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Pathogenesis, Diagnosis and Treatment of Gallstone Disease:

A Brief Review

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ABSTRACT

Gallstone disease is a gastrointestinal disease that results from the dysfunction of cholesterol, bile, and bilirubin metabolism. Gallstones in the gallbladder are common and form through cholelithiasis. They can also grow in biliary ducts through choledocholithiasis. In industrial countries, gallstone disease has increased in prevalence and affects up to 20% of the adult population. Its major risk factors are female gender, age, obesity, type 2 diabetes, rapid weight loss, physical inactivity, and genetic traits. Various systems for gallstone classification are available. Gallstones are classified as cholesterol, pigmented, and mixed gallstones in accordance with their chemical composition. Gallstone disease is either asymptomatic or has symptoms that manifest as pain in the right upper part of the abdomen, fever, and jaundice. The pathogenesis of this disease is related to the interaction between genetic and environmental factors, which include hepatic cholesterol hypersecretion, bile supersaturation, mucin, inflammatory changes, intestinal hypomotility, intestinal cholesterol hyperabsorption, and gut microbe alterations. The major genetic factors of this disease are the mutations in the hepatic cholesterol transporter ABCC8 and the cholecystokinin a receptor gene. Metabolic syndrome, insulin resistance, and type 2 diabetes increase the risk of developing gallstone disease. The standard diagnostic method for gallstone disease is ultrasound imaging. Medical treatment involves the administration of bile acid drugs and/or cholecystectomy.

1. Introduction

Gallstones are solid deposits of bile salts that are formed in the gallbladder or bile ducts. They are formed by cholesterol, bile pigments, and calcium ions. Gallstones develop in the gallbladder through cholelithiasis, whereas they develop in the bile ducts through choledocholithiasis (Ghai, 2012). Bile salts are the potassium and sodium salts of the bile acids that are conjugated with glycine. Bile is secreted from hepatocytes and stored in the gallbladder. It consists of cholesterol, bile acids, pigments, lecithin, and fatty acids (Ramaswamy et al., 2015; Cox et al., 2018; Di Ciaula et al., 2018). Gallbladder contraction is stimulated by cholecystokinin, which is secreted from the intestinal lumen for the digestion and absorption of fats after emulsification (Reshetnyak, 2012; Ramaswamy et al., 2015). Bile salts also perform choleretic, cholagogue, and laxative actions (Ghai, 2012).

Gallstone disease is one of the most painful diseases in adults and has a high prevalence among populations worldwide (Ramaswamy et al., 2015). The prevalence of gallstone disease is higher among adults than among children (Kaechele et al., 2006). Gallstones affect 5%–25% of the adult population in the western world (Lammert et al., 2016) and approximately 16.6% of women and 7.9% of men (Everhart et al., 1999). The prevalence of this disease varies among consumers and is frequently high in industrialized countries (Buch et al., 2007). In the United States, approximately 20 million adults have gallstone disease, and among Mexican Americans, gallstones affect 26.7% of women and 8.9% of men. The prevalence of gallstone disease

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in China is approximately 4%–11% and that in Russia is 3%–12% (Tsukanov et al., 2007). The prevalence of gallstone disease is associated with a high morbidity rate (Ruhl & Everhart, 2011). Gallstones cause numerous health complications, including the destruction of bile ducts and the inflammation of the gallbladder and liver (Dai et al., 2013).

Many factors increase the risk of gallstone formation in populations. These factors include obesity, especially in women; rapid weight loss, which increases cholesterol in biliary secretions; estrogen, especially in birth control medications, which decreases gallbladder contractility; and diabetes, which causes neuropathy and reduces gallbladder contractility (Shabanzadeh, 2018). The many reasons for gallstone development include (Ghai, 2012) reductions in lecithin and bile salts, excess cholesterol, excess calcium ions, low bile salt production, disturbances in cholesterol metabolism, bile duct obstruction, gallbladder epithelium inflammation (mucin, water, and bile salt dysfunction), decreased gallbladder motility, cholesterol supersaturation, increased biliary bilirubin load, and decreased phosphatidylcholine (prevention of cholesterol crystallization). The factors that participate in gallstone formation are divided into four main groups: factors that cause bile cholesterol supersaturation; factors that cause cholesterol precipitation, core crystallization, and formation; factors that cause gallbladder dysfunction; and factors that cause bile–hepatic circulation dysfunction (Chong, 2005).

The first and second factors include the increased secretion of mucin from gallbladder mucosa, which increases bile viscosity. The third factor involves the low contractility rate and increased volume of the gallbladder that impair motility and enhance gallstone formation (Olokoba et al., 2008). This impairment is associated with rapid weight loss, iron deficiency anemia, celiac disease, and gallbladder cholesterosis (Grigorieva, 2007; Pamuk et al., 2009). The fourth factor involves some bowel diseases, such as Crohn's disease, that affect acid absorption or cause bile loss (Ilychenko, 2004). The main risk factors of gallstone development include female gender, pregnancy, family history, genetic traits, obesity, type 2 diabetes, high triglyceride levels, hyperinsulinemia, low high-density lipoprotein levels, high-carbohydrate and -fat diets, rapid weight loss, folic acid and B12 vitamin deficiencies, oral contraceptive use, and Helicobacter pylori infection (Wang et al., 2012).

The majority of gall stones are clinically silent and do not develop symptoms. This type is incidentally found through abdominal ultrasound (US) (Halldestam et al., 2004). Asymptomatic gallstones may develop into symptomatic gallstones (biliary pain) with a low rate of complications of approximately 1%–2% per year (Friedman, 1993). This rate is increased in patients with large gallbladders (>3 cm) who develop gallbladder cancers; in those with sickle cell disease who develop pigmented gall stones; patients with organ transplants; and patients undergoing bariatric surgery (Ebert et al., 2010).

Differentiating true gallstone pain or its complications from general abdominal pain, such as dysplasia, is important. Most patients exhibit a certain pattern of symptoms that are considered important for the selection of cholecystectomy. These symptoms include persistent severe pain in the right upper quadrant of the abdomen, nausea, vomiting, fever, and jaundice (Ruhl & Everhart, 2011). In functional gallbladder disease (acalculous gallstones), biliary pain resulting from stone formation in cystic ducts impairs gallbladder and sphincter contraction. This type of gallbladder disease is also called gallbladder dyskinesia or biliary dyskinesia and can be detected through cholecystokinin–cholescintigraphy (DiBaise et al., 2011). Gallstone symptoms include weight loss, chills, sepsis, clay colored stools, and biliary colic (Chiapponi et al., 2010).

Numerous mechanisms underlying the development and formation of gallstones have been suggested (Afdhal, 2007; Cox et al., 2018). Most studies on gall stones have elucidated the correlation between stone compositions and patient abnormalities (Ramaswamy et al., 2015). The most critical factors in the pathogenesis of gallstone disease are genetic factors; liver and gallbladder factors, which involve hepatic activity in cholesterol secretion, cholesterol transport in bile, gallbladder inflammation, and mucin hypersecretion; and intestinal factors, which include intestinal motility, gut microbiome alterations, and cholesterol absorption (Wang et al., 2017).

Gallstone disease is a major epidemiological disease worldwide and exerts an economic burden. Its common form is cholesterol gallstones. Pathogenesis studies are at the frontline of ongoing studies, such as prevention or treatment studies, on gallstone disease because of the complex interactions among the pathogenic factors of this disease. Given the previous consideration, understanding the pathogenesis of gallstone disease is important to provide detailed information to support researchers. In this review, we present updates and brief studies related to the classification, pathogenesis, diagnosis, and treatment of cholesterol gallstones.

2. Materials and Methods

2.1. Gallstone Classification

The major components of gallstones are unesterified cholesterol, bilirubin calcium salts, unconjugated bilirubin, calcium carbonate, calcium phosphate, fatty acids, and mucin glycoproteins. Gallstones are classified into three types in accordance with their chemical composition: (i) Cholesterol stones are oval and light yellow to dark green stones with a central dark spot (Ilychenko, 2004). They are commonly found in the gall bladder. They consist of cholesterol monohydrate (70%), calcium salts, bile acids, and glycoprotein. Electron microscopy has shown that their major components are lamellar vesicles with lipophilic and hydrophilic compounds. Bilirubin is arranged individually on the surfaces of sections (Reshetnyak, et al., 2009). (ii) Pigmented stones are black and brown stones. Black gallbladder stones are small, compact stones with a prevalence of 20%–30%. They are composed of cholesterol (less than 30%), calcium bilirubinate, carbonate, and phosphate (Origa et al., 2009). Brown gallbladder stones are large soft stones and are commonly found in bile ducts. They account for 10%–20% of gallstone cases. They are composed of cholesterol (less than 30%), calcium palmitate and stearate, calcium bilirubinate, free saturated fatty acids, bile acids, and phospholipase A1 (Uchiyama et al., 2007). The gallstones that form in children consist of calcium carbonate, which results from high mucin production by gallbladder epithelial cells (Sayers et al., 2007). (iii) Mixed gallbladder stones are heavy stones with various shapes and sizes and poor combustibility. They consist of either a single (protein–bilirubin) stone or multiple mixed stones (protein–

bilirubin) (Loginov et al., 1998). The types of gallstones are showed in Figure 1.

Fig.1. The types of gallstones. A: cholesterol gallstones, b: pigmented gallstones, c: mixed gallstones (Abdullah et al., 2015).

2.2. Pathogenesis Of Gallstone Disease

2.2.1. Pathogenic factors, Genes and gene–environment interactions

Family history plays a critical role in the incidence of gallstone disease (Hsing et al., 2007). In humans, increased susceptibility to gallstone disease is linked to variations in ATP-binding cassette transporters (ABCG5-R50C and ABCG8-D19H), which have been found to be expressed in gallstones in Indian, Chinese, and German populations (Rudkowska & Jones, 2008; Von Kampen et al., 2013; von Schönfels et al., 2013). Hepatic cholesterol secretion is regulated by ABCG5/G8 genes. Variations in the Farnesoid X receptor gene, rs35724, rs11110385, and rs11110386 (Hirobe-Jahn et al., 2015) and the polymorphisms of mucin genes (Chuang et al., 2012), the apolipoprotein E4 allele (Martinez-Lopez et al., 2015), and rs3758650 (mucin-like protocadherin gene) lead to symptomatic gallstone development (Chuang et al., 2011). The mutation in the ATP-binding cassette transporter B4 leads to the lack of phospholipids in bile because it regulates hepatic phospholipid secretion (Poupon et al., 2013). Genetic factors account for the occurrence of approximately 25%–30% of symptomatic gallstones (Nakeeb et al., 2002; Katsika et al., 2005).

The interactions between genes and environmental factors affect the expression of genes that are involved in insulin resistance and fat deposition (Di Ciaula et al., 2013; Di Ciaula & Portincasa, 2014; Wang et al., 2017). Genetic factors include microRNAs. The miRNA miR-122 is involved in cholesterol homeostasis (Moore et al., 2010). Wang et al. (2015) showed that obese patients with insulin resistance have high miR-122 levels, which are considered as one of the risk factors for cholesterol gallstones. Genetic variations in the human CCKAR gene enhance susceptibility to cholesterol gallstones through two principal mechanisms: (i) the development of bile stagnation and biliary sludge formation and (ii) delayed small intestinal transit (Wang et al., 2017).

2.2.2. Intestinal Factors

In gallstone disease, bile supersaturation is related to the imbalance between the absorption and synthesis of cholesterol (Kern, 1994). Intestinal factors depend on dietary cholesterol (Wang, 2007; Wang & Lee, 2008) and on the expression of sterol transport proteins on the enterocyte brush border membrane, which is regulated by many genes (Wang, 2007). The dysfunction of these genes leads to cholesterol gallstone formation (Wang et al., 2011). Cholesterol homeostasis affects the occurrence of insulin resistance (independent of obesity) by increasing cholesterol synthesis and reducing intestinal cholesterol absorption (Gylling et al., 2010; Paramsothy et al., 2011).

Patients with gallstones exhibit reduced cholesterol absorption and unchanged or increased de novo cholesterol synthesis (Krawczyk et al., 2012; Renner et al., 2013). Osteopontin (OPN) is a soluble cytokine that is involved in cholesterol homeostasis (Takemoto et al., 1999). OPN knockout mice are protected against lithogenic diet-induced gallstone formation (Lin et al., 2017). Estrogen decreases bile acid synthesis and enhances cholesterol synthesis via the upregulation of the α estrogen receptor and G protein-coupled receptor 30 (De Bari et al., 2015). Lipid-induced lipotoxicity to the gallbladder leads to defects in smooth muscle contraction and relaxation (Amaral et al., 2001). Excessive cholesterol absorption causes the inflammation and proliferation of gallbladder mucosa; the resulting hypomotility leads to stone growth through cholesterol nucleation (Wang et al., 2008).

Recently, Villanacci et al. (2016) found reductions in the neurons, enteric glial cells, mast cells, and interstitial cells of Cajal in patients with cholesterol stones and acalculous gallbladders. Patients with cholesterol gallstones present intestinal dysbiosis that may play an important role in disease pathogenesis. The ceca of patients with gallstones contain high amounts of Gram-positive anaerobic bacteria and increased concentrations of the lithogenic secondary bile acid deoxycholate (Thomas et al., 2005). The gut microbiota of patients with gallstones are diverse, whereas patients undergoing cholecystectomy show reductions in *Roseburia* spp and patients without treatment show enrichments in *Oscillospira* spp, which are positively correlated with the concentration of secondary bile acids (Keren et al., 2015). Exposure to organochlorine pesticides, such as dichlorodiphenyldichloroethylene, causes abnormalities in gut microbiota that then result in changes in bile acid composition, the decreased expression of genes regulating bile acid reabsorption, and the increased expression of genes responsible for hepatic bile acid synthesis (Liu et al., 2017).

2.3. Pathogenicity

The pathogenesis of gallstone disease originates from the interaction between environmental and genetic factors (Sun et al., 2009). Cholesterol stones result from the hypomotility of the gallbladder and the increased secretion of cholesterol and mucin (Carey, 1993). Their formation involves three processes: saturation, crystallization, and growth. High cholesterol concentration that is associated with low phospholipid and or bile salt levels results in the development of phospholipid vesicles (bile cholesterol) that form unstable unilamellar and multilamellar vesicles (liposomal) with liquid crystal structures (liquid–crystalline phase). Aggregated and fused unilamellar vesicles act as the core of gallstones by precipitating in the form of cholesterol monohydrate crystals during the reduction in gallbladder contractility (Cohen et al., 1993). The interaction of these crystals with bile protein molecules and with unconjugated bilirubin results in the formation of the structural components of human gallstones and lithogenic bile salts (Loginov et al., 1998). Mucin hypersecretion has a critical role in the pathogenesis of gallstones, and gallbladder wall inflammation increases mucin secretion that then results in lipid peroxidation, which enhances cholesterol crystal formation (Jüngst et al., 2007). The pathogenesis of gallstones is illustrated in Figure 2.

Under healthy conditions, bile has bactericidal activity (Hofmann, 2007). As bile salt composition changes under disease conditions, bacteria promote bile lithogenesis and secrete phospholipid A2, which causes the hydrolysis of phospholipids and the accumulation of fatty acids, such as arachidonic acid, that enhance the production of leukotrienes, prostaglandins, and thromboxane from gall bladder mucosa and then increase mucin secretion. Moreover, cholic acid is converted into lithocholic acid, which enhances the aggregation of cholesterol monohydrate crystals especially when secreted in high amounts (Uchiyama et al., 2007). The morphological change in the gallbladder mucosa impairs the absorption of water and electrolytes; this impairment, along with the hypersecretion of mucin, leads to the formation of a viscoelastic glycoprotein–mucin gel. This gel contributes to phospholipid vesicle aggregation (cholesterol monohydrate crystals) or bilirubin precipitation. All these components, along with bilirubinate granules, form the pigmented matrix that serves as the core of cholesterol gallstones. Intrahepatic stones are related to biliary tract infection, which is caused by opportunistic bacteria, such as *Escherichia coli, streptococci, staphylococci, and typhoid bacilli*. Various types of stones are formed depending on the type of microorganism that causes the biliary tract infection (Stewart et al., 2006).

Pigmented stones: The high production of bile pigment (bilirubin) in the bile is related to hemolytic anemia (sickle cell anemia or hereditary spherocytosis), biliary tract infections, or liver cirrhosis. This phenomenon leads to the combination of bilirubin with other bile constituents, such as calcium, phosphate, and carbonate, to form the pigment salts of bilirubin. These poorly dissolved pigments aggregate with each other to form particles and then develop into stones with black-brown coloration (Cox et al., 2018).

Mixed stones: Mixed stones are a mixture of varying proportions of cholesterol and bilirubin stones (bilirubin salts). They contain other compounds, such as calcium bilirubinate, carbonate, palmitate, phosphate, and stearate (Singh et al., 2008). Stones in the gallbladder or in the ducts (hepatic, cystic, or bile ducts) can block bile flow and cause inflammation in other parts that result in severe damage to the gallbladder, liver, and pancreas, including cholangitis, gallstone ileus, pancreatitis, and gall bladder cancer (Iqbal et al., 2019). The lack of treatment leads to chronic diseases and then death (Cox et al., 2018).

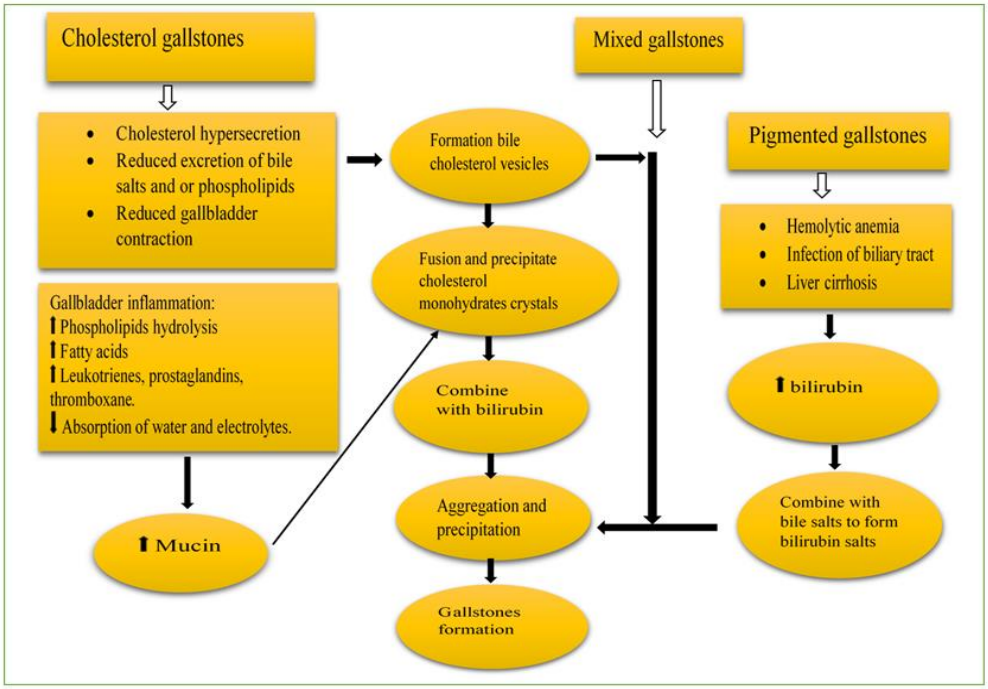

Fig. 2: the pathogenesis of cholesterol, pigmented and mixed gallstones.

3. Results & Discussion

3.1. Diagnosis and Treatment

Gallstones are diagnosed either through physiological examination, which is dependent on the presence of pain in the right upper quadrant of the abdomen. This symptom overlaps with the symptoms of other diseases, such as myocardial infarction or hepatic or duodenal ulcer (Iqbal et al., 2019). Gallstones are also diagnosed via blood tests as follows: (i) Complete blood count. Some cases show elevated white blood cell counts. (ii) Liver function test, which includes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and ALT/AST levels. (iii) Serum levels of lipase and amylase. (iv) Urinalysis. (vi) Stool test in cases with intestinal bleeding.

The final and most important diagnostic method is imaging examination, which is considered as the essential and standard choice for the diagnosis of all types and complications of gallstone disease. This method prevents

unnecessary treatment by excluding other abdominal diseases, such as renal stones, pancreatitis, and intestinal obstruction, with symptoms that overlap with gallstone symptoms; it is also used for early diagnosis and for preventing future complications (Aslam et al., 2013; Heuman et al., 2019). Ultrasonography (US) is the gold standard for the diagnosis of gallstone because of its accuracy, lack of ionizing radiation, noninvasiveness, and low cost with high sensitivity (97%) and specificity (93.6%) (Giljaca et al., 2015). Computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) are recommended for undefined cases (Febyan, 2020).

Gallstone treatment includes medical treatment and surgical treatment. Medical treatment involves the oral administration of bile acids to dissolve gallstones. Bile acids include deoxycholic, chenodeoxy cholic, and ursodeoxy cholic acids. Patients treated with these drugs must be monitored appropriately for side effects (Guarino et al., 2013). Biliary colic is treated with pethidine combined with atropine or glycopyrronium (antispasmodic agents). The acute biliary duct is treated with nonsteroidal anti-inflammatory drugs and antispasmodic drugs (Tazuma et al., 2017). Surgical treatment is the standard treatment for gallstone disease. Patients with symptomatic gallstones either exhibit simple biliary colic or gallstone complications. Most symptomatic patients are treated through laparoscopic cholecystectomy, which shows similar results (surgical time and complication rate) but results in shorter hospital stays and convalescence periods when compared with open surgery (Keus et al., 2006). The use of open surgery or laparoscopic surgery depends on the sex, age, and gallbladder wall thickness of the patient and presence of acute cholecystitits (Tayeb et al., 2005; Berger et al., 2003). Cholecystectomy is characterized by the low risk of gallstone recurrence and bile complications and relevance for most patients (Gutt et al., 2020; Bagepally et al., 2021).

4. Conclusions

This review presents several mechanisms for gallstone formation, including the pathway of cholesterol homeostasis and alterations in the gut microbiota. Recent studies have tended to focus on changes in the genes involved in the pathways of cellular signaling and the influence of epigenetic factors. Gallstone risk factors have been observed to interfere with the pathogenic pathways of obesity, insulin resistance, and type 2 diabetes. The pathogenesis profile of stone formation is useful for developing prevention strategies for patients with moderate or high gallstone risk; nonsurgical therapy; and controlling exogenous triggering factors, such as lifestyle.

References

Abdullah, U. Y., Jassim, H. M., Baig, A. A., Khorsheed, R. M., Al-Khayat, A. M., Sulong, A. F., ... & Yassin, W. A. (2015). Gallstones in patients with inherited hemolytic diseases. International Journal of Pharmacy and Pharmaceutical Sciences, 7(7), 9-15.

Afdhal, N. H. (2007). Diseases of the Gallbladder and Bile Ducts/Ed. by L. Goldman, D. Ausiello. Cecil Textbook of Medicine.—23rd ed.—Philadelphia: Saunders Elsevier.

Amaral, J., Xiao, Z. L., Chen, Q., Yu, P., Biancani, P., & Behar, J. (2001). Gallbladder muscle dysfunction in patients with chronic acalculous disease. Gastroenterology, 120(2), 506-511. https://doi.org/10.1053/gast.2001.21190

Aslam, H. M., Saleem, S., Edhi, M. M., Shaikh, H. A., Hafiz, M., & Saleem, M. (2013). Assessment of gallstone predictor: comparative analysis of ultrasonographic and biochemical parameters. International archives of medicine, 6(1), 1-7. https://doi.org/10.1186/1755-7682-6-17

Bagepally, B. S., Haridoss, M., Sasidharan, A., Jagadeesh, K. V., & Oswal, N. K. (2021). Systematic review and meta-analysis of gallstone disease treatment outcomes in early cholecystectomy versus conservative management/delayed cholecystectomy. BMJ open gastroenterology, 8(1), e000675. http://dx.doi.org/10.1136/bmjgast-2021-000675

Berger, M. Y., & Bohnen, A. M. (2003). Abdominal symptoms: do they disappear after cholecystectomy?. Surgical Endoscopy And Other Interventional Techniques, 17(11), 1723-1728. https://doi.org/10.1007/s00464-002-9154-6

Buch, S., Schafmayer, C., Völzke, H., Becker, C., Franke, A., von Eller-Eberstein, H., ... & Hampe, J. (2007). A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. Nature genetics, 39(8), 995-999. https://doi.org/10.1038/ng2101

Carey, M. C. (1993). Pathogenesis of gallstones. The American journal of surgery, 165(4), 410-419. https://doi.org/10.1016/S0002-9610(05)80932-8

Chiapponi, C., Wirth, S., & Siebeck, M. (2010). Acute gallbladder perforation with gallstones spillage in a cirrhotic patient. World Journal of Emergency Surgery, 5(1), 1-4. https://doi.org/10.1186/1749-7922-5-11

Chong, V. H. (2005). Iatrogenic biliary stone. Surgical technology international, 14, 147-155.

Chuang, S. C., Hsi, E., & Lee, K. T. (2012). Mucin genes in gallstone disease. Clinica Chimica Acta, 413(19-20), 1466-1471. https://doi.org/10.1016/j.cca.2012.06.015

Chuang, S. C., Hsi, E., Wang, S. N., Yu, M. L., Lee, K. T., & Juo, S. H. H. (2011). Polymorphism at the mucin-like protocadherin gene influences susceptibility to gallstone disease. Clinica Chimica Acta, 412(23-24), 2089-2093. https://doi.org/10.1016/j.cca.2011.07.015

Cohen, D. E., Kaler, E. W., & Carey, M. C. (1993). Cholesterol carriers in human bile: are “lamellae” involved?. Hepatology, 18(6), 1522-1531. https://doi.org/10.1002/hep.1840180635

Cox, M. R., Eslick, G. D., & Padbury, R. (Eds.). (2018). The management of gallstone disease: a practical and evidence-based approach. Springer.

Dai, X. Z., Li, G. Q., Zhang, F., Wang, X. H., & Zhang, C. Y. (2013). Gallstone ileus: case report and literature review. World Journal of Gastroenterology: WJG, 19(33), 5586. https://dx.doi.org/10.3748%2Fwjg.v19.i33.5586

De Bari, O., Wang, T. Y., Liu, M., Portincasa, P., & Wang, D. Q. (2015). Estrogen induces two distinct cholesterol crystallization pathways by activating ERα and GPR30 in female mice. Journal of Lipid Research, 56(9), 1691-1700. https://doi.org/10.1194/jlr.M059121

DiBaise, J. K., Richmond, B. K., Ziessman, H. H., Everson, G. T., Fanelli, R. D., Maurer, A., ... & Tulchinsky, M. (2011). Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. Clinical Gastroenterology and Hepatology, 9(5), 376-384. https://doi.org/10.1016/j.cgh.2011.02.013

Di Ciaula, A., & Portincasa, P. (2014). Fat, epigenome and pancreatic diseases. Interplay and common pathways from a toxic and obesogenic environment. European Journal of Internal Medicine, 25(10), 865-873. https://doi.org/10.1016/j.ejim.2014.10.012

Di Ciaula, A., Wang, D. Q. H., & Portincasa, P. (2018). An update on the pathogenesis of cholesterol gallstone disease. Current opinion in gastroenterology, 34(2), 71. https://dx.doi.org/10.1097%2FMOG.0000000000000423

Di Ciaula, A., Wang, D. Q. H., Bonfrate, L., & Portincasa, P. (2013). Current views on genetics and epigenetics of cholesterol gallstone disease. Cholesterol, 2013.

Ebert, E. C., Nagar, M., & Hagspiel, K. D. (2010). Gastrointestinal and hepatic complications of sickle cell disease. Clinical gastroenterology and hepatology, 8(6), 483-489. https://doi.org/10.1016/j.cgh.2010.02.016

Everhart, J. E., Khare, M., Hill, M., & Maurer, K. R. (1999). Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology, 117(3), 632-639. https://doi.org/10.1016/S0016-5085(99)70456-7

Febyan, F. (2020). Cholelithiasis: A Brief Review on Diagnostic Approach and Management in Clinical Practice. International Journal of Medical Reviews, 7(3), 98-101. https://doi.org/10.19080/argh.2020.15.555913

Friedman, G. D. (1993). Natural history of asymptomatic and symptomatic gallstones. The American journal of surgery, 165(4), 399-404. https://doi.org/10.1016/s0002-9610(05)80930-4

Ghai, C. L. (2012). A textbook of practical physiology. JP Medical Ltd.

Giljaca, V., Gurusamy, K. S., Takwoingi, Y., Higgie, D., Poropat, G., Štimac, D., & Davidson, B. R. (2015). Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones. Cochrane Database of Systematic Reviews, (2). https://doi.org/10.1002/14651858.CD011549

Grigorieva, I. N. (2007). Major risk factors of cholelithiasis. Rossiyskiy Zhurnal Gastroenterologii, Gepatologii i Koloproktologii, 6, 17-19.

Guarino, M. P. L., Cocca, S., Altomare, A., Emerenziani, S., & Cicala, M. (2013). Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed. World Journal of Gastroenterology: WJG, 19(31), 5029. https://dx.doi.org/10.3748%2Fwjg.v19.i31.5029

Gutt, C., Schläfer, S., & Lammert, F. (2020). The treatment of gallstone disease. Deutsches Ärzteblatt International, 117(9), 148. https://dx.doi.org/10.3238%2Farztebl.2020.0148

Gylling, H., Hallikainen, M., Pihlajamäki, J., Simonen, P., Kuusisto, J., Laakso, M., & Miettinen, T. A. (2010). Insulin sensitivity regulates cholesterol metabolism to a greater extent than obesity: lessons from the METSIM Study 1. Journal of lipid research, 51(8), 2422-2427. https://doi.org/10.1194/jlr.P006619

Halldestam, I., Enell, E. L., Kullman, E., & Borch, K. (2004). Development of symptoms and complications in individuals with asymptomatic gallstones. Journal of British Surgery, 91(6), 734-738. https://doi.org/10.1002/bjs.4547.

Heuman, D.M., Mihas, A.A., Allen, J. (2019). Gallstones (Cholelithiasis). Emedicine.medscape.com. Retrieved 29 March 2022, from https://emedicine.medscape.com/article/175667-overview.

Hirobe-Jahn, S., Harsch, S., Renner, O., Richter, D., Müller, O., & Stange, E. F. (2015). Association of FXR gene variants with cholelithiasis. Clinics and research in hepatology and gastroenterology, 39(1), 68-79. https://doi.org/10.1016/j.clinre.2014.07.002

Hofmann, A. F. (2007). Biliary secretion and excretion in health and disease: current concepts. Annals of hepatology, 6(1), 15-27.

Hsing, A. W., Bai, Y., Andreotti, G., Rashid, A., Deng, J., Chen, J., ... & Gao, Y. T. (2007). Family history of gallstones and the risk of biliary tract cancer and gallstones: a population-based study in Shanghai, China. International journal of cancer, 121(4), 832-838. https://doi.org/10.1002/ijc.22756

Ilychenko, A. A. (2004). Gallstone disease. Lechashchiy Vrach, 4, 27-33.

Iqbal, M. N., Iqbal, M. A., Javaid, R., & Abbas, M. W. (2019). Gall stones: A fundamental clinical review.

Jüngst, C., Sreejayan, N., Eder, M. I., Von Stillfried, N., Zündt, B., Spelsberg, F. W., ... & Von Ritter, C. (2007). Lipid peroxidation and mucin secretagogue activity in bile of gallstone patients. European journal of clinical investigation, 37(9), 731-736. https://doi.org/10.1111/j.1365-2362.2007.01853.x

Kaechele, V., Wabitsch, M., Thiere, D., Kessler, A. L., Haenle, M. M., Mayer, H., & Kratzer, W. (2006). Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of

obesity, sex, and pubertal development. Journal of pediatric gastroenterology and nutrition, 42(1), 66-70.

Katsika, D., Grjibovski, A., Einarsson, C., Lammert, F., Lichtenstein, P., & Marschall, H. U. (2005). Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. Hepatology, 41(5), 1138-1143. https://doi.org/10.1002/hep.20654

Keren, N., Konikoff, F. M., Paitan, Y., Gabay, G., Reshef, L., Naftali, T., & Gophna, U. (2015). Interactions between the intestinal microbiota and bile acids in gallstones patients. Environmental microbiology reports, 7(6), 874-880. https://doi.org/10.1111/1758-2229.12319

Kern, F. (1994). Effects of dietary cholesterol on cholesterol and bile acid homeostasis in patients with cholesterol gallstones. The Journal of clinical investigation, 93(3), 1186-1194. https://doi.org/10.1172/JCI117072

Keus, F., de Jong, J., Gooszen, H. G., & Laarhoven, C. J. (2006). Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane database of systematic reviews, (4). https://doi.org/10.1002/14651858.CD006231

Krawczyk, M., Lütjohann, D., Schirin-Sokhan, R., Villarroel, L., Nervi, F., Pimentel, F., ... & Miquel, J. F. (2012). Phytosterol and cholesterol precursor levels indicate increased cholesterol excretion and biosynthesis in gallstone disease. Hepatology, 55(5), 1507-1517. https://doi.org/10.1002/hep.25563

Lammert, F., Gurusamy, K., Ko, C. W., Miquel, J. F., Méndez-Sánchez, N., Portincasa, P., ... & Wang, D. Q. H. (2016). Gallstones. Nature reviews Disease primers, 2(1), 1-17. https://doi.org/10.1038/nrdp.2016.24

Lin, J., Shao, W. Q., Chen, Q. Z., Zhu, W. W., Lu, L., Jia, H. L., & Chen, J. H. (2017). Osteopontin deficiency protects mice from cholesterol gallstone formation by reducing expression of intestinal NPC1L1. Molecular medicine reports, 16(2), 1785-1792. https://doi.org/10.3892/mmr.2017.6774

Liu, Q., Shao, W., Zhang, C., Xu, C., Wang, Q., Liu, H., ... & Gu, A. (2017). Organochloride pesticides modulated gut microbiota and influenced bile acid metabolism in mice. Environmental pollution, 226, 268-276. https://doi.org/10.1016/j.envpol.2017.03.068

Loginov, A. S., Chebanov, S. M., Petrakov, A. V., Saparin, G. V., Obyden, S. K., & Ivannikov, P. V. (1998). Investigation of cholesterol, bilirubin, and protein distribution in human gallstones by color cathodoluminescence scanning electron microscopy and transmission electron microscopy. Scanning: The Journal of Scanning Microscopies, 20(1), 17-22. https://doi.org/10.1002/sca.1998.4950200103

Martinez-Lopez, E., Curiel-Lopez, F., Hernandez-Nazara, A., Moreno-Luna, L. E., Ramos-Marquez, M. E., Roman, S., & Panduro, A. (2015). Influence of ApoE and FABP2 polymorphisms and environmental factors in the susceptibility to gallstone disease. Annals of hepatology, 14(4), 515-523.

Moore, K. J., Rayner, K. J., Suárez, Y., & Fernández-Hernando, C. (2010). microRNAs and cholesterol metabolism. Trends in Endocrinology & Metabolism, 21(12), 699-706. https://doi.org/10.1016/j.tem.2010.08.008

Nakeeb, A., Comuzzie, A. G., Martin, L., Sonnenberg, G. E., Swartz-Basile, D., Kissebah, A. H., & Pitt, H. A. (2002). Gallstones: genetics versus environment. Annals of surgery, 235(6), 842. https://dx.doi.org/10.1097%2F00000658-200206000-00012

Olokoba, A. B., Bojuwoye, B. J., Olokoba, L. B., Wahab, K. W., Salami, A. K., Braimoh, K. T., & Inikori, A. K. (2008). The relationship between gallstone disease and gall bladder volume. Nigerian journal of clinical practice, 11(2), 89-93.

Origa, R., Galanello, R., Perseu, L., Tavazzi, D., Domenica Cappellini, M., Terenzani, L., ... & Piga, A. (2009). Cholelithiasis in thalassemia major. European journal of haematology, 82(1), 22-25. https://doi.org/10.1111/j.1600-0609.2008.01162.x

Pamuk, G. E., Ümit, H., Harmandar, F., & Yeşil, N. (2009). Patients with iron deficiency anemia have an increased prevalence of gallstones. Annals of hematology, 88(1), 17-20. https://doi.org/10.1007/s00277-008-0557-x

Paramsothy, P., Knopp, R. H., Kahn, S. E., Retzlaff, B. M., Fish, B., Ma, L., & Ostlund Jr, R. E. (2011). Plasma sterol evidence for decreased absorption and increased synthesis of cholesterol in insulin resistance and obesity. The American journal of clinical nutrition, 94(5), 1182-1188. https://doi.org/10.3945/ajcn.110.006668

Poupon, R., Rosmorduc, O., Boëlle, P. Y., Chrétien, Y., Corpechot, C., Chazouillères, O., ... & Barbu, V. (2013). Genotype-phenotype relationships in the low-phospholipid-associated cholelithiasis syndrome: a study of 156 consecutive patients. Hepatology, 58(3), 1105-1110. https://doi.org/10.1002/hep.26424

Ramaswamy, K., Killilea, D. W., Kapahi, P., Kahn, A. J., Chi, T., & Stoller, M. L. (2015). The elementome of calcium-based urinary stones and its role in urolithiasis. Nature Reviews Urology, 12(10), 543-557. https://doi.org/10.1038/nrurol.2015.208

Renner, O., Lütjohann, D., Richter, D., Strohmeyer, A., Schimmel, S., Müller, O., ... & Harsch, S. (2013). Role of the ABCG8 19H risk allele in cholesterol absorption and gallstone disease. BMC gastroenterology, 13(1), 1-11. https://doi.org/10.1186/1471-230X-13-30

Reshetnyak, T. M., Saparin, G. V., Ivannikov, P. V., & Reshetnyak, V. I. (2009). Corticosteroids and cholelithiasis in systemic lupus erythematosus. Scholarly Research Exchange, 2009.

Reshetnyak, V. I. (2012). Concept of the pathogenesis and treatment of cholelithiasis. World journal of hepatology, 4(2), 18. https://dx.doi.org/10.4254%2Fwjh.v4.i2.18

Rudkowska, I., & Jones, P. J. (2008). Polymorphisms in ABCG5/G8 transporters linked to hypercholesterolemia and gallstone disease. Nutrition reviews, 66(6), 343-348. https://doi.org/10.1111/j.1753-4887.2008.00042.x

Ruhl, C. E., & Everhart, J. E. (2011). Gallstone disease is associated with increased mortality in the United States. Gastroenterology, 140(2), 508-516. https://doi.org/10.1053/j.gastro.2010.10.060

Sayers, C., Wyatt, J., Soloway, R. D., Taylor, D. R., & Stringer, M. D. (2007). Gallbladder mucin production and calcium carbonate gallstones in children. Pediatric surgery international, 23(3), 219-223. https://doi.org/10.1007/s00383-006-1867-5

Shabanzadeh, D. M. (2018). New determinants for gallstone disease. Dan Med J, 65(2), B5438.

Singh, V. K., Singh, V., Rai, A. K., Thakur, S. N., Rai, P. K., & Singh, J. P. (2008). Quantitative analysis of gallstones using laser-induced breakdown spectroscopy. Applied Optics, 47(31), G38-G47. https://doi.org/10.1364/AO.47.000G38

Stewart, L., Grifiss, J. M., Jarvis, G. A., & Way, L. W. (2006). Biliary bacterial factors determine the path of gallstone formation. The American journal of surgery, 192(5), 598-603. https://doi.org/10.1016/j.amjsurg.2006.08.001

Sun, H., Tang, H., Jiang, S., Zeng, L., Chen, E. Q., Zhou, T. Y., & Wang, Y. J. (2009). Gender and metabolic differences of gallstone diseases. World journal of gastroenterology: WJG, 15(15), 1886. https://dx.doi.org/10.3748%2Fwjg.15.1886

Takemoto, M., Tada, K., Nakatsuka, K., Moriyama, Y., Kazui, H., Yokote, K., ... & Mori, S. (1999). Effects of aging and hyperlipidemia on plasma osteopontin level. Nihon Ronen Igakkai zasshi. Japanese journal of geriatrics, 36(11), 799-802. https://doi.org/10.3143/geriatrics.36.799

Tayeb, M., Raza, S. A., Khan, M. R., & Azami, R. (2005). Conversion from laparoscopic to open cholecystectomy: multivariate analysis of preoperative risk factors. Journal of postgraduate medicine, 51(1), 17.

Tazuma, S., Unno, M., Igarashi, Y., Inui, K., Uchiyama, K., Kai, M., ... & Shimosegawa, T. (2017). Evidence-based clinical practice guidelines for cholelithiasis 2016. Journal of gastroenterology, 52(3), 276-300. https://doi.org/10.1007/s00535-016-1289-7

Thomas, L. A., Veysey, M. J., Murphy, G. M., Russell-Jones, D., French, G. L., Wass, J. A. H., & Dowling, R. H. (2005). Octreotide induced prolongation of colonic transit increases faecal anaerobic bacteria, bile acid metabolising enzymes, and serum deoxycholic acid in patients with acromegaly. Gut, 54(5), 630-635. http://dx.doi.org/10.1136/gut.2003.028431

Tsukanov, V. V., Nozdrachev, K. G., IuL, T., Bronnikova, E. P., & Eliu, K. (2007). The mechanism of reverse cholesterol transport and cholelithiasis in northern ethnic groups. Klinicheskaia meditsina, 85(2), 33-35.

Uchiyama, K., Kawai, M., Tani, M., Terasawa, H., Tanimura, H., & Yamaue, H. (2007). Pathogenesis of hepatolithiasis based on the analysis of components of intrahepatic stones. Hepato-gastroenterology, 54(78), 1798-1804.

Villanacci, V., Del Sordo, R., Salemme, M., Cadei, M., Sidoni, A., & Bassotti, G. (2016). The enteric nervous system in patients with calculous and acalculous gallbladder. Digestive and Liver Disease, 48(7), 792-795. https://doi.org/10.1016/j.dld.2016.03.014

Von Kampen, O., Buch, S., Nothnagel, M., Azocar, L., Molina, H., Brosch, M., ... & Hampe, J. (2013). Genetic and functional identification of the likely causative variant for cholesterol gallstone disease at the ABCG5/8 lithogenic locus. Hepatology, 57(6), 2407-2417. https://doi.org/10.1002/hep.26009

von Schönfels, W., Buch, S., Wölk, M., Aselmann, H., Egberts, J. H., Schreiber, S., ... & Schafmayer, C. (2013). Recurrence of gallstones after cholecystectomy is associated with ABCG5/8 genotype. Journal of gastroenterology, 48(3), 391-396. https://doi.org/10.1007/s00535-012-0639-3

Wang, D. Q. H. (2007). Regulation of intestinal cholesterol absorption. Annu. Rev. Physiol., 69, 221-248. https://doi.org/10.1146/annurev.physiol.69.031905.160725

Wang, D. Q. H., & Lee, S. P. (2008). Physical chemistry of intestinal absorption of biliary cholesterol in mice. Hepatology, 48(1), 177-185. https://doi.org/10.1002/hep.22286

Wang, D. Q. H., Neuschwander-Tetri, B. A., & Portincasa, P. (2012). The Biliary System, Colloquium Series on Integrated Systems Physiology: From Molecule to Function. Morgan & Claypool, 109-145.

Wang, H. H., Li, T., Portincasa, P., Ford, D. A., Neuschwander-Tetri, B. A., Tso, P., & Wang, D. Q. H. (2017). New insights into the role of Lith genes in the formation of cholesterol-supersaturated bile. Liver Research, 1(1), 42-53. https://doi.org/10.1016/j.livres.2017.05.005

Wang, H. H., Portincasa, P., & Wang, D. Q. (2008). Molecular pathophysiology and physical chemistry of cholesterol gallstones. Front Biosci, 13(4), 401-423.

Wang, L. J., Wang, J., Li, N., Ge, L., Li, B. L., & Song, B. L. (2011). Molecular characterization of the NPC1L1 variants identified from cholesterol low absorbers. Journal of Biological Chemistry, 286(9), 7397-7408. https://doi.org/10.1074/jbc.M110.178368

Wang, R., Hong, J., Cao, Y., Shi, J., Gu, W., Ning, G., & Wang, W. (2015). Elevated circulating microRNA-122 is associated with obesity and insulin resistance in young adults. Eur J Endocrinol, 172(3), 291-300. https://doi.org/10.1530/eje-14-0867