	15	93.0 (47.0,245.0)	32	93.5 (51.0,361.7)	8	85.0 (44.0,225.5)
Plasma 5-HIAA	18	32.5 (9.0,127.0)	2	48.0 (9.0,87.0)	16	32.5 (10.7,197.5)	8	41.0 (11.0,550.0)	13	32.0 (12.5,148.0)	3	41.0 (8.0,391.0)
Urine 5-HIAA mg/24 h	31	5.3 (3.0,13.0)	9	3.0 (2.1,3.6)	22	6.5 (4.5,19.8)	8	8.9 (5.7,551.5)	17	6.7 (4.4,47.0)	5	6.4 (4.2,9.5)
Number with liver metastases	29		5		24		9		22		2	
Total fecal BA, μmol/48 h	52	3514.0 (2053.7,6320.7)	15	2016.0 (627.0,3363.0)	37	4448.0 (3011.5,8483.5)	13	4801 (3514.0,7554.5)	27	4448.0 (3220.0,9302.0)	10	4143.0 (2408.7,6203.7)
1° fecal BA, %	52	36.5 (9.2,91.1)	15	17.5 (8.9,52.0)	37	60.0 (14.0,95.7)	13	34.5 (8.0,92.1)	27	60.0 (8.7,95.8)	10	50.6 (16.6,93.0)
Fecal fat, g/24 h	42	13.0 (6.0,35.2)	12	6.5 (5.2,14.5)	30	16.5 (8.7,38.0)	8	17.5 (12.2,51.5)	23	14.0 (9.0,38.0)	7	33.0 (6.0,38.0)
Fecal weight, g/48 h	51	716.0 (480.0,1089.0)	15	553.0 (344.0,850.0)	36	835.5 (530.5,1144.2)	13	855.0 (633.5,1129.5)	27	873.0 (580.0,1201.0)	9	653.0 (439.0,1029.5)
Fasting 7αC4 ng/mL	30	53.1 (34.9,142.0)	7	20.5 (6.4,49.6)	23	72.4 (39.5,187.0)	13	114 (44.8,170.5)	17	72.4 (39.5,170.5)	6	85.1 (39.3,224.5)
Fecal elastase μg/g	13	344.0 (20.0,443.0)	2	179.0 (14.0,344.0)	11	368.0 (24.0,497.0)	3	28 (24.0,368.0)	10	370 (27.0,497.7)	1	14.0 (14.0,14.0)

*Among 45 patients with ileum resection, exact length of resection was available in 36 patients upon medical record review

BA = bile acids; 1° fecal BA = primary fecal bile acids (chenodeoxycholic acid + cholic acid);

Abnormal values: Serum chromogranin A > 93 ng/ml; Urine 5-HIAA > 10.0 mg/24 h; plasma 5-HIAA > 22 ng/ml; Total fecal bile acids > 2337 μmol/48 h; Primary fecal bile acids > 10%; Total fecal fat > 7 g/24 h; Fasting serum 7αC4 > 52.5 ng/ml; Fecal elastase < 200 μg/g

Table 2 Number of abnormal bile acid and fat malabsorption tests in patients with neuroendocrine tumors and diarrhea

Bile acid or fat malabsorption test	All patients with available data (Total $N=67$)		Patients without ileal resection ($N=22$)		All patients with ileum resection ($n=45$)							
					Patients with any ileum resection ($N=45$)		Patients with ileum resection <25 cm ($N=17$)		Patients with cholecystectomy ($N=35$)		Patients without cholecystectomy ($N=10$)	
	n	% abnormal	N	% abnormal	n	% abnormal	n	% abnormal	n	% abnormal	n	% abnormal
Fecal weight $>$ 400 g/48 h	51	82.3%	15	33.3%	36	88.9%	13	92.3%	27	92.6%	9	77.8%
Total fecal BA >2337 μmol/48 h	52	71.1%	15	40.0%	37	83.8%	13	84.6%	27	85.1%	10	80.0%
1° fecal BA >10%	52	75.0%	15	73.3%	37	75.7%	13	69.2%	27	74.1%	10	80.0%
Total fecal BA >1000 μmol/48 h and 1° fecal BA >4%	52	78.8%	15	53.3%	37	89.1%	13	84.6%	27	88.9%	10	90.0%
Fasting 7αC4 >52 ng/mL	30	50.0%	7	14.3%	23	60.9%	13	69.2%	17	58.8%	6	66.7%
Fecal fat ≥ 7 g/24 h	42	73.8%	12	50.0%	30	83.3%	8	87.5%	23	86.9%	7	71.4%
Fecal elastase <200 μg/g	13	38.5%	2	50.0%	11	36.4%	3	66.7%	10	30.0%	1	100%

BA = bile acids, 1°fecal BA = primary fecal bile acids (chenodeoxycholic acid+cholic acid)

Twenty-two patients had not undergone ileal resection; their primary neuroendocrine tumors were: 6 ileocolonic, 6 lung, 6 pancreatic, 1 rectal, 3 unknown primary site. Fifteen of these patients had fecal bile acid measurements; 13/15 (87%) had elevated fecal bile acids (by one or more of the diagnostic parameters based on 48 h stool measurements); 7 of 13 patients with elevated fecal bile acids had undergone prior cholecystectomy, whereas 6 had not. Of 6 patients with pancreatic neuroendocrine tumors, 4 had liver metastases, and 4/5 had bile acid malabsorption.

Fecal Fat Measurements in Patients with Neuroendocrine Tumors

Among 42 patients with fecal fat measurement, 18/42 had fecal fat ≥ 15 g/24 h.

In 19 patients with ileal resection >25 cm, the median fecal fat was 33.0 g/day (29.0). In 8 patients with ileal resection >25 cm and fecal fat ≥ 15 g/24 h, fecal fat was 38.0 g/day (38.0); 6 (4 octreotide and 2 lanreotide) of these 8 patients were being treated with somatostatin analogs (5 long- and 1 short-acting).

In 17 patients with ileal resection <25 cm, the median fecal fat was 17.5 g/day (39.25).

In 4 (3 octreotide and 1 lanreotide) patients with ileal resection <25 cm and fecal fat >15/day, fecal fat was 44.0 g/day (40.5). All 4 patients were receiving somatostatin analogs (3 long- and 1 short-acting).

Fecal elastase was measured in 13 patients, of whom 11 also had quantitative fecal fat and 10 had proven steatorrhea (>7 g fat/day). Among the 10 patients with steatorrhea, fecal elastase was low (that is, <200 μg/g) in 4 patients, 3 of whom had undergone ileal resection and 1 had prior pancreatic resection for NET. Three of the 4 patients with low fecal elastase were also receiving somatostatin analogs (2 long- and 1 short-acting).

Discussion

This study showed that 92% of patients with NET had evidence of bile acid malabsorption, even patients with ileal resection <25 cm. Moreover, 87% of those with NET and no ileal resection had bile acid malabsorption. A third observation is that extensive ileal resection, typically >50 cm, and treatment with somatostatin analogs are associated with steatorrhea in patients with NET. There was no significant effect of cholecystectomy on the bile acid malabsorption in patients with NET who underwent ileal resection. Therefore, the observed bile acid malabsorption cannot be attributed to prior cholecystectomy.

It is often assumed that bile acid malabsorption is observed when ileal involvement/resection is >100 cm [1]. However, with ileal resections >100 cm, steatorrhea occurred secondary to bile acid deficiency due to chronic loss, whereas bile acid malabsorption responsive to bile acid sequestrant resulted from resections <100 cm [11, 12]. There is also evidence that ileal resections <50 cm for Crohn's disease may result in bile acid malabsorption [24].

In prior studies [25], the mean primary fecal bile acid excretion in IBS with diarrhea was 14%, and, in IBS-diarrhea
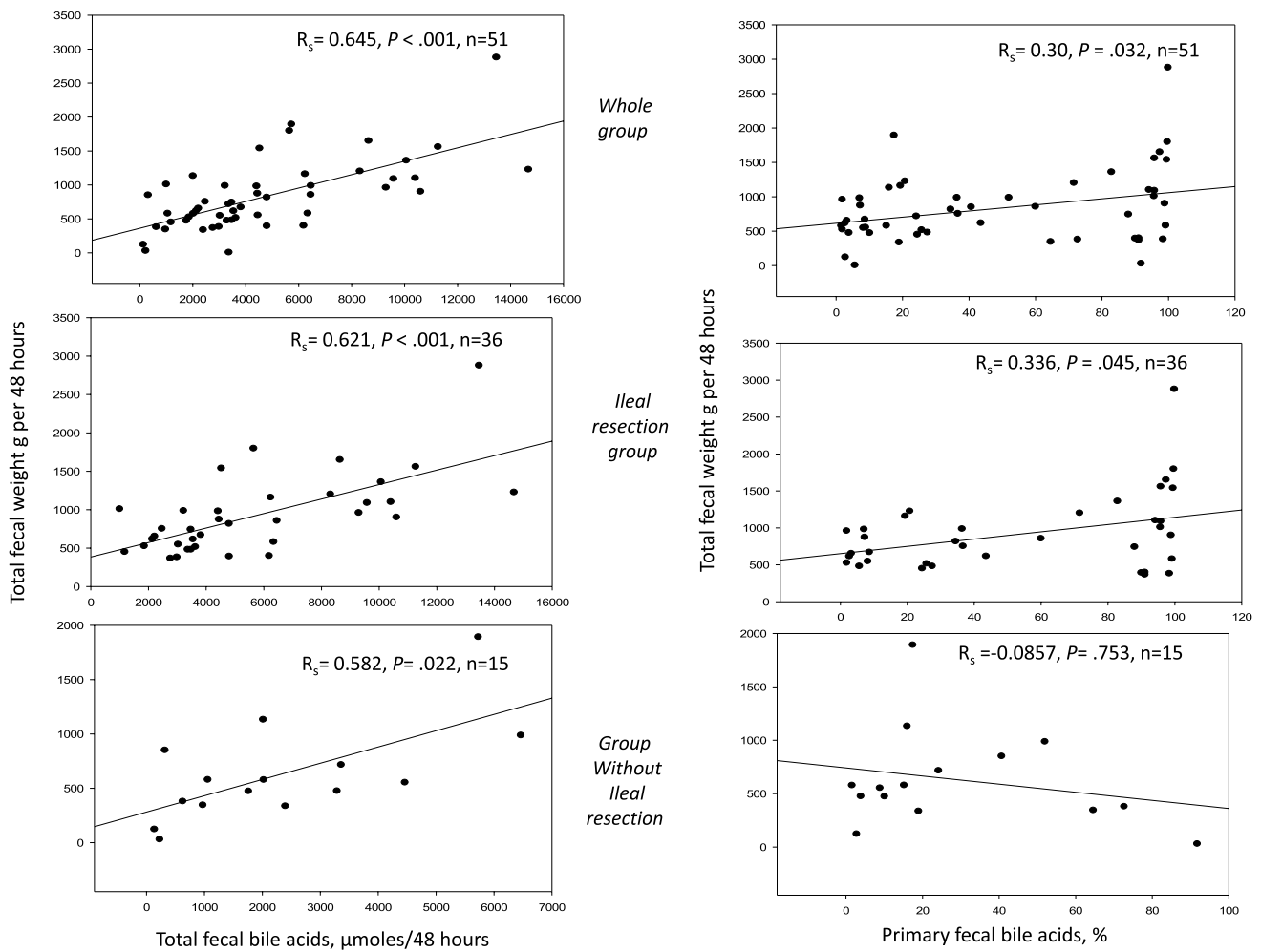
Fig. 1 Correlation of fecal total (left panel) and primary bile acids (right panel) in 48 h collection and 48 h stool weight in all patients (upper row) and in patients with ileal resection (lower row) for neuroendocrine tumors and diarrhea. Bile acid malabsorption is diagnosed based on total bile acids > 2337μ moles/48 h or > 10% primary bile acids (chenodeoxycholic acid + cholic acid) or combination of total bile acids > 1000μ moles/48 h and > 4% primary bile acids (chenodeoxycholic acid + cholic acid)

with increased total fecal bile acid excretion, the mean fecal primary bile acid excretion was 21%. In the current cohort of 67 patients, the mean primary fecal bile acid excretion was 47.5% (median 36.5%) as shown in Table 1. This higher proportion of primary bile acids suggests that rapid colonic transit precluded bacterial dehydroxylation or, conceivably, changes in colonic microbiota with reduced dihydroxylation capacity. Studies of colonic microbiota are indicated in future prospective studies.

The mechanism resulting in bile acid malabsorption in patients with ileal resection is likely to be due to the reduction in the active reabsorption of bile acids by the apical sodium-dependent bile acid transporter (ASBT, aka ileal bile acid transporter). However, this does not apply in patients with no ileal resection.

We considered several factors as potential mechanisms leading to bile acid malabsorption in these patients with

NET and diarrhea. First, it is possible that some of the products of the NET such as serotonin, histamine, prostaglandins, kallikrein, neurokinin, and tachykinins may inhibit the function of the ASBT. This is unlikely since injection of 1 mg serotonin intraperitoneally in fasting mice was associated with significant induction of ASBT expression [26]. In addition, in cholangiocytes that also express ASBT, pretreatment with 5-HT did not abrogate the chloride ion secretion [27] in response to taurocholate, which requires a functioning ASBT. These results suggest that neuroendocrine products are unlikely to cause the bile acid malabsorption observed even in patients with limited (< 25 cm) or no ileal resections.

A second potential mechanism is that the rapid transit of chyme through the ileum [17, 28] potentially precludes ASBT active absorption of bile acids in patients with NET and diarrhea [17, 28]. Accelerated small bowel transit has been associated with elevated fecal fat [29] excretion index
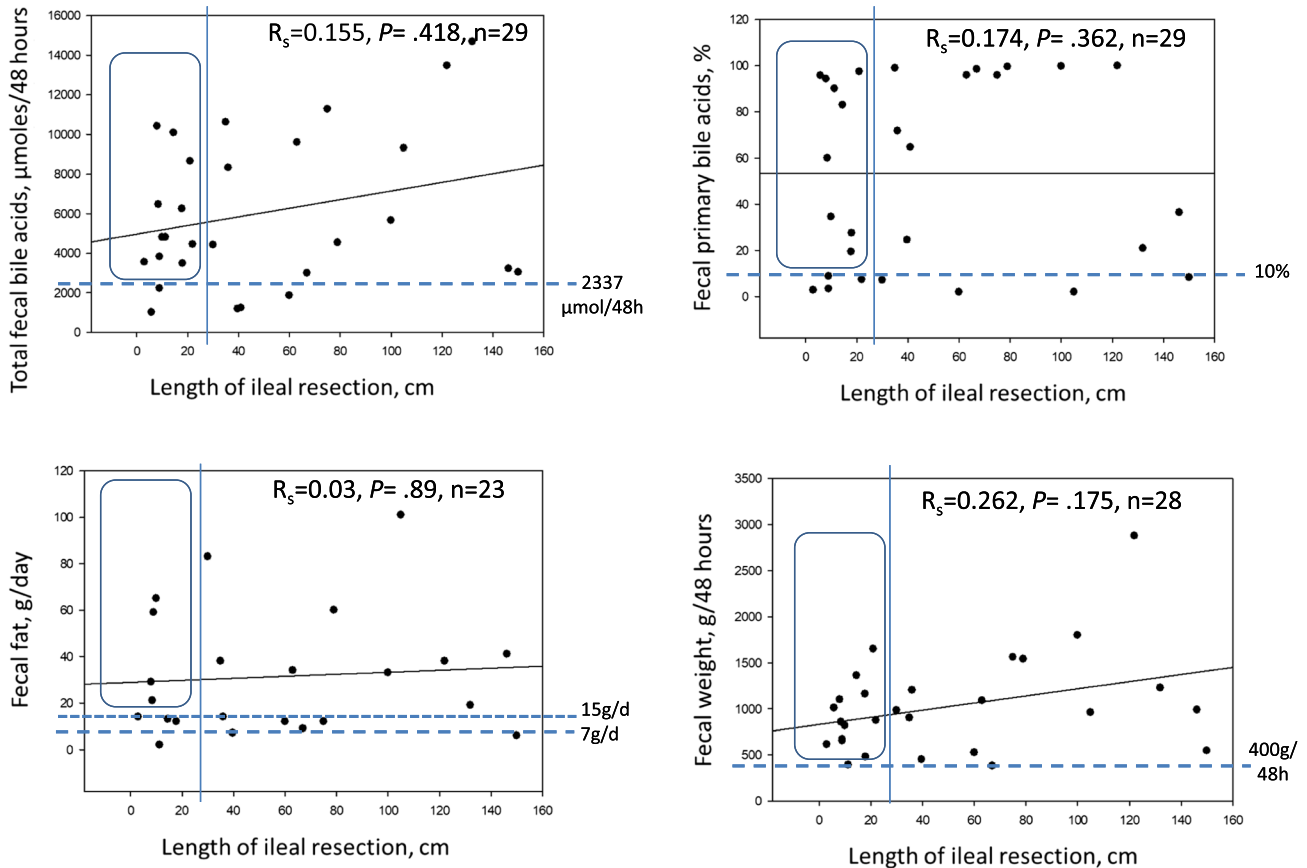
Fig. 2 Relationship of length of resection of ileum ($n = 45$) and fecal measurements of bile acids, fat and weight; note 92% of patients with <25 cm resection have increased fecal total bile acid excretion as well as increased fecal primary bile acids (>10%) and fecal weight (>400 g/48 h)

(% of the 44 g fat intake during a 24 h study) in 15 patients with NET and mean ileal resection of 33 cm [29]. This rapid transit could be significantly retarded by long-acting [29] or short-acting [30] somatostatin analogs.

A third mechanism is that steatorrhea may predispose to bile acid malabsorption. Fecal fat excretion is associated with increased 48-h fecal weight [31], and there is evidence that spontaneously occurring idiopathic chronic diarrhea is often associated with increased endogenous bile acid excretion [32]. Somatostatin and its analogs, which are frequently used in the treatment of diarrhea in patients with NET, may inhibit pancreatic exocrine function, leading to steatorrhea. In our cohort, 23 of the 67 patients were receiving somatostatin analogs (18 octreotide and 5 lanreotide) and, among those with measurements of fecal elastase, there was evidence of pancreatic insufficiency, suggesting the latter may have contributed to type III bile acid malabsorption. Diarrhea secondary to somatostatin-induced steatorrhea responded to treatment with pancreatic enzyme supplements in 14/19 patients in one observational cohort [33]. It has also been demonstrated that octreotide may increase the 7α-dehydroxylation of bile acids in the colon, and this may result in the production of the secretory bile acid, deoxycholic acid, from the primary (non-secretory) bile acid, cholic acid [34]. In the current cohort of patients with NET and diarrhea, the sensitivity of the fecal elastase test in patients with proven steatorrhea based on fecal fat was relatively low (4/10 or 40%). Importantly, those with fecal elastase < 200 μg/g had significant co-factors, that is, ileal or pancreatic resection and concomitant treatment with somatostatin analogs. It appears, therefore, that fecal elastase is less useful in the absence of such co-factors.

A fourth potential mechanism for the bile acid malabsorption as well as steatorrhea is small intestinal bacterial overgrowth. Abdominal imaging showed no intestinal dilatation likely to predispose to this complication; however, formal diagnostic studies were not performed.

The implicit limitations of our retrospective study include lack of prospectively acquired, standard

information (e.g., length of resection based on operative reports) and inconsistent investigations of the causes of diarrhea. Since this was a retrospective study, there was no formal assessment of the clinical response or objective assessment of the fecal bile acid excretion in the patients who received a bile acid sequestrant. Therefore, it is appropriate to designate the patients as having bile acid malabsorption rather than bile acid diarrhea in the absence of therapeutic benefit with a bile acid sequestrant. These limitations provide the impetus for future prospective studies which should include routine evaluations for pancreatic exocrine function and tests to evaluate small intestinal bacterial overgrowth, as well as assessment of subjective and objective responsiveness to bile acid sequestrants. This may require concomitant transit measurements by scintigraphy or intubation and aspiration of the small intestine, since glucose-hydrogen breath testing may be associated with false positivity [35] resulting from rapid transit associated with the NET or the diarrhea itself.

Nevertheless, despite the limitations, the strengths of the study include the large number of patients with NET and the "real-world" acquisition of the information that documented the two main findings: the high prevalence of bile acid malabsorption and the association even in patients with ileal resections < 25 cm in length.

In summary, given the high prevalence of bile acid malabsorption in the patients with NET and diarrhea, inclusive of patients with < 25 cm or no ileal resection, the data suggest that screening for bile acid malabsorption should be considered early in the management algorithm [1], concomitantly with fecal elastase measurements. The availability of a screening test based on fasting serum 7αC4 and percent of primary bile acids in a random stool sample facilitates the evaluation of diarrhea in patients with neuroendocrine tumors.

Declarations

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