Changes in bile acid homeostasis and stool habits after cholecystectomy

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Sponsor-investigator

Lars Kristian Munck
Senior Physician, DMSci
Zealand University Hospital, Køge
Department of Internal Medicine
Lykkebækvej 1, 4600 Køge
47 32 24 00 (secretary/office)

Locations

Department of Internal medicine
Sjællands Universitetshospital, Køge
Medicinsk Afdeling
Lykkebækvej 1, 4600 Køge, Danmark.

Department of abdominal surgery
Sjællands Universitetshospital, Køge
Medicinsk Afdeling
Lykkebækvej 1, 4600 Køge, Danmark.

Coolaborators

Department of Clinical Biochemistry
Sjællands Universitetshospital, Køge
Lykkebækvej 1, 4600 Køge, Danmark.

Departement de Chimie
Sorbonne Universités,
UPMC Univ Paris 06, Paris, France INSERM-ERL 1157,
CHU Saint-Antoine 27, Paris, Frankrig

The hospital Pharmacy for Region Zealand
Afdeling for Klinisk Farmakologi
Ringstedgade 65,
4700 Næstved, Danmark.

Monitorering

The GCP Unit at Copenhagen University hospitals
Bispebjerg Hospital, Bygning 51, 3.sal
Bispebjerg Bakke 23
2400 København NV, Danmark

Abbreviations

BAD: galdesyrediarré (Bile Acid Diarrhoea), C4: 7α-hydroxy-4-cholesten-3-on, CDCA: chenodeoxycholsyre, ELISA: enzyme linked immunosorbent assay, GIQLI: gastrointestinal quality of life index, HPLC: high performance liquid chromatography, LC-MS/MS: liquid chromatography tandem mass spectrometry, SeHCAT: ^{75}Selenium konjugeret til taurin-homocholsyre, FGF19: fibroblast vækstfaktor 19.

Aim

To explore the effect of cholecystectomy on the biomarkers of bile acid diarrhea fibroblast vækstfaktor 19 (FGF19) and 7α-hydroxy-4-cholesten-3-one (C4) during fasting and after stimulation with chenodeoxycholsyre (CDCA). Secondarily the effect on changes in stool pattern in general and correlated to changes in biomarkers are explored.

Background

Bile acid diarrhoea (BAD) is a common cause of chronic watery diarrhea that impairs quality of life (1). BAD is classified into three types - type 1: secondary to disease of the terminal ileum incl. resection or radiation-damaged terminal ileum. Type 2: primary or idiopathic and type 3: secondary to other disease such as microscopic colitis or cholecystectomy (2). The prevalence of BAD is up to 30% among unselected patients with chronic watery diarrhea (3), ca. 40% of patients with microscopic colitis (4) and 20-30% of patients with irritable bowel syndrome with diarrhea (5-7) and BAD contribute to diarrhea in Crohn's disease with terminal ileitis and after small bowel resection (8). BAD occurs with a higher prevalence after cholecystectomy (9). Overall, the prevalence of BAD is estimated at 1% of the population (10). Clarification of whether a patient has BAD is therefore important in the investigation of chronic watery diarrhea, as there is medical treatment of BAD (3, 6, 11, 12). The current study to diagnose BAD is called SeHCAT named after the isotope ^{75}Selenium conjugated with tauro-homocholic acid called ^{75}Se-HCAT (13). After seven days, the retention is measured and the fraction between γ-radiation on day 7 and day 0 is the test result. There are arbitrarily set limits of retention <5% severe, <10% moderate, and <15% mild BAD. There is often a long wait for SeHCAT and doctors often refer late for the examination, so patients wait a long time before being diagnosed.

New biomarkers of bile acid diarrhoea

In recent years, greater physiological knowledge has emerged about the circulation and regulation of bile acids at a molecular level. (14) and the regulation of bile acid synthesis (15). This has led to the identification of possible biochemical markers for BAD that correlate with SeHCAT retention and inventories further show a close inverse correlation between high values of 7α-hydroxy-4-cholesten-3-one (C4) and low SeHCAT retention (16).

The hormone FGF19 is released primarily by enterocytes in the terminal ileum in response to bile acid absorption from active absorption in the terminal ileum and exerts negative feedback on the bile acid synthesis in the liver. The concentration of FGF19 increases postprandially and reaches a maximum after 100-120 minutter (17). FGF19 increases with oral administration of bile salts and decreases with administration of cholestyramine (18). The bile acid chenodeoxycholic acid (CDCA) is a potent agonist of FXR and thus transcription of FGF19 (19). C4 is an intermediate product in bile acid synthesis and is a marker for new formation of bile acid. Walters et al. (2, 20) has hypothesized that defective FGF19 synthesis or signaling is the mechanism behind idiopathic BAD and has shown that fasting FGF19 correlates inversely to C4 (16) and subsequently, that low fixed values of FGF19 correlate to BAD measured by SeHCAT (21). Measurements of C4 are made experimentally in the diagnosis of BAD in countries where SeHCAT is not available, primarily the USA, but the measurement requires analysis of high-performance liquid chromatography (HPLC) and therefore has low availability (3). Therefore, the hope has been that FGF19 either alone or together with C4 could replace SeHCAT. However, variance in FGF19 values and overlap between patients with BAD and healthy means that a single fasting sample does not have sufficient diagnostic power to make the diagnosis. (21). We have found that the postprandial increase in FGF19 is smaller in patients with BAD than in healthy people in a single measurement 60 minutes after a meal. (22). Furthermore, in a prospective, exploratory pilot study, we have confirmed this and mapped the temporal hormonal response after stimulation with food and the bile acid chenodeoxycholic acid (CDCA) (23).

Bile acid diarrhoea after cholecystektomy

The prevalence of chronic diarrhea after cholecystectomy is estimated at 5-10% (2), but this is not well examined. However, diarrhea complaints after cholecystectomy are frequently seen in gastroenterological outpatient clinics and many of these patients have bile acid diarrhea (2). FGF19 is formed in addition to the intestine also in the endothelium of the gallbladder and excreted via the bile in high concentrations to the intestine, but the effect of this is unknown (18). In a prospective study of 106 patients referred for elective cholecystectomy, stool pattern was compared with 37 women referred for laparoscopic sterilization. The cholecystectomized women reported less sensation of constipation and marginally more frequent defecation, but no actual change in bowel movements. (2). Cholecystectomy thus presumably triggers increased fluid in the stool in the colon, which in most cases is reabsorbed and therefore does not clinically lead to diarrhea. In another prospective study of 51 patients before and after cholecystectomy, patients reported having more and thinner stools and found increased production of bile acids detected by C4 (24).

Recently, Barrera et al examined 8 patients who had cholecystectomy due to gallstones and 8 patients who had their gallbladder removed for another reason. (25). Before and after cholecystectomy, fasting blood samples were taken at 08:00h and after a breakfast serial blood tests. FGF19 was maximal at 12:00 before cholecystectomy 250 pg/mL, and after cholecystectomy only 150 pg/mL. Cholecystectomy doubled fasting C4 and the association between C4 and FGF19 (16) disappeared after cholecystectomy. No stool pattern was measured.

Problem statement

The significance of the gallbladder in the hormonal balance of bile acids is unclear. Our blood test for BAD is based on changes in FGF19 from fasting to 90 – 150 minutes after stimulation with food and CDCA. The present study aims to elucidate the effect of cholecystectomy on bile acid homeostasis and on the feedback mechanisms. A study of how cholecystectomy affects FGF19 is further important to investigate the association between stool changes and FGF19 after cholecystectomy. The primary purpose of the study is to describe the effect of cholecystectomy on fasting as well as meal plus CDCA stimulated FGF19 and C4 during the time period relevant to our test.

Design

Prospective, non-randomized, open label. 20 patients are examined before and after cholecystectomy.

Inclusion criteria

Patients referred for elective cholecystectomy

- ≥ 18 years old
- ≤ 80 years old

Exclusion criteria

- Small bowel resection
- Right sided hemocolectomy
- Know diarrheal disease
    - Celiac disease
    - Lactose intollerancy
    - Inflammatory bowel disease, incl. Microscopic colitis
- Pregnancy
- Allergy to eggs
- Contraindications to Xenbilox:
    - allergy to constituenmts in the xenbilox capsules
    - medical contraindications:
        - chronic or acute cholecytitis within two months.
        - Cirrosis
        - Suspected obstructive choledocholithiasis.
        - Icterus
            - Plasma bilirubin > 1.5 times upper normal limit

Withdrawal criteria

Operative complications during or after the cholecystectomy

- Lesion of ductus choledochus

Methods

The below procedures are done before cholecystectomy and scheduled 3–5 months postoperative. Bowel habits are registered for seven days ahead of each study visit. The Bristol type of each stool is registered.
Study visits 1 and 2 – ie. before and after cholecystectomy: the patient meets in the after an overnight fast. A catheter is placed in the cubital vein and a fasting blood sample is collected. This sample must be taken before 10:00 AM. The patient takes 1,250mg chenodeoxycholic acid (CDCA) (5 Xenbilox capsules of 250mg) and ingests the study meal within 15 minutes. The meal consists of 2 slices of toast, two boiled eggs and 500 mL water.

Blood samples are taken trhough the catheter at 60, 90, 120 og 150 minutes after ingestion of CDCA)

Questionaires

At visit 1 and visit 2 the following quistionnaires are completed

1. Abdominal symptoms
2. Short Health Scale
3. gastrointestinal quality of life index (GIQLI).

Laboratory analyses

FGF19 is analyzed with a commercial ELISA researchkit (R&D systems, MN, USA). Bile acids including C4 and CDCA are analyzed with liquid chromatography tandem mass spectrometry (LC-MS/MS).

Statistics

Stimulated FGF19 peak values at 150 minutes were estimated to 350 pg/mL (25, 29) and after cholecystectomy to 250–300 pg/mL (20), 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 10–34 patients with paired measurements. We decided on 16 patients to detect a 75 pg/mL change in Δ0-150FGF19 with 80% power.
Results are described with means or medians according to distribution. Results are paired and are analysed with either paired t-tests or Wilcoxon test (IBM SPSS 24 Inc., Chicago, IL, USA.)

Primary endpoint:

- Change in CDCA stimulated FGF19 (Δ 150 – 0 min) after cholecystektomy

Secondary endpoints:

- Change in CDCA absorption to plasma (AUC) after cholecystektomy
- Change in fasting and stimulated C4 after cholecystektomy

- Change in fasting FGF19 after cholecystektomy.
- Change in stool pattern after cholecystektomy.
    - Mean stools per day (frequency)
    - Mean Bristol stool type per stool (consistency)
- Change in stool frequency correlated to changes in
    - Fasting FGF19
    - Fasting C4
- Change in plasma triglycerides after cholecystectomy
- Change in patient reported diarrhea correlated to changes in
    - Fasting FGF19
    - Fasting C4

References

1. Gracie DJ, Kane JS, Mumtaz S, Scarsbrook AF, Chowdhury FU, Ford AC. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. Neurogastroenterol Motil. 2012;24(11):983-e538.
2. Hearing SD, Thomas LA, Heaton KW, Hunt L. Effect of cholecystectomy on bowel function: a prospective, controlled study. Gut. 1999;45(6):889-94.
3. Vijayvargiya P, Camilleri M, Shin A, Saenger A. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol. 2013;11(10):1232-9.
4. Bjornbak C, Engel PJ, Nielsen PL, Munck LK. Microscopic colitis: clinical findings, topography and persistence of histopathological subgroups. Aliment Pharmacol Ther. 2011;34(10):1225-34.
5. Kurien M, Evans KE, Leeds JS, Hopper AD, Harris A, Sanders DS. Bile acid malabsorption: an under-investigated differential diagnosis in patients presenting with diarrhea predominant irritable bowel syndrome type symptoms. Scand J Gastroenterol. 2011;46(7-8):818-22.
6. Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2009;30(7):707-17.
7. Bajor A, Tornblom H, Rudling M, Ung KA, Simren M. Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in IBS. Gut. 2014.
8. Wildt S, Norby Rasmussen S, Lysgard Madsen J, Rumessen JJ. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. Scand J Gastroenterol. 2003;38(8):826-30.
9. Fromm H, Malavolti M. Bile acid-induced diarrhoea. Clin Gastroenterol. 1986;15(3):567-82.
10. Walters JR. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. Expert Rev Gastroenterol Hepatol. 2010;4(5):561-7.
11. Borghede MK, Schlutter JM, Agnholt JS, Christensen LA, Gormsen LC, Dahlerup JF. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med. 2011;22(6):e137-40.
12. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther. 2014;39(9):923-39.
13. Thaysen EH, Pedersen L. Idiopathic bile acid catharsis. Gut. 1976;17(12):965-70.
14. Dawson PA, Lan T, Rao A. Bile acid transporters. J Lipid Res. 2009;50(12):2340-57.
15. Chiang JY. Bile acids: regulation of synthesis. J Lipid Res. 2009;50(10):1955-66.
16. Pattni SS, Brydon WG, Dew T, Walters JR. Fibroblast Growth Factor 19 and 7alpha-Hydroxy-4-Cholesten-3-one in the Diagnosis of Patients With Possible Bile Acid Diarrhea. Clin Transl Gastroenterol. 2012;3:e18.
17. 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. The Journal of clinical endocrinology and metabolism. 2014;99(2):E241-5.
18. Lundasen T, Galman C, Angelin B, Rudling M. Circulating intestinal fibroblast growth factor 19 has a pronounced diurnal variation and modulates hepatic bile acid synthesis in man. J Intern Med. 2006;260(6):530-6.
19. Zhang JH, Nolan JD, Kennie SL, Johnston IM, Dew T, Dixon PH, 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(10):G940-8.
20. Walters JR, Tasleem AM, Omer OS, Brydon WG, Dew T, le Roux CW. A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis. Clin Gastroenterol Hepatol. 2009;7(11):1189-94.
21. Pattni SS, Brydon WG, Dew T, Johnston IM, Nolan JD, Srinivas M, et al. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. Aliment Pharmacol Ther. 2013;38(8):967-76.

22. Borup C, Syversen C, Bouchelouche P, Damgaard M, Graff J, Rumessen JJ, et al. Diagnosis of bile acid diarrhoea by fasting and postprandial measurements of fibroblast growth factor 19. Eur J Gastroenterol Hepatol. 2015;27(12):1399-402.
23. Borup C, Wildt S, Rumessen JJ, Bouchelouche PN, Graff J, Damgaard M, et al. Chenodeoxycholic acid stimulated fibroblast growth factor 19 response - a potential biochemical test for bile acid diarrhoea. Aliment Pharmacol Ther. 2017;45(11):1433-42.
24. Sauter GH, Moussavian AC, Meyer G, Steitz HO, Parhofer KG, Jungst D. Bowel habits and bile acid malabsorption in the months after cholecystectomy. Am J Gastroenterol. 2002;97(7):1732-5.
25. Barrera F, Azocar L, Molina H, Schalper KA, Ocares M, Liberona J, et al. Effect of cholecystectomy on bile acid synthesis and circulating levels of fibroblast growth factor 19. Ann Hepatol. 2015;14(5):710-21.