ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2022 September 27; 14(9): 877-1088

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 9 September 27, 2022

MINIREVIEWS

877 Oncologic aspects of the decision-making process for surgical approach for colorectal liver metastases progressing during chemotherapy

Araujo RLC, Carvalho CGCY, Maeda CT, Milani JM, Bugano DG, de Moraes PHZ, Linhares MM

887 Research progress on the immune microenvironment of the gallbladder in patients with cholesterol gallstones

Jiao JY, Zhu XJ, Zhou C, Wang P

ORIGINAL ARTICLE

Retrospective Study

896 Central pancreatectomy for benign or low-grade malignant pancreatic tumors in the neck and body of the pancreas

Chen YW, Xu J, Li X, Chen W, Gao SL, Shen Y, Zhang M, Wu J, Que RS, Yu J, Liang TB, Bai XL

904 Irinotecan- *vs* oxaliplatin-based regimens for neoadjuvant chemotherapy in colorectal liver metastasis patients: A retrospective study

Liu W, Chen FL, Wang K, Bao Q, Wang HW, Jin KM, Xing BC

918 Predictors of difficult endoscopic resection of submucosal tumors originating from the muscularis propria layer at the esophagogastric junction

Wang YP, Xu H, Shen JX, Liu WM, Chu Y, Duan BS, Lian JJ, Zhang HB, Zhang L, Xu MD, Cao J

930 Liver transplantation with simultaneous splenectomy increases risk of cancer development and mortality in hepatocellular carcinoma patients

Fan HL, Hsieh CB, Kuo SM, Chen TW

940 Development of an innovative nomogram of risk factors to predict postoperative recurrence of gastrointestinal stromal tumors

Guan SH, Wang Q, Ma XM, Qiao WJ, Li MZ, Lai MG, Wang C

950 Comparison of short-term efficacy between totally laparoscopic gastrectomy and laparoscopic assisted gastrectomy for elderly patients with gastric cancer

Zhao RY, Li HH, Zhang KC, Cui H, Deng H, Gao JW, Wei B

963 Personal predictive model based on systemic inflammation markers for estimation of postoperative pancreatic fistula following pancreaticoduodenectomy

Long ZD, Lu C, Xia XG, Chen B, Xing ZX, Bie L, Zhou P, Ma ZL, Wang R

976 Feasible management of median arcuate ligament syndrome in orthotopic liver transplantation recipients

Li SX, Fan YH, Tian GY, Lv GY

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 9 September 27, 2022

Contents

986 Study of preoperative diagnostic modalities in Chinese patients with superficial esophageal squamous cell carcinoma

Zeng YT, Sun YY, Tan WC, Luo SA, Zou BH, Luo GY, Huang CY

Observational Study

997 Oesophageal cancer metastases: An observational study of a more aggressive approach

Pickett L, Dunne M, Monaghan O, Grogan L, Breathnach O, Walsh TN

1008 Change of tumor-infiltrating lymphocyte of associating liver partition and portal vein ligation for staged hepatectomy for hepatocellular carcinoma

Wang W, Deng ZF, Wang JL, Zhang L, Bao L, Xu BH, Zhu H, Guo Y, Wen Z

1026 Blood index panel for gastric cancer detection

Guo GH, Xie YB, Zhang PJ, Jiang T

Randomized Controlled Trial

1037 Effect of cardiac output - guided hemodynamic management on acute lung injury in pediatric living donor liver transplantation

Dou XJ, Wang QP, Liu WH, Weng YQ, Sun Y, Yu WL

SYSTEMATIC REVIEWS

1049 Minimally invasive endoscopic repair of rectovaginal fistula

Zeng YX, He YH, Jiang Y, Jia F, Zhao ZT, Wang XF

META-ANALYSIS

1060 Laparoscopic appendectomy, stump closure and endoloops: A meta-analysis

Zorzetti N, Lauro A, Bellini MI, Vaccari S, Dalla Via B, Cervellera M, Cirocchi R, Sorrenti S, D'Andrea V, Tonini V

CASE REPORT

1072 Retrorectal mucinous adenocarcinoma arising from a tailgut cyst: A case report and review of literature

Wang YS, Guo QY, Zheng FH, Huang ZW, Yan JL, Fan FX, Liu T, Ji SX, Zhao XF, Zheng YX

LETTER TO THE EDITOR

1082 Successful treatment of acute symptomatic extensive portal venous system thrombosis by 7-day systemic thrombolysis

Gao FB, Wang L, Zhang WX, Shao XD, Guo XZ, Qi XS

1086 Prediction factors for ischemia of closed-loop small intestinal obstruction

Pavlidis ET, Pavlidis TE

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 9 September 27, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Shu-You Peng, FACS, FRCP (Hon), MD, Full Professor, Department of Surgery, Medical School of Zhejiang University, Hangzhou 310009, Zhejiang Province, China. zrwkpsy@zju.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

PUBLICATION DATE
September 27, 2022

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 September 27; 14(9): 887-895

DOI: 10.4240/wjgs.v14.i9.887

ISSN 1948-9366 (online)

MINIREVIEWS

Research progress on the immune microenvironment of the gallbladder in patients with cholesterol gallstones

Jing-Yi Jiao, Xiao-Jun Zhu, Chun Zhou, Peng Wang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gupta R, India; Hori T, Japan

Received: June 4, 2022
Peer-review started: June 4, 2022
First decision: August 1, 2022
Revised: August 19, 2022
Accepted: September 8, 2022
Article in press: September 8, 2022
Published online: September 27, 2022

Jing-Yi Jiao, Peng Wang, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Jing-Yi Jiao, Medical School, Nantong University, Nantong 226001, Jiangsu Province, China

Xiao-Jun Zhu, Department of Hepatobiliary Surgery, Nantong First People's Hospital, Nantong 226001, Jiangsu Province, China

Chun Zhou, Department of General Practitioner, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Corresponding author: Peng Wang, MD, PhD, Chief Physician, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, No. 20 West Temple Road, Nantong 226001, Jiangsu Province, China. dankongwang@ntu.edu.cn

Abstract

Cholesterol gallstones are very common in hepatobiliary surgery and have been studied to a certain extent by doctors worldwide for decades. However, the mechanism of cholesterol gallstone formation is not fully understood, so there is currently no completely effective drug for the treatment and prevention of cholesterol gallstones. The formation and development of cholesterol gallstones are caused by a variety of genetic and environmental factors, among which genetic susceptibility, intestinal microflora disorders, impaired gallbladder motility, and immune disorders are important in the pathogenesis of cholesterol gallstones. This review focuses on recent advances in these mechanisms. We also discuss some new targets that may be effective in the treatment and prevention of cholesterol gallstones, which may be hot areas in the future.

Key Words: Microflora; Cholesterol gallstones; Gallbladder; Pathogenesis; Immune disorders

Core Tip: Cholesterol gallstone disease is very common. At present, some new progress has been made in the research on the pathogenesis of cholesterol gallstones, and we have also gained a new understanding of this disease. Here, we discuss the latest research progress of genetic susceptibility, intestinal microflora disorders, impaired gallbladder motility, and immune disorders in the formation of cholesterol gallstones and some new drug targets.

Citation: Jiao JY, Zhu XJ, Zhou C, Wang P. Research progress on the immune microenvironment of the gallbladder in patients with cholesterol gallstones. *World J Gastrointest Surg* 2022; 14(9): 887-895
URL: https://www.wjgnet.com/1948-9366/full/v14/i9/887.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i9.887

INTRODUCTION

Gallstones occur in about 20% of adults in western countries and are one of the most common diseases of hepatobiliary surgery[1]. In past research studies[2], we found that more than 90% of gallstones are mainly composed of cholesterol, called cholesterol gallstones.

Normally, mixed micelles are composed of cholesterol, phospholipids (mainly phosphatidylcholine), and bile salts in bile. Under the action of mixed micelles, bile is thermodynamically stable and cholesterol does not precipitate. When the cholesterol molecules in bile exceed the maximum limit that the mixed micelles can accommodate, cholesterol is in a supersaturated state and cholesterol is prone to precipitate[3]. The relative saturation of cholesterol in bile varies with the concentration of bile salts and phospholipids[4].

In past studies, we found that risk factors for cholesterol gallstones comprise both unmodifiable and modifiable factors. Non-modifiable factors include age, sex, race, and genetic factors. Modifiable factors include the following: metabolic syndrome features such as diabetes[5], insulin resistance, and obesity [6]; dietary habits such as high-calorie and low-fiber diets[7]; intestinal damage such as colectomy[8]; Crohn's disease; drug factors such as octreotide[9], lipid-lowering drugs, and hormones; and impaired gallbladder motility.

More than 20% of patients with cholesterol gallstones develop symptoms, such as biliary colic, during their lifetime and are at risk of developing cholecystitis, gallbladder cancer[10] and pancreatitis[11]. To date, surgery is the best way to treat cholesterol gallstone patients when they develop these symptoms or complications, but it comes with heavy economic and social burdens[12]. Therefore, it is urgent and important to treat and prevent cholesterol gallstones by studying the pathogenesis of gallstones and taking corresponding intervention measures for specific pathogenic links.

In this review, we focus on the important roles of genetic susceptibility, intestinal microflora disorders, and impaired gallbladder motility. We also discuss some strategies for the treatment and prevention of cholesterol gallstones, which inhibit some of the pathogenic aspects of cholesterol gallstones.

IMMUNE DISORDERS LEAD TO CHOLESTEROL GALLSTONES

Immune disorders play a crucial role in the formation and development of cholesterol gallstones. First, low concentrations of various immunoglobulins including IgA, IgG, and IgM were contained in bile [13]. Among them, IgM is the most effective Ig in promoting the formation of cholesterol gallstones in supersaturated bile, while IgG is less effective and IgA is the least effective[14-16]. In addition, the formation of cholesterol gallstones is closely related to mucin (MUC) gel accumulation in human and animal models, and MUC gel accumulation occurs before cholesterol gallstone formation and is an important cause of cholesterol gallstone formation[17-22]. At the same time, MUC may be positively correlated with the calcification of cholesterol gallstones[23]. Some MUC genes are expressed in human bile duct epithelial cells such as MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC5B, and MUC6[24], and the expression of these MUC genes and the production and secretion of MUC are regulated by inflammatory mediators in the immune system[25-27]. Cholesterol secretion can also be promoted by inflammatory mediators, which promote liver lipid metabolism and secretion, lead to bile cholesterol supersaturation, and promote cholesterol gallstone formation. For example, in mice, the formation of cholesterol gallstones can be promoted by the administration of lipopolysaccharide (LPS) or pro-inflammatory cytokines [interleukin (IL)-1, tumor necrosis factor (TNF)], because these result in elevated serum cholesterol levels and increase the production of 3-hydroxy-3-methylglutarate mono-acyl-coenzyme A reductase (HMG-CoA reductase)[28-30]. In addition, cholesterol catabolism can be inhibited by LPS, which reduces the production of cholesterol 7 alpha-hydroxylase (CYP7A1), CYP7B1, or CYP27A1 protein, leading to bile supersaturation and cholesterol gallstone formation[31,32]. Recent studies have

found that immune factors can also influence the formation of cholesterol gallstones by influencing the movement of gallbladder contraction. Interstitial Cajal-like cells (ICLCs) are widespread in the gallbladder and bile duct and play a significant role in the regulation of gallbladder contractile motion. The density of ICLCs in the gallbladder is significantly reduced in patients with cholelithiasis, suggesting that decreased gallbladder contraction and cholesterol gallstone formation are closely associated with reduced ICLCs. Ursodeoxycholic acid protects ICLCs in the gallbladder from apoptosis by inhibiting the TNF-α/caspase 8/caspase 3 pathway[33], thereby protecting the contractile activity of the gallbladder and ultimately inhibiting the formation of cholesterol gallstones. These objective results indicate that immune disorders play a crucial role in the formation and development of cholesterol gallstones.

The role of adaptive immunity in cholesterol gallstone formation was analyzed by giving *Helicobacter pylori* (*H. pylori*)-infected and uninfected homozygous mice, as well as homozygous immunodeficient Rag mice, a lithogenic diet in a former study. Lymphocyte metastasis studies were also performed to determine which cell subsets are responsible for cholesterol gallstone formation[34]. *H. pylori* usually causes disease by inducing a pro-inflammatory immune response mediated by T-assisted type 1[35,36]. When fed the lithogenic diet for 2 mo, more cholesterol gallstones were found in non-immunodeficient mice than in Rag mice. There was a statistically significant increase in cholesterol gallstone prevalence in *H. pylori*-infected mice compared with uninfected mice. In addition, T lymphocyte transfer to Rag mice significantly increased the prevalence of cholesterol gallstones, while B lymphocyte transfer did not significantly increase cholesterol gallstones. A detailed description of the association between adaptive immunity and cholesterol gallstone formation was provided in this study, which suggested that T cells are an important link in the formation of cholesterol gallstones in mice (Figure 1).

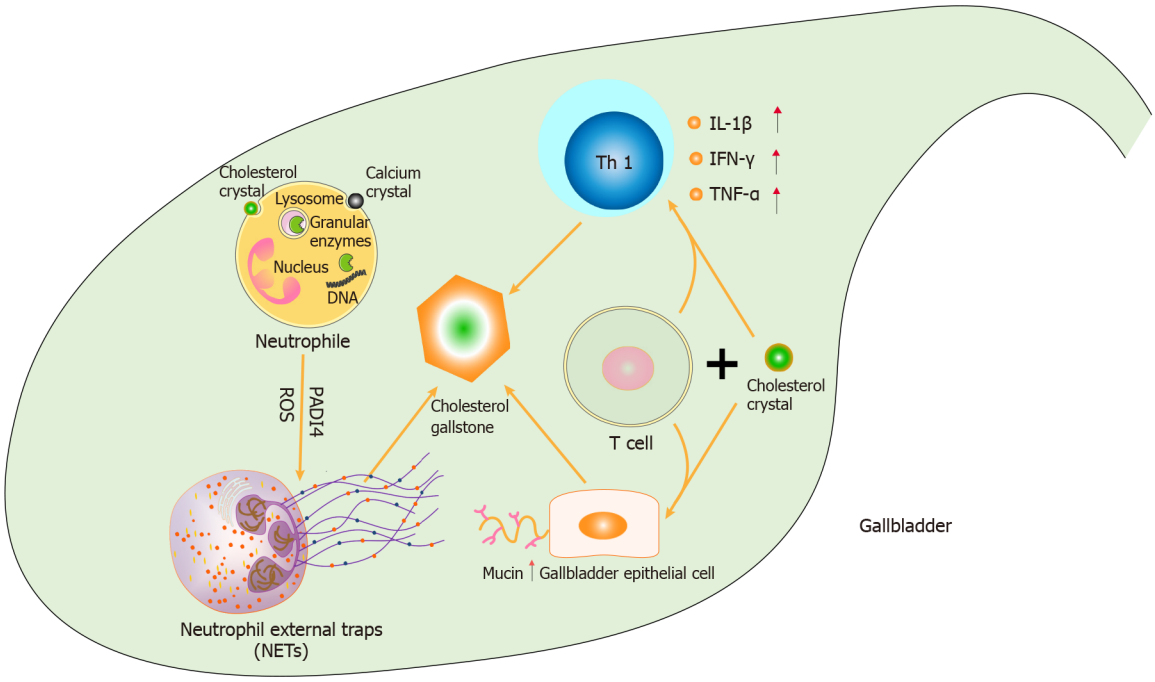
The vital role of neutrophil external traps (NETs) in cholesterol gallstone formation and development was expounded upon in a recent study[37]. By fluorescence microscopy, patchy extracellular DNA (ecDNA), large ecDNA aggregates, and strong neutrophil elastase activity were found in both human and porcine cholesterol gallstones. In previous reports, obesity is related to the release of ecDNA into plasma in mice and humans[38], and ecDNA in peripheral circulation has contact with the risk of metabolic syndrome[39], both of which are risk factors for cholesterol gallstones. Upon contact with neutrophils, cholesterol or calcium crystals are ingested by neutrophils. This process of pinocytosis causes the granular enzymes in lysosomes to leak and bind to the DNA in the cytoplasm, ultimately decondensed chromatin and externalizing to form NETs. Cholesterol crystals and calcium crystals in the bile of the gallbladder are aggregated to form cholesterol gallstones by the "glue" role of NETs. Meanwhile, the formation of NETs is dependent on the activity of peptidyl arginine deiminase type 4 and the production of reactive oxygen species. In addition, this study confirmed that the formation and development of cholesterol gallstones can be effectively reduced by the inhibition of NET formation or neutrophils. The results of this study verify that the formation of NETs is the key link in the formation of cholesterol gallstones caused by the accumulation of crystals in bile, and the formation of neutrophils and NETs may be new targets for the prevention and treatment of cholesterol gallstones (Figure 1).

Together, these findings suggest that immune dysfunction is also an important link in the formation and development of cholesterol gallstones. Targeting immune disorders in the pathogenesis of cholesterol gallstones will be a new hotspot in the treatment and prevention of cholesterol gallstones in the future.

ROLE OF INTESTINAL FLORA DYSREGULATION IN CHOLESTEROL GALLSTONES

Bacteria are present in the bile, cholesterol gallstones, and even gallbladder tissue of patients with cholesterol gallstones[1]; however, the role of these bacteria in cholesterol gallstone formation is not fully understood. A lower incidence of cholesterol gallstones in germ-free mice was found in one of the earliest studies[40]. Another study showed that mice infected with enterohepatic *H. pylori* had an increased risk of cholesterol gallstones[41]. A recent study comparing the biliary microbiota of lithiasis and non-lithiasis groups found that the Alcaligenaceae reached higher relative abundance in lithiasis samples[42]. In this family, *Alcaligenes recti* are reportedly involved in the metabolism of various bile acids. These findings suggest that cholesterol gallstone formation appears to be related to intestinal microbiome dysregulation. With the abundance and diversity of intestinal flora decreased, the number of *Firmicutes* decreased, and the ratio of *Firmicutes* to *Bacteroidetes* decreased in mice with gallstones[43]. In addition, the intestinal bacteria phylum *Proteobacteria* were significantly increased, while *Faecalibacterium*, *Lachnospira*, and *Roseburia* were significantly decreased[44]. The number of Gram-positive fecal anaerobes in the cecum was increased in patients with gallstones compared with those without gallstones, and 7α-dehydroxylation activity was also increased, which seemed to explain the increased concentration of hydrophobic secondary bile acid deoxycholic acid in patients with gallstones[45].

Enrichment of *Desulfovibrionales* has been found in patients with metabolic syndrome and obesity associated with cholesterol gallstones[46], but the specific link between the bacteria and cholesterol gallstones has not been clarified. A recent study found that the abundance of *Desulfovibrionales* in the feces of cholesterol gallstone patients and cholesterol gallstone-susceptible mice was significantly higher



DOI: 10.4240/wjgs.v14.i9.887 **Copyright** ©The Author(s) 2022.

Figure 1 Role of neutrophils and T cells in cholesterol gallstone formation. In gallbladder bile, cholesterol or calcium crystals are ingested by neutrophils as pinocytosis, inducing leakage of lysosomes and granular enzymes in neutrophils. The intracellular chromatin of neutrophils is decondensed by granular enzymes and externalized to extrachromosomal DNA, resulting in the formation of neutrophil external traps (NETs). Cholesterol crystals and calcium crystals in the bile of the gallbladder are aggregated to form cholesterol gallstones by the "glue" role of NETs. On the other hand, mucin gene expression and mucin gel accumulation in gallbladder epithelial cells can be induced by the joint action of T cells and cholesterol crystals, promoting the formation of cholesterol gallstones. T cells and cholesterol crystals can also induce T helper type 1 cytokines (such as interleukin-1 beta, interferon gamma, tumor necrosis factor-alpha), which cause gallbladder inflammation, gallbladder tissue damage, and gallbladder dysfunction, leading to cholesterol gallstones.

than that in the non-gallstone population, and that the transplantation of intestinal flora from cholesterol gallstone patients into cholesterol gallstone-resistant mice resulted in a statistically significant increase in cholesterol gallstone prevalence[47]. The production of secondary bile acids will be promoted by a large number of *Desulfovibrionales* rich in the cecum, and the hydrophobicity of bile acids will therefore increase, resulting in increased absorption of intestinal cholesterol and easy to cause cholesterol gallstones. In addition, the intestinal lipid absorption process is regulated by CD36. The expression of CD36 can be induced by *Desulfovibrionales*; thus, the intestinal lipid absorption is enhanced, which may also lead to the formation of cholesterol gallstones[48]. On the other hand, hydrogen sulfide, a metabolite of *Desulfovibrionales*, can induce farnesoid X receptor and inhibit the expression of CYP7A1. The expression of cholesterol transporter ATP-binding cassette transporter G5/G8 (ABCG5/ABCG8) in the mouse liver was also induced by *Desulfovibrionales*, which promoted cholesterol secretion in the biliary tract. This study shows that cholesterol gallstone formation is promoted by intestinal *Desulfovibrionales*, which influences bile acid and cholesterol metabolism, further supporting the important role of intestinal microbiome imbalance in cholesterol gallstone formation.

GENETIC SUSCEPTIBILITY TO CHOLESTEROL GALLSTONES

In addition to these two mechanisms, there are other factors that contribute to the formation of cholesterol gallstones, such as genetic factors and gallbladder dyskinesia[49]. Indigenous populations in North and South America are reported to be at highest risk of gallstones in the world. Prevalence rates are lower in Asian populations and lowest in African populations[1]. A study of 43141 twins with gallstone disease in Sweden showed that about 25% of gallstones were caused by a genetic susceptibility [50]. These objective results suggest that gallstone risk and genetic susceptibility are inextricably linked.

Lipid composition in the biliary tract is regulated by complex ATP-binding cassette (ABC) transporters on the hepatocyte canalicular membrane. The transport of bile salts into the biliary tract is carried out by the ABC transporter ABCB11[51]. The transport of phosphatidylcholine into the biliary tract is carried out by the ABC transporter ABCB4[52]. The transport of cholesterol into the biliary tract is carried out by the ABC transporters ABCG5 and ABCG8[53].

Mutations and variants of ABCB4 inhibit the secretion of phospholipids from the liver to the bile ducts, resulting in a decrease or deficiency of phospholipids in bile and the formation of cholesterol gallstones, known as low phospholipid-associated cholelithiasis. A recent study compared the chemical composition of fresh gallbladder bile between ABCB4 knockout and wild-type mice and found cholesterol supersaturation and the presence of cholesterol crystals in gallbladder bile in the former but not in the latter. The results of this study demonstrate the critical role of ABCB4 in phospholipid transport and the important role of ABCB4 mutations in the formation of cholesterol gallstones[54]. A strong association between gallstone disease and ABCG8 was shown in a genome-wide association study (GWAS) involving 280 patients with gallstones and 360 controls in 2007[55]. ABCG8 is responsible for transporting cholesterol into the biliary tract and intestinal lumen, and its association with cholesterol gallstones is attributed to a familiar variant that causes guanine at position 55 to become cytosine, resulting in the replacement of aspartic acid, the amino acid residue at position 19 of the transporter, by histidine (ABCG8D19H, RS11887534). ABCG8D19H constitutes a functional acquisition mutation, which increases the transport activity of ABCG8 by three-fold, increases the hepatic cholesterol discharge into the biliary tract, increases the absolute cholesterol saturation in bile, and ultimately leads to the occurrence of cholesterol gallstones[55-57].

In 2016, four new gallstones susceptibility loci, namely SULT2A1, TM4SF4, GCKR, and CYP7A1, were identified in a large GWAS (there were 8720 gallstones patients and 55152 people who did not have gallstones in the discovery set, and 6489 gallstones patients and 62797 people who did not have gallstones in the validation set), and the association between ABCG8 and gallstones were confirmed [58]. The metabolism of cholesterol into bile acid in the liver is mainly regulated by cholesterol CYP7A1, and its reduced function may lead to the formation and development of cholesterol gallstones by reducing the catabolism of cholesterol into bile acid[59]. The transport of cholesterol from the intestinal lumen into intestinal cells and from bile into liver cells is in the charge of Niemann-Pick C1-like protein 1 (NPC1L1). Reduced activity of the NPC1L1 gene leads to reduced uptake of cholesterol from the lumen to intestinal cells and from bile to liver cells, resulting in increased cholesterol content in the biliary tract, increased absolute cholesterol saturation in the biliary tract, and increased risk of cholesterol gallstone formation[60].

According to a 2019 study, six new gallstone-related or highly related variants were associated with blood cholesterol levels (HNF4A, HNF1A, FUT2, FADS2, MARCH 8, and JMJD1C)[61]. However, the association between these variants and cholesterol gallstone formation and development is unclear. In the future, GWASs will find more new cholesterol-gallstones related variants, and further studies are needed to determine the molecular basis behind these variants[62].

CHOLESTEROL GALLSTONE FORMATION BY IMPAIRED GALLBLADDER MOTILITY

Whatever mechanism causes cholesterol gallstones to form, these processes are slow. Cholesterol gallstones cannot form if the gallbladder is completely emptied several times a day. Therefore, the total or partial extension of bile storage due to impaired gallbladder movement seems to be another important condition for cholesterol gallstone formation. Insufficient gallbladder motility contributes to cholesterol gallstone formation and is impaired under many risk factors for cholesterol gallstone formation, such as pregnant women, obese patients, and their rapid weight loss, diabetes mellitus, and patients receiving total parenteral nutrition[63]. A recent study showed that 78 of 959 patients (8%) who underwent laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy developed symptomatic gallstone disease within 24 mo[64]. In patients without gallstones before RYGB surgery, ursodeoxycholic acid treatment reduced the occurrence of symptomatic gallstone disease compared with placebo[65]. On an empty stomach, bile drained from the liver is stored in the gallbladder. After eating, bile is discharged by the gallbladder into the duodenum and small intestine. The motor function of the smooth muscle of the gallbladder is mainly regulated by cholecystokinin (CCK), a key gastrointestinal hormone. The release of CCK is mainly caused by the stimulation of dietary lipids and proteins. Insufficient gallbladder contraction during fasting is caused by reduced gallbladder stimulation. Patients using the somatostatin analog octreotide may develop cholesterol gallstones because postprandial CCK release and gallbladder contraction was inhibited by octreotide[9]. Injection of CCK in patients receiving total parenteral nutrition, or the addition of dietary fat to promote the release of CCK in the gastrointestinal tract of people who lose weight quickly, enhances the ability of their gallbladder to contract and prevents the formation of cholesterol gallstones[66,67]. Mice with reduced CCK or damaged CCK-1 receptor genes had slower small bowel movement[68,69], suggesting that CCK not only promotes contraction of gallbladder smooth muscle but also speeds up intestinal transport through a CCK-1 receptor signaling cascade. Loss of the CCK-1 receptor gene in mice led to reduced gallbladder contraction and reduced intestinal transport, which in turn led to cholestasis and increased intestinal cholesterol absorption, ultimately increasing the risk of gallstone formation[69]. In addition, ICLCs are widespread in the gallbladder and bile duct and play a significant role in the regulation of gallbladder contractile motion[70,71]. Previous studies have found that the density of ICLCs in the gallbladder is significantly reduced in patients with cholesterol gallstones, suggesting that

decreased gallbladder contraction and cholesterol gallstone formation are closely associated with reduced ICLCs[72-74].

CONCLUSION

Cholesterol gallstones are common in hepatobiliary surgery and their incidence is increasing. At present, surgery is the preferred treatment for symptomatic cholesterol gallstones disease, but there is still a lack of primary prevention drugs for cholesterol gallstones. The pathogenesis of cholesterol gallstones is extremely complex. We identified the modifiable factors in the pathogenesis of cholesterol gallstones through research to provide strategies for the prevention of cholesterol gallstones disease in high-risk groups. At the same time, more emphasis should be placed on the prevention of cholesterol gallstones, which seems to be a better option than cholecystectomy.

FOOTNOTES

Author contributions: Jiao JY and Zhu XJ contributed equally to this work; Wang P and Zhou C were responsible for conceiving the study; Jiao JY was responsible for writing the first draft of the article; Zhu XJ was responsible for the revision and supplement of the article.

Supported by the Wu Jiping Medical Foundation, No. 320.6750.18396; and Nantong "14th Five-Year" Science and Education to Strengthen Health Project, General Surgery Medical Key Discipline.

Conflict-of-interest statement: The authors declare having no conflict of interests for this article.

Country/Territory of origin: China

ORCID number: Jing-Yi Jiao 0000-0002-9560-4725; Xiao-Jun Zhu 0000-0001-5265-6800; Chun Zhou 0000-0003-2640-5842; Peng Wang 0000-0003-3735-1229.

S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Zhang H

REFERENCES

1 **Wang Y**, Qi M, Qin C, Hong J. Role of the biliary microbiome in gallstone disease. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 1193-1205 [PMID: 30791792 DOI: 10.1080/17474124.2018.1533812]
2 **Lammert F**, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers* 2016; **2**: 16024 [PMID: 27121416 DOI: 10.1038/nrdp.2016.24]
3 **Rudling M**, Laskar A, Straniero S. Gallbladder bile supersaturated with cholesterol in gallstone patients preferentially develops from shortage of bile acids. *J Lipid Res* 2019; **60**: 498-505 [PMID: 30610083 DOI: 10.1194/jlr.S091199]
4 **Dosch AR**, Imagawa DK, Jutric Z. Bile Metabolism and Lithogenesis: An Update. *Surg Clin North Am* 2019; **99**: 215-229 [PMID: 30846031 DOI: 10.1016/j.suc.2018.12.003]
5 **Wang F**, Wang J, Li Y, Yuan J, Yao P, Wei S, Guo H, Zhang X, Yang H, Wu T, He M. Gallstone Disease and Type 2 Diabetes Risk: A Mendelian Randomization Study. *Hepatology* 2019; **70**: 610-620 [PMID: 30515881 DOI: 10.1002/hep.30403]
6 **Camilleri M**, Malhi H, Acosta A. Gastrointestinal Complications of Obesity. *Gastroenterology* 2017; **152**: 1656-1670 [PMID: 28192107 DOI: 10.1053/j.gastro.2016.12.052]
7 **Di Ciaula A**, Garruti G, Frühbeck G, De Angelis M, de Bari O, Wang DQ, Lammert F, Portincasa P. The Role of Diet in the Pathogenesis of Cholesterol Gallstones. *Curr Med Chem* 2019; **26**: 3620-3638 [PMID: 28554328 DOI: 10.2174/0929867324666170530080636]
8 **Mark-Christensen A**, Brandsborg S, Laurberg S, Johansen N, Pachler JH, Thorlacius-Ussing O, Kjær MD, Qvist N, Preisler L, Hillingsø J, Rosenberg J, Jepsen P. Increased Risk of Gallstone Disease Following Colectomy for Ulcerative Colitis. *Am J Gastroenterol* 2017; **112**: 473-478 [PMID: 28117363 DOI: 10.1038/ajg.2016.564]
9 **Moschetta A**, Stolk MF, Rehfeld JF, Portincasa P, Slee PH, Koppeschaar HP, Van Erpecum KJ, Vanberge-Henegouwen GP. Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; **15**: 181-185 [PMID: 11148435

DOI: 10.1046/j.1365-2036.2001.00924.x]

10 **Barahona Ponce C**, Scherer D, Brinster R, Boekstegers F, Marcelain K, Gárate-Calderón V, Müller B, de Toro G, Retamales J, Barajas O, Ahumada M, Morales E, Rojas A, Sanhueza V, Loader D, Rivera MT, Gutiérrez L, Bernal G, Ortega A, Montalvo D, Portiño S, Bertrán ME, Gabler F, Spencer L, Olloquequi J, Fischer C, Jenab M, Aleksandrova K, Katzke V, Weiderpass E, Bonet C, Moradi T, Fischer K, Bossers W, Brenner H, Hveem K, Eklund N, Völker U, Waldenberger M, Fuentes Guajardo M, Gonzalez-Jose R, Bedoya G, Bortolini MC, Canizales-Quinteros S, Gallo C, Ruiz-Linares A, Rothhammer F, Lorenzo Bermejo J. Gallstones, Body Mass Index, C-Reactive Protein, and Gallbladder Cancer: Mendelian Randomization Analysis of Chilean and European Genotype Data. *Hepatology* 2021; **73**: 1783-1796 [PMID: 32893372 DOI: 10.1002/hep.31537]

11 **Boxhoorn L**, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC, Besselink MG. Acute pancreatitis. *Lancet* 2020; **396**: 726-734 [PMID: 32891214 DOI: 10.1016/S0140-6736(20)31310-6]

12 **Everhart JE**, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009; **136**: 1134-1144 [PMID: 19245868 DOI: 10.1053/j.gastro.2009.02.038]

13 **Reynoso-Paz S**, Coppel RL, Mackay IR, Bass NM, Ansari AA, Gershwin ME. The immunobiology of bile and biliary epithelium. *Hepatology* 1999; **30**: 351-357 [PMID: 10421640 DOI: 10.1002/hep.510300218]

14 **Harvey PR**, Upadhya GA, Strasberg SM. Immunoglobulins as nucleating proteins in the gallbladder bile of patients with cholesterol gallstones. *J Biol Chem* 1991; **266**: 13996-14003 [PMID: 1856228]

15 **Harvey PR**, Upadhya GA. A rapid, simple high capacity cholesterol crystal growth assay. *J Lipid Res* 1995; **36**: 2054-2058 [PMID: 8558092]

16 **Upadhya GA**, Harvey PR, Strasberg SM. Effect of human biliary immunoglobulins on the nucleation of cholesterol. *J Biol Chem* 1993; **268**: 5193-5200 [PMID: 8444895]

17 **Lee SP**, LaMont JT, Carey MC. Role of gallbladder mucus hypersecretion in the evolution of cholesterol gallstones. *J Clin Invest* 1981; **67**: 1712-1723 [PMID: 7240416 DOI: 10.1172/jci110209]

18 **Lammert F**, Wang DQ, Wittenburg H, Bouchard G, Hillebrandt S, Taenzler B, Carey MC, Paigen B. Lith genes control mucin accumulation, cholesterol crystallization, and gallstone formation in A/J and AKR/J inbred mice. *Hepatology* 2002; **36**: 1145-1154 [PMID: 12395324 DOI: 10.1053/jhep.2002.36821]

19 **LaMont JT**, Smith BF, Moore JR. Role of gallbladder mucin in pathophysiology of gallstones. *Hepatology* 1984; **4**: 51S-56S [PMID: 6546237 DOI: 10.1002/hep.1840040809]

20 **Lee KT**, Liu TS. Mucin gene expression in gallbladder epithelium. *J Formos Med Assoc* 2002; **101**: 762-768 [PMID: 12517055]

21 **Wang HH**, Afdhal NH, Gendler SJ, Wang DQ. Targeted disruption of the murine mucin gene 1 decreases susceptibility to cholesterol gallstone formation. *J Lipid Res* 2004; **45**: 438-447 [PMID: 14703511 DOI: 10.1194/jlr.M300468-JLR200]

22 **Wang HH**, Afdhal NH, Gendler SJ, Wang DQ. Evidence that gallbladder epithelial mucin enhances cholesterol cholelithogenesis in MUC1 transgenic mice. *Gastroenterology* 2006; **131**: 210-222 [PMID: 16831603 DOI: 10.1053/j.gastro.2006.04.011]

23 **Hu FL**, Chen HT, Guo FF, Yang M, Jiang X, Yu JH, Zhang FM, Xu GQ. Biliary microbiota and mucin 4 impact the calcification of cholesterol gallstones. *Hepatobiliary Pancreat Dis Int* 2021; **20**: 61-66 [PMID: 33341401 DOI: 10.1016/j.hbpd.2020.12.002]

24 **Andrianifahanana M**, Moniaux N, Batra SK. Regulation of mucin expression: mechanistic aspects and implications for cancer and inflammatory diseases. *Biochim Biophys Acta* 2006; **1765**: 189-222 [PMID: 16487661 DOI: 10.1016/j.bbcan.2006.01.002]

25 **Zen Y**, Harada K, Sasaki M, Tsuneyama K, Katayanagi K, Yamamoto Y, Nakanuma Y. Lipopolysaccharide induces overexpression of MUC2 and MUC5AC in cultured biliary epithelial cells: possible key phenomenon of hepatolithiasis. *Am J Pathol* 2002; **161**: 1475-1484 [PMID: 12368220 DOI: 10.1016/S0002-9440(10)64423-9]

26 **Ikeda H**, Sasaki M, Ishikawa A, Sato Y, Harada K, Zen Y, Kazumori H, Nakanuma Y. Interaction of Toll-like receptors with bacterial components induces expression of CDX2 and MUC2 in rat biliary epithelium in vivo and in culture. *Lab Invest* 2007; **87**: 559-571 [PMID: 17417665 DOI: 10.1038/labinvest.3700556]

27 **Finzi L**, Barbu V, Burgel PR, Mergey M, Kirkwood KS, Wick EC, Scoazec JY, Peschaud F, Paye F, Nadel JA, Housset C. MUC5AC, a gel-forming mucin accumulating in gallstone disease, is overproduced *via* an epidermal growth factor receptor pathway in the human gallbladder. *Am J Pathol* 2006; **169**: 2031-2041 [PMID: 17148666 DOI: 10.2353/ajpath.2006.060146]

28 **Feingold KR**, Pollock AS, Moser AH, Shigenaga JK, Grunfeld C. Discordant regulation of proteins of cholesterol metabolism during the acute phase response. *J Lipid Res* 1995; **36**: 1474-1482 [PMID: 7595071]

29 **Hardardóttir I**, Moser AH, Memon R, Grünfeld C, Feingold KR. Effects of TNF, IL-1, and the combination of both cytokines on cholesterol metabolism in Syrian hamsters. *Lymphokine Cytokine Res* 1994; **13**: 161-166 [PMID: 7948424]

30 **Feingold KR**, Hardardottir I, Memon R, Krul EJ, Moser AH, Taylor JM, Grunfeld C. Effect of endotoxin on cholesterol biosynthesis and distribution in serum lipoproteins in Syrian hamsters. *J Lipid Res* 1993; **34**: 2147-2158 [PMID: 8301233]

31 **Feingold KR**, Spady DK, Pollock AS, Moser AH, Grunfeld C. Endotoxin, TNF, and IL-1 decrease cholesterol 7 alpha-hydroxylase mRNA levels and activity. *J Lipid Res* 1996; **37**: 223-228 [PMID: 9026521]

32 **Memon RA**, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. In vivo and in vitro regulation of sterol 27-hydroxylase in the liver during the acute phase response. potential role of hepatocyte nuclear factor-1. *J Biol Chem* 2001; **276**: 30118-30126 [PMID: 11406622 DOI: 10.1074/jbc.M102516200]

33 **Wan JF**, Chu SF, Zhou X, Li YT, He WB, Tan F, Luo P, Ai QD, Wang Q, Chen NH. Ursodeoxycholic acid protects interstitial Cajal-like cells in the gallbladder from undergoing apoptosis by inhibiting TNF-α expression. *Acta Pharmacol Sin* 2018; **39**: 1493-1500 [PMID: 29770794 DOI: 10.1038/aps.2017.206]

34 **Maurer KJ**, Rao VP, Ge Z, Rogers AB, Oura TJ, Carey MC, Fox JG. T-cell function is critical for murine cholesterol gallstone formation. *Gastroenterology* 2007; **133**: 1304-1315 [PMID: 17919501 DOI: 10.1053/j.gastro.2007.07.005]

35 **Whary MT**, Morgan TJ, Dangler CA, Gaudes KJ, Taylor NS, Fox JG. Chronic active hepatitis induced by Helicobacter hepaticus in the A/JCr mouse is associated with a Th1 cell-mediated immune response. *Infect Immun* 1998; **66**: 3142-3148

[PMID: 9632578 DOI: 10.1128/IAI.66.7.3142-3148.1998]

36 **Fox JG**, Beck P, Dangler CA, Whary MT, Wang TC, Shi HN, Nagler-Anderson C. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. *Nat Med* 2000; **6**: 536-542 [PMID: 10802709 DOI: 10.1038/75015]

37 **Muñoz LE**, Boeltz S, Bilyy R, Schauer C, Mahajan A, Widulin N, Grüneboom A, Herrmann I, Boada E, Rauh M, Krenn V, Biermann MHC, Podolska MJ, Hahn J, Knopf J, Maueröder C, Paryzhak S, Dumych T, Zhao Y, Neurath MF, Hoffmann MH, Fuchs TA, Leppkes M, Schett G, Herrmann M. Neutrophil Extracellular Traps Initiate Gallstone Formation. *Immunity* 2019; **51**: 443-450.e4 [PMID: 31422870 DOI: 10.1016/j.immuni.2019.07.002]

38 **Nishimoto S**, Fukuda D, Higashikuni Y, Tanaka K, Hirata Y, Murata C, Kim-Kaneyama JR, Sato F, Bando M, Yagi S, Soeki T, Hayashi T, Imoto I, Sakaue H, Shimabukuro M, Sata M. Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance. *Sci Adv* 2016; **2**: e1501332 [PMID: 27051864 DOI: 10.1126/sciadv.1501332]

39 **Celec P**, Janovičová Ľ, Gurecká R, Koborová I, Gardlík R, Šebeková K. Circulating extracellular DNA is in association with continuous metabolic syndrome score in healthy adolescents. *Physiol Genomics* 2021; **53**: 309-318 [PMID: 34097532 DOI: 10.1152/physiolgenomics.00029.2021]

40 **Frey C**, Thorpe C, Abrams G. Gallstone formation in the germ-free mouse. *Am J Surg* 1968; **115**: 75-81 [PMID: 5634678 DOI: 10.1016/0002-9610(68)90132-3]

41 **Maurer KJ**, Ihrig MM, Rogers AB, Ng V, Bouchard G, Leonard MR, Carey MC, Fox JG. Identification of cholelithogenic enterohepatic helicobacter species and their role in murine cholesterol gallstone formation. *Gastroenterology* 2005; **128**: 1023-1033 [PMID: 15825083 DOI: 10.1053/j.gastro.2005.01.008]

42 **Feng R**, Zhang T, Kayani MUR, Wang Z, Shen Y, Su KL, Bielike K, Chen L. Patients with Primary and Secondary Bile Duct Stones Harbor Distinct Biliary Microbial Composition and Metabolic Potential. *Front Cell Infect Microbiol* 2022; **12**: 881489 [PMID: 35548466 DOI: 10.3389/fcimb.2022.881489]

43 **Wang Q**, Jiao L, He C, Sun H, Cai Q, Han T, Hu H. Alteration of gut microbiota in association with cholesterol gallstone formation in mice. *BMC Gastroenterol* 2017; **17**: 74 [PMID: 28599622 DOI: 10.1186/s12876-017-0629-2]

44 **Wu T**, Zhang Z, Liu B, Hou D, Liang Y, Zhang J, Shi P. Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics* 2013; **14**: 669 [PMID: 24083370 DOI: 10.1186/1471-2164-14-669]

45 **Thomas LA**, Veysey MJ, Murphy GM, Russell-Jones D, French GL, Wass JA, Dowling RH. Octreotide induced prolongation of colonic transit increases faecal anaerobic bacteria, bile acid metabolising enzymes, and serum deoxycholic acid in patients with acromegaly. *Gut* 2005; **54**: 630-635 [PMID: 15831907 DOI: 10.1136/gut.2003.028431]

46 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

47 **Hu H**, Shao W, Liu Q, Liu N, Wang Q, Xu J, Zhang X, Weng Z, Lu Q, Jiao L, Chen C, Sun H, Jiang Z, Gu A. Gut microbiota promotes cholesterol gallstone formation by modulating bile acid composition and biliary cholesterol secretion. *Nat Commun* 2022; **13**: 252 [PMID: 35017486 DOI: 10.1038/s41467-021-27758-8]

48 **Petersen C**, Bell R, Klag KA, Lee SH, Soto R, Ghazaryan A, Buhrke K, Ekiz HA, Ost KS, Boudina S, O'Connell RM, Cox JE, Villanueva CJ, Stephens WZ, Round JL. T cell-mediated regulation of the microbiota protects against obesity. *Science* 2019; **365** [PMID: 31346040 DOI: 10.1126/science.aat9351]

49 **Sun H**, Warren J, Yip J, Ji Y, Hao S, Han W, Ding Y. Factors Influencing Gallstone Formation: A Review of the Literature. *Biomolecules* 2022; **12** [PMID: 35454138 DOI: 10.3390/biom12040550]

50 **Katsika D**, Grjibovski A, Einarsson C, Lammert F, Lichtenstein P, Marschall HU. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. *Hepatology* 2005; **41**: 1138-1143 [PMID: 15747383 DOI: 10.1002/hep.20654]

51 **Gerloff T**, Stieger B, Hagenbuch B, Madon J, Landmann L, Roth J, Hofmann AF, Meier PJ. The sister of P-glycoprotein represents the canalicular bile salt export pump of mammalian liver. *J Biol Chem* 1998; **273**: 10046-10050 [PMID: 9545351 DOI: 10.1074/jbc.273.16.10046]

52 **Smit JJ**, Schinkel AH, Oude Elferink RP, Groen AK, Wagenaar E, van Deemter L, Mol CA, Ottenhoff R, van der Lugt NM, van Roon MA. Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. *Cell* 1993; **75**: 451-462 [PMID: 8106172 DOI: 10.1016/0092-8674(93)90380-9]

53 **Yu L**, Hammer RE, Li-Hawkins J, Von Bergmann K, Lutjohann D, Cohen JC, Hobbs HH. Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. *Proc Natl Acad Sci U S A* 2002; **99**: 16237-16242 [PMID: 12444248 DOI: 10.1073/pnas.252582399]

54 **Wang HH**, Portincasa P, Liu M, Wang DQ. Genetic Analysis of *ABCB4* Mutations and Variants Related to the Pathogenesis and Pathophysiology of Low Phospholipid-Associated Cholelithiasis. *Genes (Basel)* 2022; **13** [PMID: 35741809 DOI: 10.3390/genes13061047]

55 **Buch S**, Schafmayer C, Völzke H, Becker C, Franke A, von Eller-Eberstein H, Kluck C, Bässmann I, Brosch M, Lammert F, Miquel JF, Nervi F, Wittig M, Rosskopf D, Timm B, Höll C, Seeger M, ElSharawy A, Lu T, Egberts J, Fändrich F, Fölsch UR, Krawczak M, Schreiber S, Nürnberg P, Tepel J, Hampe J. A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. *Nat Genet* 2007; **39**: 995-999 [PMID: 17632509 DOI: 10.1038/ng2101]

56 **Berge KE**, von Bergmann K, Lutjohann D, Guerra R, Grundy SM, Hobbs HH, Cohen JC. Heritability of plasma noncholesterol sterols and relationship to DNA sequence polymorphism in ABCG5 and ABCG8. *J Lipid Res* 2002; **43**: 486-494 [PMID: 11893785]

57 **Acalovschi M**, Ciocan A, Mostean O, Tirziu S, Chiorean E, Keppeler H, Schirin-Sokhan R, Lammert F. Are plasma lipid levels related to ABCG5/ABCG8 polymorphisms? *Eur J Intern Med* 2006; **17**: 490-494 [PMID: 17098593 DOI: 10.1016/j.ejim.2006.04.012]

58 **Joshi AD**, Andersson C, Buch S, Stender S, Noordam R, Weng LC, Weeke PE, Auer PL, Boehm B, Chen C, Choi H, Curhan G, Denny JC, De Vivo I, Eicher JD, Ellinghaus D, Folsom AR, Fuchs C, Gala M, Haessler J, Hofman A, Hu F, Hunter DJ, Janssen HL, Kang JH, Kooperberg C, Kraft P, Kratzer W, Lieb W, Lutsey PL, Darwish Murad S, Nordestgaard BG, Pasquale LR, Reiner AP, Ridker PM, Rimm E, Rose LM, Shaffer CM, Schafmayer C, Tamimi RM, Uitterlinden AG, Völker U, Völzke H, Wakabayashi Y, Wiggs JL, Zhu J, Roden DM, Stricker BH, Tang W, Teumer A, Hampe J, Tybjærg-Hansen A, Chasman DI, Chan AT, Johnson AD. Four Susceptibility Loci for Gallstone Disease Identified in a Meta-analysis of Genome-Wide Association Studies. *Gastroenterology* 2016; **151**: 351-363.e28 [PMID: 27094239 DOI: 10.1053/j.gastro.2016.04.007]

59 **Qayyum F**, Lauridsen BK, Frikke-Schmidt R, Kofoed KF, Nordestgaard BG, Tybjærg-Hansen A. Genetic variants in CYP7A1 and risk of myocardial infarction and symptomatic gallstone disease. *Eur Heart J* 2018; **39**: 2106-2116 [PMID: 29529257 DOI: 10.1093/eurheartj/ehy068]

60 **Lauridsen BK**, Stender S, Tybjærg-Hansen A. Genetic Variation in NPC1L1 and Risk of Gallstone Disease. *J Am Coll Cardiol* 2015; **66**: 1086 [PMID: 26314540 DOI: 10.1016/j.jacc.2015.05.076]

61 **Gellert-Kristensen H**, Dalila N, Fallgaard Nielsen S, Grønne Nordestgaard B, Tybjaerg-Hansen A, Stender S. Identification and Replication of Six Loci Associated With Gallstone Disease. *Hepatology* 2019; **70**: 597-609 [PMID: 30325047 DOI: 10.1002/hep.30313]

62 **Krawczyk M**, Müllenbach R, Weber SN, Zimmer V, Lammert F. Genome-wide association studies and genetic risk assessment of liver diseases. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 669-681 [PMID: 21045792 DOI: 10.1038/nrgastro.2010.170]

63 **van Erpecum KJ**, Venneman NG, Portincasa P, Vanberge-Henegouwen GP. Review article: agents affecting gall-bladder motility--role in treatment and prevention of gallstones. *Aliment Pharmacol Ther* 2000; **14** Suppl 2: 66-70 [PMID: 10903008 DOI: 10.1046/j.1365-2036.2000.014s2066.x]

64 **Haal S**, Guman MSS, Bruin S, Schouten R, van Veen RN, Fockens P, Dijkgraaf MGW, Hutten BA, Gerdes VEA, Voermans RP. Risk Factors for Symptomatic Gallstone Disease and Gallstone Formation After Bariatric Surgery. *Obes Surg* 2022; **32**: 1270-1278 [PMID: 35143012 DOI: 10.1007/s11695-022-05947-8]

65 **Haal S**, Guman MSS, Boerlage TCC, Acherman YIZ, de Brauw LM, Bruin S, de Castro SMM, van Hooft JE, van de Laar AWJM, Moes DE, Schouten M, Schouten R, van Soest EJ, van Veen RN, de Vries CEE, Fockens P, Dijkgraaf MGW, Gerdes VEA, Voermans RP. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial. *Lancet Gastroenterol Hepatol* 2021; **6**: 993-1001 [PMID: 34715031 DOI: 10.1016/S2468-1253(21)00301-0]

66 **Sitzmann JV**, Pitt HA, Steinborn PA, Pasha ZR, Sanders RC. Cholecystokinin prevents parenteral nutrition induced biliary sludge in humans. *Surg Gynecol Obstet* 1990; **170**: 25-31 [PMID: 2104681]

67 **Gebhard RL**, Prigge WF, Ansel HJ, Schlasner L, Ketover SR, Sande D, Holtmeier K, Peterson FJ. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. *Hepatology* 1996; **24**: 544-548 [PMID: 8781321 DOI: 10.1002/hep.510240313]

68 **Wang HH**, Liu M, Portincasa P, Tso P, Wang DQ. Lack of endogenous cholecystokinin promotes cholelithogenesis in mice. *Neurogastroenterol Motil* 2016; **28**: 364-375 [PMID: 26604077 DOI: 10.1111/nmo.12734]

69 **Wang DQ**, Schmitz F, Kopin AS, Carey MC. Targeted disruption of the murine cholecystokinin-1 receptor promotes intestinal cholesterol absorption and susceptibility to cholesterol cholelithiasis. *J Clin Invest* 2004; **114**: 521-528 [PMID: 15314689 DOI: 10.1172/JCI16801]

70 **Pasternak A**, Gajda M, Gil K, Matyja A, Tomaszewski KA, Walocha JA, Kulig J, Thor P. Evidence of interstitial Cajal-like cells in human gallbladder. *Folia Histochem Cytobiol* 2012; **50**: 581-585 [PMID: 23264222 DOI: 10.5603/19673]

71 **Ahmadi O**, Nicholson Mde L, Gould ML, Mitchell A, Stringer MD. Interstitial cells of Cajal are present in human extrahepatic bile ducts. *J Gastroenterol Hepatol* 2010; **25**: 277-285 [PMID: 19793166 DOI: 10.1111/j.1440-1746.2009.05980.x]

72 **Pasternak A**, Gil K, Gajda M, Tomaszewski KA, Matyja A, Walocha JA. Interstitial cajal-like cell: a new player in cholelithiasis? *Am J Gastroenterol* 2014; **109**: 603-604 [PMID: 24698872 DOI: 10.1038/ajg.2013.251]

73 **Franks I**. Gallbladder: Loss of interstitial Cajal-like cells in the gallbladder might contribute to gallstone formation. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 689 [PMID: 23165238 DOI: 10.1038/nrgastro.2012.224]

74 **Pasternak A**, Gil K, Matyja A, Gajda M, Sztefko K, Walocha JA, Kulig J, Thor P. Loss of gallbladder interstitial Cajal-like cells in patients with cholelithiasis. *Neurogastroenterol Motil* 2013; **25**: e17-e24 [PMID: 23121223 DOI: 10.1111/nmo.12037]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com