Laboratory Investigation (2018) 98, 4–6

EDITORIAL

Cholecystectomy: a way forward and back to metabolic syndrome?

Gabriella Garruti[1], David Q-H Wang[2], Agostino Di Ciaula[3] and Piero Portincasa[4]

The gallbladder provides rhythmic secretion of concentrated bile acids (BAs) during fasting and postprandially contributes to digestion of dietary lipids. In addition, BAs activate metabolic pathways governing gluco-lipid homeostasis and energy expenditure via the farnesoid X nuclear receptor (FXR), G protein-coupled BA receptor 1 (GPBAR-1), and fibroblast growth factor 19 (FGF19) in the liver, intestine, brown fat, and muscle. Cholecystectomy is standard treatment worldwide for symptomatic gallstone patients. As excellently reviewed by Chen *et al*, cholecystectomy may disrupt enterohepatic recycling of, and signaling by, BAs. Further studies are needed to investigate whether gallbladder removal is an independent risk factor for development of the metabolic syndrome.
Laboratory Investigation (2018) **98,** 4–6; doi:10.1038/labinvest.2017.129

Cholecystectomy is the gold standard treatment of symptomatic gallstones of any type.[1] In their review, Chen *et al*[2] discuss the links between cholecystectomy and various components of the metabolic syndrome, and conclude that the procedure may be not safe as considered since decades.

The gallbladder is a 'controller' operating in concert with key pathways governing metabolic homeostasis. Hepatic bile is physiologically stored and concentrated in the gallbladder where cholesterol is solubilized together with phospholipids and bile acids (BAs) assembled as simple/mixed micelles and unilamellar/multilamellar vesicles. Secreted BAs, the major fraction of biliary lipids, undergo continuous enterohepatic recycling following active ileal transport (85%) and passive colonic diffusion (15%). Thus, BAs are essential for dietary fat absorption. Beside their mere 'digestive' effect, however, BAs are critical signaling agents controlling systemic homeostatic pathways of glucose, lipids and lipoproteins metabolism.[3,4] Abnormalities in BA synthesis, secretion, and absorption have been implicated in metabolic disorders.[3] Chen *et al*[2] argue that cholecystectomy may dysregulate the homeostasis of whole-body metabolism. This topic deserves further attention because cholecystectomy, from time to time, would act as an additional risk factor and 'a way forward' for maturating the metabolic syndrome, or a 'way back' to perpetuate or aggravate the metabolic syndrome itself in patients with prior gallstones.

[1]Section of Endocrinology, Department of Emergency and Organ Transplantations, University of Bari 'Aldo Moro' Medical School, Bari, Italy; [2]Department of Medicine, Division of Gastroenterology and Liver Diseases, Marion Bessin Liver Research Center, Albert Einstein College of Medicine, Bronx, NY, USA; [3]Division of Internal Medicine, Hospital of Bisceglie, Bisceglie, Italy and [4]Clinica Medica 'A Murri', Department of Biomedical Sciences & Human Oncology, University of Bari Medical School, Bari, Italy
E-mail: piero.portincasa@uniba.it

Cholesterol cholelithiasis as a 'fellow traveler' with metabolic syndrome

Cholesterol cholelithiasis is a 'fellow traveler' with metabolic syndrome, as originally foreseen by S Grundy.[5] Chen *et al*[2] also stresses this remarkable liason in the early section of their review. On one side, pathogenetic factors for cholesterol cholelithiasis are: gene polymorphism and expression,[6,7] hepatic hypersecretion of cholesterol, gallbladder factors (stasis, inflammation, mucin accumulation facilitating crystallization of excess cholesterol), and intestinal factors (absorption of cholesterol,[8] gut microbiota).[9] On the other hand, sedentary life, and metabolic disorders with insulin resistance, diabetes mellitus, overweight and obesity, rapid weight loss, and high dietary cholesterol,[8] intersect and are associated with pathogenetic factors of cholesterol cholelithiasis.[10] Epigenetic factors and microRNAs[11] regulate complex gene–environment interactions[12] and also have an impact on insulin resistance and metabolic syndrome.[13]

Cholecystectomy is not a neutral event

Laparoscopic cholecystectomy is the preferred therapeutic option for the treatment of gallbladder

stones of any type.[1,14] A careful identification of 'true' symptomatic gallstone patients (ie, those with biliary colicky pain and/or gallstone-related complications) is mandatory before surgery, as surgery is not indicated in asymptomatic gallstone patients or in those with nonspecific symptoms.[1] Chen *et al*[2] underscore the central role played by the gallbladder in metabolic homeostasis, and accurately quotes nine studies showing increased prevalence of metabolic syndrome in cholecystectomized patients,[15] and in complicated gallstone disease.[16] Although the BA pool and dietary fat absorption are unaffected following cholecystectomy, the missing gallbladder function may favour single or multiple components of the metabolic syndrome, such as glucose,[15] lipid homeostasis (serum cholesterol, triglycerides), blood pressure and cardiovascular disease,[17] hepatic steatosis.[18] Notably, epigenetic changes involved in homeostasis of metabolic processes, ie, methylation of peroxisome proliferator-activated receptor gamma, coactivator 1-alpha, transcription factor A, interleukin-1 beta, interleukin-6, and tumor necrosis factor-α promoters, were detected one day after cholecystectomy in nonobese patients and in obese non-diabetic patients undergoing bariatric surgery by Roux-en-Y gastric bypass.[19]

The gallbladder is a physiological pacemaker of the enterohepatic circulation of BAs, and is controlled by complex neuro-hormonal regulatory mechanisms involving liver and intestine.[20] Following the postprandial cholecystokinin-mediated contraction, gallbladder refilling before the next meal is regulated by the vasointestinal peptide and intraluminal BAs, which act as natural signaling agents of the gallbladder GPBAR-1 (also named TGR5 and highly expressed in the epithelium and smooth muscle),[21] and the human protein FGF19 (also highly expressed in the mucosa).[22] In figure 1, Chen *et al*[2] depict BAs reaching the terminal ileum, entering the enterocytes and rhytmically activating the nuclear farnesoid X receptor (FXR) (the physiological intracellular 'sensor' of BAs). In turn, FXR stimulates the secretion of FGF19 into the portal circulation, activates its FGFR4 liver receptor leading to decreased gluconeogenesis and glycemia. The BA/FXR interaction in the hepatocyte is also involved in glucose homeostasis, lipid metabolism,[23] and BA homeostasis itself, by modulating a set of gene expression involved in hepatic synthesis, uptake, and secretion,[24] as well as intestinal absorption of BAs.[25] BAs also activate the intestinal GPBAR-1 axis, providing further metabolic effects in the intestine (increased GLP-1 and insulin secretion), and brown fat/skeletal muscle (increased 3,5,3′-triiotothyronine and energy expenditure).

In this framework, cholecystectomy significantly deprives the body from a number of gallbladder functions acting as concentrating and pacing organ, with paramount 'endocrine' consequences during fasting and postprandially. Disrupted concentration, blunted transintestinal flow, and fast enterohepatic re-circulation of BAs acting as signaling molecules,[26] will ultimately interfere with gene expression of BAs/FXR, and BA/GPBAR-1 axes.[25] A missing gallbladder will also impoverish the circulating levels of FGF19,[27] and eliminate the gallbladder GPBAR-1. As reviewed by Chen *et al*[2] this is a condition which promotes the shift toward unstable systemic abnormalities at root of the metabolic syndrome.

Future perspectives

Cholecystectomy is the standard surgical procedure performed in the subgroup of patients that develop symptoms and/or complications by gallstones of any type. In their review, Chen *et al*[2] argue that cholecystectomy *per se* may cause metabolic abnormalities, and makes cholecystectomized patients metabolically different from gallstone patients with the gallbladder *in situ.* After cholecystectomy, metabolic abnormalities are likely mediated by the gallbladder loss-of-function (ie, concentrating effect and rhythmic episodes of contraction/refilling during fasting and fed periods, decrease of circulating FGF19 and GPBAR-1 density originating from the gallbladder). This, in turn, leads to disrupted transintestinal flow of BAs that produce abnormal metabolic signaling on gene expression, BA/FXR and BA/GPBAR-1, FGF19 axes in the liver, intestine, adipose tissue, and muscle. In this scenario, cholecystectomy becomes an additional 'way forward' or 'a way back' to metabolic syndrome in concert with genetic, epigenetic, dietary, and other metabolic dysfunctions in patients with prior gallstone disease.

As the prevalence of cholecystectomy is high worldwide, further studies need to address whether gallbladder removal is an independent risk factor for the development of the metabolic syndrome.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

1. Lammert F, Acalovschi M, Ercolani G, *et al.* EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol 2016;65:146–181.

2. Chen Y, Wu S, Tian Y. Cholecystectomy as a risk factor of metabolic syndrome: from epidemiologic clues to biochemical mechanisms. Lab Invest 2017; doi: 10.1038/labinvest.2017.95.
3. Chavez-Talavera O, Tailleux A, Lefebvre P, *et al.* Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease. Gastroenterology 2017;152:1679–1694 e1673.
4. Vitek L, Haluzik M. The role of bile acids in metabolic regulation. J Endocrinol 2016;228:R85–R96.
5. Grundy SM. Cholesterol gallstones: a fellow traveler with metabolic syndrome? Am J Clin Nutr 2004;80:1–2.
6. Joshi AD, Andersson C, Buch S, *et al.* Four susceptibility loci for gallstone disease identified in a meta-analysis of genome-wide association studies. Gastroenterology 2016;151:351–363 e328.
7. Di Ciaula A, Wang DQ, Bonfrate L, *et al.* Current views on genetics and epigenetics of cholesterol gallstone disease. Cholesterol 2013;2013:298421.
8. Lammert F, Gurusamy K, Ko CW, *et al.* Gallstones. Nat Rev Dis Primers 2016;2:16024.
9. Keren N, Konikoff FM, Paitan Y, *et al.* Interactions between the intestinal microbiota and bile acids in gallstones patients. Environ Microbiol Rep 2015;7:874–880.
10. Mendez-Sanchez N, Chavez-Tapia NC, Motola-Kuba D, *et al.* Metabolic syndrome as a risk factor for gallstone disease. World J Gastroenterol 2005;11:1653–1657.
11. Wang R, Hong J, Cao Y, *et al.* Elevated circulating microRNA-122 is associated with obesity and insulin resistance in young adults. Eur J Endocrinol 2015;172:291–300.
12. Di Ciaula A, Portincasa P. Fat, epigenome and pancreatic diseases. Interplay and common pathways from a toxic and obesogenic environment. Eur J Intern Med 2014;25:865–873.
13. Gonzalez-Bulnes A, Astiz S, Ovilo C, *et al.* Nature and nurture in the early-life origins of metabolic syndrome. Curr Pharm Biotechnol 2016;17:573–586.
14. Csikesz NG, Singla A, Murphy MM, *et al.* Surgeon volume metrics in laparoscopic cholecystectomy. Dig Dis Sci 2010;55:2398–2405.
15. Shen C, Wu X, Xu C, *et al.* Association of cholecystectomy with metabolic syndrome in a Chinese population. PLoS ONE 2014;9:e88189.
16. Ata N, Kucukazman M, Yavuz B, *et al.* The metabolic syndrome is associated with complicated gallstone disease. Can J Gastroenterol 2011;25:274–276.
17. Chavez-Tapia NC, Kinney-Novelo IM, Sifuentes-Renteria SE, *et al.* Association between cholecystectomy for gallstone disease and risk factors for cardiovascular disease. Ann Hepatol 2012;11:85–89.
18. Kwak MS, Kim D, Chung GE, *et al.* Cholecystectomy is independently associated with nonalcoholic fatty liver disease in an Asian population. World J Gastroenterol 2015;21:6287–6295.
19. Kirchner H, Nylen C, Laber S, *et al.* Altered promoter methylation of PDK4, IL1 B, IL6, and TNF after Roux-en Y gastric bypass. Surg Obes Relat Dis 2014;10:671–678.
20. Portincasa P, Di Ciaula A, Wang HH, *et al.* Coordinate regulation of gallbladder motor function in the gut-liver axis. Hepatology 2008;47:2112–2126.
21. Maruyama T, Miyamoto Y, Nakamura T, *et al.* Identification of membrane-type receptor for bile acids (M-BAR). Biochem Biophys Res Commun 2002;298:714–719.
22. Zweers SJ, Booij KA, Komuta M, *et al.* The human gallbladder secretes fibroblast growth factor 19 into bile: towards defining the role of fibroblast growth factor 19 in the enterobiliary tract. Hepatology 2012;55:575–583.
23. Fu L, John LM, Adams SH, *et al.* Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. Endocrinology 2004;145:2594–2603.
24. Parks DJ, Blanchard SG, Bledsoe RK, *et al.* Bile acids: natural ligands for an orphan nuclear receptor. Science 1999;284:1365–1368.
25. Martinot E, Sedes L, Baptissart M, *et al.* Bile acids and their receptors. Mol Aspects Med 2017;56:2–9.
26. Yun S, Choi D, Lee KG, *et al.* Cholecystectomy causes ultrasound evidence of increased hepatic steatosis. World J Surg 2016;40:1412–1421.
27. 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.