Effect of cholecystectomy on bile acid diarrhoea biomarkers: A prospective clinical study

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Summary

Background: The pathophysiological mechanisms of bile acid diarrhoea after cholecystectomy are unknown. Therefore, we aimed to explore the effects of cholecystectomy on the plasma biomarkers of bile acid diarrhoea: fibroblast growth factor 19 and 7α-hydroxy-4-cholesten-3-one.

Methods: Patients were examined prospectively before and after cholecystectomy. Diary registration of bowel habits with the Bristol stool scale was done for 7 days before each visit. Blood was collected at fasting and after ingestion of a solid study meal with 1250 mg unconjugated chenodeoxycholic acid. Plasma fibroblast growth factor 19 was measured with enzyme-linked immunosorbent assay and the complete bile acid profile including 7α-hydroxy-4-cholesten-3-one with high-performance liquid chromatography–tandem mass spectrometry.

Results: Eighteen patients completed the study. The median postoperative follow-up time was 4.6 months (interquartile range [IQR] 3.9-5.8). Diary-registered bowel movement frequency and stool consistency were unchanged; none developed diarrhoea. Before cholecystectomy, mean fibroblast growth factor 19 was 102 pg/mL (95% CI 74-141) vs 92 pg/mL (67-125) after (P = .29; paired t test). Following the meal, the median 150-minute increment from fasting in fibroblast growth factor 19 was 81 pg/mL (IQR: −20 to 274) before and 186 pg/mL (111-382) after cholecystectomy (P = .03; Wilcoxon-test). Mean fasting 7α-hydroxy-4-cholesten-3-one was unchanged 6.0 ng/mL (4.1-8.7) vs 7.5 ng/mL (5.5-10.0) (P = .63; paired t test).

Conclusions: The stimulated postprandial response in fibroblast growth factor 19 increased after cholecystectomy, whereas fasting plasma biomarkers and bowel habits did not change significantly 3-6 months after cholecystectomy. ClinicalTrials.gov: NCT03168555.
1 | INTRODUCTION

Chronic watery diarrhoea is a common complaint after cholecystectomy, with an estimated cumulative incidence of 9%, and bile acid diarrhoea may account for 66% of this. Bile acid diarrhoea is caused by excess bile acids spilling over from the small intestine to the large intestine, triggering secretion and peristalsis. Ultimately this leads to diarrhoea that may be socially debilitating. Fort et al found that cholecystectomy generally accelerated colonic transit time, which correlated clinically with increased stool frequency and looser consistency. However, in most patients this did not result in diarrhoea. It is unclear why some patients develop diarrhoea after cholecystectomy and whether this involves an altered bile acid homeostasis. Both faster enterohepatic cycling of bile acids with increased bile acid synthesis and a changed composition of the bile acid pool could play a role. The bile synthesis rate may be assessed with plasma 7α-hydroxy-4-cholesten-3-one (C4), whereas ileal reabsorption of bile acids may be assessed with plasma fibroblast growth factor 19 (FGF19). Patients with bile acid diarrhoea diagnosed with the gold standard 75-seleno Tauro-homocholic acid (SeHCAT) retention test have lower fasting FGF19 and higher fasting C4 than diarrhoea controls as does patients with postcholecystectomy bile acid diarrhoea. Reports on the specific effects of cholecystectomy on the biomarkers are limited—however, two studies found substantial changes in FGF19 and C4 but only minor impact on bowel habits. The reference ranges for FGF19 and C4, therefore, may need adjustment for cholecystectomy status. Because cholecystectomy decouples the meal-coordinated release of bile acids, it is likely that the postprandial and bile acid stimulated kinetics of FGF19 are altered. More knowledge of the postcholecystectomy bile homeostasis is needed for accurate use of the biomarkers in the assessment of postcholecystectomy diarrhoea. We, therefore, aimed to explore the effects of laparoscopic cholecystectomy on the biomarkers assessed both at fasting and after ingestion of a stimulation meal with chenodeoxycholic acid.

2 | METHODS

2.1 | Eligibility

This prospective exploratory clinical study recruited between 17 May 2017 and 15 May 2019. Patients aged 18-80 years referred for elective laparoscopic cholecystectomy were invited. Exclusion criteria were small bowel resection, right hemicolecction, coeliac disease, lactose intolerance, inflammatory bowel disease, pregnancy, chronic or acute cholecystitis within 2 months, cirrhosis, jaundice (plasma bilirubin >1.5 normal upper limit), allergy to eggs or chenodeoxycholic acid. Withdrawal criteria were perioperative lesion of the common hepatic duct or the common bile duct.

2.2 | Procedures

The study specified a preoperative visit and a visit to be scheduled 3-5 months postoperatively. The patients registered bowel habits in a Bristol stool scale diary for 7 days before each visit and answered the short health scale and the gastrointestinal quality of life index questionnaires, both with a 2-week recall. We defined diarrhoea as more than three bowel movements per day or more than one liquid stool (Bristol stool scale type 6 or 7) per day. The patients attended each visit after an overnight fast and ingested 1250 mg unconjugated chenodeoxycholic acid (Xenbilox®) with a solid meal consisting of two slices of toast and two boiled eggs as previously described. Blood was collected before and 60, 90, 120 and 150 minutes after ingestion of the chenodeoxycholic acid capsules.

2.3 | Biochemistry

Fasting cholesterols (total, high and low-density lipoprotein cholesterol), triglycerides and glucose were analysed with standard laboratory techniques. FGF19, C4 and plasma bile acids were analysed as described previously.

The results of the plasma bile acids are presented as sums of unconjugated and conjugated forms (taurine, glycine or sulphate) of the primary bile acids (chenodeoxycholic acid and cholic acid) and the secondary bile acids (deoxycholic acid, lithocholic acid, ursodeoxycholic acid and hyodeoxycholic acid) unless else is specified.

2.4 | Endpoints

All endpoints compared preoperative with postoperative measurements. The primary endpoint was the increment in FGF19 from fasting until 150 minutes after the meal with chenodeoxycholic acid stimulation \(\Delta_{0-150}\)FGF19. Secondary endpoints included changes in (1) the total area under the curve (AUC) in plasma chenodeoxycholic acid, (2) fasting C4 and FGF19, (3) fasting plasma lipids, (4) stool number and consistency, (5) correlations of FGF19 and C4 to changes in stool pattern and reported symptoms.

2.5 | Power calculation

Stimulated FGF19 peak values at 150 minutes \(\Delta_{0-150}\)FGF19 were estimated to 350 pg/mL before and 250-300 pg/mL after cholecystectomy, both with a standard deviation of 100. We expected no significant change in fasting FGF19 relative to the peak levels. With two-sided \(\alpha = 0.05\) and \(\beta = 0.20\) we needed 16 patients to detect a 75 pg/mL change in \(\Delta_{0-150}\)FGF19 with 80% power.

2.6 | Statistical analysis

The normality of data distribution was assessed with probability–probability plots. FGF19 and C4 were lognormally distributed and reported as means with 95% CIs and analysed with paired t-tests.
Other data were largely non-parametrically distributed. These data were analysed with the Wilcoxon signed-rank test and are reported as medians with interquartile (Q1-Q3) ranges. Confidence intervals for proportions were calculated with Wilson’s method. The total AUCs were calculated with the trapezoid rule. Associations between continuous parameters were assessed with Spearman correlations. Two-sided P < .05 were considered significant; no adjustment for multiple statistical testing was made. Statistical analyses were performed in SPSS version 27.

3 | RESULTS

3.1 | Recruitment

Invitations were sent to 198 patients referred to the surgical outpatient clinic for evaluation of a possible cholecystectomy. Sixty patients (60% female) were scheduled for cholecystectomy; of these, 23 were enrolled, and 18 completed the study (see Figure S1 for a detailed recruitment flow chart).

3.2 | Demographic characteristics

The median participant age was 55 (interquartile range, IQR 42-63) years; 50% were female. Baseline biochemistry was normal. The median time from the operation date to the postoperative visit was 4.6 months (3.9-5.8; minimum 3.2, maximum 10.2) (Table 1). Alcohol and lipid-lowering medications may influence FGF19 and C4.27,28 One patient took atorvastatin during the study; none reported excessive alcohol intake.

3.3 | Clinical outcomes

There were no surgical complications. Diary results were available for 17 patients as one diary was lost. Cholecystectomy did not change diary-recorded stool frequency and consistency (Table 2) or plasma lipid levels (Table S1). One patient fulfilled the diarrhoea criteria both at baseline with 3.3 daily bowel movements and after cholecystectomy with 3.7 daily bowel movements. During the 7-day diary registration this patient had one loose stool (Bristol type 6) before cholecystectomy, and after cholecystectomy the patient had six loose stools (Bristol type 6) with five being in 1 day. However overall, this patient had no subjective complaints of diarrhoea. None of the other participants developed diarrhoea. The postcholecystectomy diarrhoea incidence, therefore, was 0% (95% CI: 0%-20%).

3.4 | Bile acid biomarkers

There was no significant effect of cholecystectomy on fasting C4 with a mean of 6.0 ng/mL (95% CI 4.1-8.7) before and 7.5 ng/mL (5.5-10.0) after cholecystectomy (P = .63) (Table 3). Likewise, mean fasting FGF19 did not change significantly: 102 pg/mL (74-141) before vs 92 pg/mL (67-125) after, (P = .29) (Figure 1). With the observed means and standard deviations, the study had 80% power to detect a 36 pg/mL change in FGF19 and a 5.0 ng/mL change in C4. Compared with preoperative measurements, the stimulated response in FGF19 after cholecystectomy increased significantly at 120 minutes (P = .04) and 150 minutes (P = .01) (Figure 2). The primary effect parameter, the median increment in FGF19 from fasting (t = 0 minutes) to 150 minutes (Δt0-150FGF19) was 81 pg/mL (IQR: −20 to 274) before and 186 pg/mL (111-382) after cholecystectomy (P = .03). Accordingly, there was a trend for the FGF19 total AUC to increase (P = .07) (Figure 2).

Fasting FGF19 and fasting C4 did not correlate significantly before cholecystectomy (r = −.15, P = .54), but after cholecystectomy there was a strong correlation (r = −.62, P = .006). There was no correlation between postcholecystectomy follow-up time with a range of 3.2-10.2 months and fasting FGF19 (r = −.01, P = .97) or fasting C4 (r = −.10, P = .68). Neither FGF19 nor C4 correlated significantly with the diary-registered mean number of stools before (r = −.26, r = .29; P > .05) or after cholecystectomy (r = .09, r = −.31; P > .05) respectively.

3.5 | Plasma bile acid species

The serial plasma measurements of unconjugated chenodeoxycholic acid reflected the ingestion of this bile acid with the meal (Table 4). Peak levels (P = .59) and total AUCs (P = .59) were similar before and after cholecystectomy. There were no significant changes in the bile acid composition measured in plasma at fasting. The total AUC for the summed secondary bile acids increased from median 269 µM · minutes (186-349) to 347 µM · minutes (187-432) (P = .02) after cholecystectomy, driven by deoxycholic acid that increased from median 207 µM · minutes (157-300) to 283 µM · minutes (156-387) (P = .02). There were no significant changes in the AUC for the total
bile acids or the summed primary bile acids. After cholecystectomy, the total AUC for deoxycholic acid correlated strongly with the total AUC of FGF19 \((r = .57, P = .014)\), but before cholecystectomy it did not \((r = .28, P = .26)\).

### 3.6 Patient-reported symptoms

Most patients (12/18) reported occasional abdominal pain before cholecystectomy. After cholecystectomy, 13/18 reported never having abdominal pain \((P = .003)\) (Table S3). Before cholecystectomy, the patients reported some degree of health-related worry with 4 (IQR: 1-5) on the short health scale item 3, which after cholecystectomy decreased to 1 (1-1) \((P = .005)\) (Table S2). Likewise, the gastrointestinal quality of life index items “being nervous related to illness” and “worry about medical treatment” were increased but normalised postoperatively \((P = .01)\) (Table S3).

There were no differences in the reported frequency of the gastrointestinal quality of life index items “frequent bowel movements”, “diarrhoea”, “urgent defecation”, or “sudden uncontrollable bowel movements” before and after the cholecystectomy \((P > .10)\).

### 3.7 Adverse events

The 23 enrolled patients in total completed 40 visits, which included ingestion of chenodeoxycholic acid. There were no serious adverse events. Non-serious adverse events were acute diarrhoea (70%),

| TABLE 2 | Diary-recorded bowel habits before and after cholecystectomy |
|---------|-------------------------------------------------------------|
| **Before cholecystectomy** | **After cholecystectomy** | **P** |
| Mean stools per day | Median (IQR) | Median (IQR) |
| 1.6 (1.1-2.0) | 1.6 (1.3-1.7) | .73 |
| Mean Bristol type per stool | 4.2 (3.7-4.8) | 4.0 (3.6-4.5) | .80 |
| Mean number of watery stools per day | 0.1 (0-0.3) | 0.1 (0-0.3) | .68 |

Note: Bowel function assessed with 7-day patient Bristol scale diary recorded before and after cholecystectomy in 17 patients. Watery stools were defined as Bristol stool scale type 6 and 7. Comparisons with Wilcoxon signed-rank test. Abbreviation: IQR, interquartile range.

| TABLE 3 | Plasma 7α-hydroxy-4-cholesten-3-one before and after cholecystectomy |
|---------|---------------------------------------------------------------------|
| **C4** | **Before cholecystectomy** | **After cholecystectomy** | **P** |
| 0 min | 6.0 (4.1-8.7) | 7.5 (5.5-10.0) | .63 |
| 60 min | 5.3 (3.5-7.8) | 7.2 (5.2-9.9) | .36 |
| 90 min | 4.8 (3.2-7.4) | 6.8 (4.8-9.5) | .33 |
| 120 min | 4.5 (3.0-6.8) | 6.2 (4.4-8.8) | .30 |
| 150 min | 4.5 (3.0-6.7) | 5.9 (4.2-8.3) | .37 |
| AUC0-150 | 774 (524-1143) | 1040 (765-1417) | .36 |

Note: 7α-hydroxy-4-cholesten-3-one (C4) measured in 18 patients at fasting \((t = 0\) min) with subsequent measurements after a stimulation meal with 1250 mg chenodeoxycholic acid. Values were log-normalised and reported as means with 95% CIs. Measurements before and after cholecystectomy were compared with Student’s paired t-test. Abbreviation: AUC0-150, total area under the curves.
abdominal pain (20%), abdominal growling sounds (18%), nausea (10%), pyrosis (5%) and bloating (5%). All adverse events were transient and disappeared within 2-72 hours.

4 | DISCUSSION

This study prospectively explored the effects of cholecystectomy on the plasma biomarkers of bile acid diarrhoea FGF19 and C4. No patient developed postcholecystectomy diarrhoea, and fasting levels of FGF19 and C4 did not change significantly. However, the meal and chenodeoxycholic acid stimulated increment in FGF19 increased after cholecystectomy, which may be a consequence of an accelerated enterohepatic circulation with increased intestinal presence of bile.7

A study found that 38 of 123 patients (31%) had diarrhoea 1 week after cholecystectomy, but only 9 (7%) had persistent diarrhoea after 3 months.29 Therefore, it is no surprise that our patients’ prospective diary recordings showed that 0 of 16 developed diarrhoea after 3-6 months. In the long term, a systematic review of retrospective studies including 361 patients with chronic diarrhoea found that the median time from cholecystectomy to
than 60 pg/mL (Figure 1), suggestive of bile acid diarrhoea, ranging from 0% to 20%. This highlights the critical question of whether the cholecystectomy and the subsequent diarrhoea are causally related, and if yes, then how they are linked. To elucidate aspects of this, we studied the effect of cholecystectomy on the plasma bile acid homeostasis in the fasting state and after a stimulation meal with chenodeoxycholic acid.

We found no significant change in the fasting plasma biomarkers 3-6 months after cholecystectomy. Three patients had FGF19 less than 60 pg/mL (Figure 1), suggestive of bile acid diarrhoea, both before and after the operation. These patients’ stool diaries were normal, reflecting the poor positive predictive value of FGF19. By contrast, no patients had elevated C4 levels above either of the thresholds of 30 ng/mL and 48-52 ng/mL that are verified for the biochemical diagnosis of bile acid diarrhoea. This consistency between normal C4 measurements and no diarrhoea symptoms supports the specificity of C4 as a biomarker for bile acid diarrhoea. Furthermore, it suggests that elevated C4 in a patient with postcholecystectomy diarrhoea is not a clinically insignificant consequence of the cholecystectomy. However, these results differ from the findings of two previous studies where cholecystectomy profoundly changed the fasting biomarkers. One study found a two-fold increase in C4 three months after cholecystectomy, with five of 10 patients having values above 48 ng/mL, and mean FGF19 decreased by 70 pg/mL. The other study also found a two-fold increase in C4 from a mean of 25 ng/mL before to 47 and 53 ng/mL one and three months after cholecystectomy respectively. Only three of 51 patients had intermittent diarrhoea after three months. Both the frequency of approximately 50% of participants having a substantial C4 increase and the lack of associated diarrhoea symptoms are puzzling. It seems disproportionate compared with an estimated 9% incidence of postcholecystectomy diarrhoea found in epidemiological studies and that elevated C4 is a strong indicator of bile acid diarrhoea. The timing of the postcholecystectomy assessment does not explain the discrepancy since it was three months in all studies. Differences in diets could play a role because diet affects bile acid pool size and composition. A high-fat diet is a proposed predictor for developing postcholecystectomy diarrhoea, and a low-fat diet is beneficial in bile acid diarrhoea.

Since no patients in this prospective cohort developed postcholecystectomy diarrhoea, extrapolation to such cases is warranted. We included seven patients with a history of cholecystectomy in a previous study on the biochemical diagnosis of bile acid diarrhoea. The seven patients had a median 1-week SeHCAT retention of 8.7% (IQR 3.4%-14.0%) and median fasting plasma C4 and FGF19 of 21 ng/mL (IQR 14-46) and 100 pg/mL (IQR 67-146) respectively. Four of the seven patients were diagnosed with bile acid diarrhoea based on SeHCAT retention values equal to or below 10%. These four patients had clinical diarrhoea with median 4.3 (IQR 3.6-6.9) daily bowel movements and median Bristol stool form per bowel movement of 6.1 (IQR 5.3-6.3). In these four, median fasting C4 and FGF19 were 23 ng/mL and 75 pg/mL respectively. Together with the present data, these observations suggest that with growing evidence and severity of postcholecystectomy bile acid diarrhoea, fasting C4 increases and fasting FGF19 decreases. Further confirmatory study is needed.

We had anticipated a lower FGF19 response after cholecystectomy as previously shown, but contrary to our hypothesis, the stimulated FGF19 response increased with measurements significantly raised at 120 and 150 minutes after the stimulation. We stimulated the FGF19 response with a solid meal and, unlike the previous study, combined with Chenodeoxycholic acid. The timing of the increase in FGF19 likely reflects the time needed for the stimulation meal to reach the terminal ileum and activate FXR receptors to produce FGF19. Since the measurements of unconjugated Chenodeoxycholic acid were similar before and after cholecystectomy, it is unlikely that this increased the FGF19 response. Rather, we found that the plasma AUC of deoxycholic acid increased postoperatively, and all other bile acids increased numerically but not statistically significant. The likely cause for both observations is that after cholecystectomy the meal-coordinated release of bile acids is lost. This increases the intestinal presence of bile, which exposes it to bacterial deconjugation and 7α-dehydroxylation forming secondary bile acids, including deoxycholic acid. Thus, the increased plasma deoxycholic acid in our data indirectly reflects that more cholic acid has been transformed by bacterial 7α-dehydroxylation. Bile acids activate the farnesoid X receptor in the ileum leading to release of FGF19. Primary bile acids are more potent farnesoid X receptor agonists than the secondary bile acids, including deoxycholic acid, so a change in the composition of the bile pool that with more secondary bile acids should in isolation lead to lower FGF19. Since the FGF19 response increased, we gather that increased intestinal presence of bile was the principal factor.

This study’s primary strength is the prospective measurements of biomarkers and structured recording of bowel habits. Our sample size was tailored to study biochemical changes and it would be sufficient to detect the substantial changes reported in previous studies. However, with a sample size of 18 our study was not designed to accurately assess the incidence of postcholecystectomy diarrhoea. It limits the study that we did not include patients with postcholecystectomy bile acid diarrhoea. We therefore retrieved data on relevant cases from a previous study. Further studies should include stool samples for assessment of microbiota and faecal bile acids.

We conclude that cholecystectomy increased the FGF19 response, which may reflect an accelerated enterohepatic circulation of bile acids. There was no change in bowel habits but fasting biomarkers of bile acid diarrhoea when assessed 3-6 months postoperatively. In contrast to previous works, these results do not suggest that the reference intervals for the fasting biomarkers need adjustment in cholecystectomised patients.
ETHICS STATEMENT
The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to. The study was conducted in compliance with the Helsinki declaration and good clinical practice. Before inclusion, written consent was provided from all participants. The study was approved by the Danish Region Zealand ethics committee (SJ-434), the Danish Medical Agency (EudraCT: 2016-004692-53), the Danish Data Protection Agency (REG-007-2017), and monitored by the good clinical practice unit at Copenhagen university hospitals. ClinicalTrials.gov number NCT03168555.

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AUTHORSHIP
Guarantor of the article: Lars Kristian Munck.
Specific author contributions: CB, SW, JJR, PNB and LKM conceived and designed the study. CB and NH collected data. PNB, DR and EG did the biochemical analyses. CB did the statistical analysis and primary interpretation with LKM, SW and JJR. CB drafted the manuscript. All authors critically revised and approved the final manuscript.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES
1. Farahmandfar MR, Chabok M, Alade M, Bouhelal A, Patel B. Post cholecystectomy diarrhoea—a systematic review. Surgical Science. 2012;3:332-338.
2. Lim SJ, Gracie DJ, Kane JS, et al. Prevalence of, and predictors of, bile acid diarrhea in outpatients with chronic diarrhea: a follow-up study. Neurogastroenterol Motil. 2019;31:e13666.
3. Ruiz-Campos L, Gisbert JP, Ysamat M, et al. Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy. Aliment Pharmacol Ther. 2019;49:242-250.
4. Mekjian HS, Phillips SF, Hofmann AF. Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. J Clin Invest. 1971;50:1569-1577.
5. Bannaga A, Kelman L, O’Connor M, Pitchford C, Walters JR, Arasaradnam RP. How bad is bile acid diarrhoea: an online survey of patient-reported symptoms and outcomes. BMJ Open Gastroenterol. 2017;4:e000116.
6. Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR. Bowel habit after cholecystectomy: physiological changes and clinical implications. Gastroenterology. 1996;111:617-622.
7. Pomare EW, Heaton KW. The effect of cholecystectomy on bile salt metabolism. Gut. 1973;14:753-762.
8. Camilleri M, Nadeau A, Tremaine WJ, et al. Measurement of serum 7alpha-hydroxy-4-cholesten-3-one (or 7alpha-C4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. Neurogastroenterol Motil. 2009;21:734-e43.
9. Chiang JY. Recent advances in understanding bile acid homeostasis. F1000Res. 2029;2017:6.
10. Walters JR, Tasleem AM, Omer OS, Brydon WG, Dew T, le Roux CW. A new mechanism for bile acid diarrhoea: defective feedback inhibition of bile acid biosynthesis. Clin Gastroenterol Hepatol. 2009;7:1189-1194.
11. Zhang JH, Nolan JD, Kennie SL, et al. Potent stimulation of fibroblast growth factor 19 expression in the human ileum by bile acids. Am J Physiol Gastrointest Liver Physiol. 2013;304:C940-C948.
12. Pattini SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. Aliment Pharmacol Ther. 2013;38:967-976.
13. Borup C, Wildt S, Rumessen J, et al. Biochemical diagnosis of bile acid diarrhea: prospective comparison with the 75seleno-taurohomocholic acid test. Am J Gastroenterol. 2020;115:2086-2094.
14. Brydon WG, Culbert P, Kingstone K, et al. An evaluation of the use of serum 7-alpha-hydroxocholensone as a diagnostic test of bile acid malabsorption causing watery diarrhea. Can J Gastroenterol Hepatol. 2011;25:319-323.
15. Brydon WG, Nyhin H, Eastwood MA, Merrick MV. Serum 7 alpha-hydroxy-4-cholesten-3-one and selenohomocholyltaurine (SeHCAT) whole body retention in the assessment of bile acid induced diarrhoea. Eur J Gastroenterol Hepatol. 1996;8:117-23.
16. Sauter GH, Munzing W, von Ritter C, Paumgartner G. Serum 7alpha-hydroxy-4-cholesten-3-one in serum. Dig Dis Sci. 1999;44:14-19.
17. Sauter GH, Moussavian AC, Meyer G, Stetz HO, Parhofer KG, Jungst D. Bowel habits and bile acid malabsorption in the months after cholecystectomy. Am J Gastroenterol. 2002;97:1732-1735.
18. Barrera F, Azocar L, Molina H, et al. Effect of cholecystectomy on bile acid synthesis and circulating levels of fibroblast growth factor 19. Ann Hepatol. 2015;14:710-721.
19. Krarup AL, Peterson E, Ringstrom G, Tornblom H, Hjortswang H, Arasaradnam RP. How bad is bile acid diarrhoea: an online survey of patient-reported symptoms and outcomes. BMJ Open Gastroenterol. 2017;4:e000116.
20. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg. 1995;82:216-222.
21. Hjortswang H, Tysk C, Bohr J, et al. Defining clinical criteria for clinical remission and disease activity in collagenous colitis. Inflamm Bowel Dis. 2009;15:1875-1881.
22. Borup C, Wildt S, Rumessen JJ, et al. Chenodeoxycholic acid stimulated fibroblast growth factor 19 response—a potential
biochemical test for bile acid diarrhoea. *Aliment Pharmacol Ther.* 2017;45:1433-1442.

23. Borup C, Syversen C, Bouchelouche P, et al. Diagnosis of bile acid diarrhoea by fasting and postprandial measurements of fibroblast growth factor 19. *Eur J Gastroenterol Hepatol.* 2015;27:1399-1402.

24. Dior M, Delagréverie H, Duboc H, et al. Interplay between bile acid metabolism and microbiota in irritable bowel syndrome. *Neurogastroenterol Motil.* 2016;28:1330-1340.

25. Humbert L, Maubert MA, Wolf C, et al. Bile acid profiling in human biological samples: comparison of extraction procedures and application to normal and cholestatic patients. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2012;899:135-145.

26. Morton GJ, Kaiyala KJ, Foster-Schubert KE, Cummings DE, Schwartz MW. Carbohydrate feeding dissociates the postprandial FGF19 response from circulating bile acid levels in humans. *J Clin Endocrinol Metab.* 2014;99:E241-E245.

27. Naoumova RP, O’Neill FH, Dunn S, et al. Effect of inhibiting HMG-CoA reductase on 7 alpha-hydroxy-4-cholesten-3-one, a marker of bile acid synthesis: contrasting findings in patients with and without prior up-regulation of the latter pathway. *Eur J Clin Invest.* 1999;29:404-412.

28. Axelson M, Mork B, Sjovall J. Ethanol has an acute effect on bile acid biosynthesis in man. *FEBS Lett.* 1991;281:155-159.

29. Yueh TP, Chen FY, Lin TE, Chuang MT. Diarrhea after laparoscopic cholecystectomy: associated factors and predictors. *Asian J Surg.* 2014;37:171-177.

30. Farrugia A, Attard JA, Hanmer S, et al. Rates of bile acid diarrhoea after cholecystectomy: a multicentre audit. *World J Surg.* 2021;45:2447-2453.

31. Vijayvargiya P, Camilleri M, Taylor A, Busciglio I, Loftus Jr EV, Donato LJ. Combined fasting serum c4 and primary bile acids from a single stool sample to diagnose bile acid diarrhea. *Gastroenterology.* 2020;159:1952-1954.e2.

32. Camilleri M, Vijayvargiya P. The role of bile acids in chronic diarrhoea. *Am J Gastroenterol.* 2020;115:1596-1603.

33. Draper CF, Vassallo I, Di Cara A, et al. A 48-hour vegan diet challenge in healthy women and men induces a BRANCH-chain amino acid related, health associated, metabolic signature. *Mol Nutr Food Res.* 2018;62:1700703.

34. Jackson A, Lalji A, Kabir M, et al. The efficacy of a low-fat diet to manage the symptoms of bile acid malabsorption—outcomes in patients previously treated for cancer. *Clin Med (Lond).* 2017;17:412-418.

35. Breuer NF, Jaekel S, Dommes P, Goebell H. Fecal bile acid excretion pattern in cholecystectomized patients. *Dig Dis Sci.* 1986;31:953-960.

36. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. *Curr Opin Gastroenterol.* 2014;30:332-338.

37. Yoon W, Kim H-N, Park E, et al. The impact of cholecystectomy on the gut microbiota: a case-control study. *J Clin Med.* 2019;8:79.

38. Zhao L, Yang W, Chen Y, et al. A Clostridia-rich microbiota enhances bile acid excretion in diarrhea-predominant irritable bowel syndrome. *J Clin Invest.* 2020;130:438-450.

39. Sagar NM, Duboc H, Kay GL, et al. The pathophysiology of bile acid diarrhoea: differences in the colonic microbiome, metabolome and bile acids. *Sci Rep.* 2020;10:20436.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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