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Obesity and Gallstones

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Abstract
Background: The prevalence of obesity has been increasing globally and represents the main risk factor for the development of gallstone disease (GD). ***Summary:*** Excess body weight represents the main cause for the development of GD; nevertheless, there have been described multiple risk factors for its development, among them modifiable risk factors as diet, lifestyle, physical inactivity, and non-modifiable risk factors as ethnicity, female sex, advanced age, parity, and genetic mutations. Body mass index, abdominal perimeter, and waist-hip index have been used to determine the degree of adiposity of a person. Hence, central abdominal fat has been mostly associated with insulin resistance with the consequent increase in the hepatic cholesterol secretion; contributing as one of the multiple mechanisms associated with the development of gallstones. This disease has a low mortality; however, it has been associated with multiple diseases such as cardiovascular diseases, carotid atherosclerosis, metabolic associated fatty liver disease, and gallbladder cancer, probably because they share many of the risk factors. ***Key Messages:*** GD continues to be considered a disease with a high medical burden, in which it is sought to intervene in modifiable risk factors to reduce its development.

Introduction

Gallstone disease (GD) is a very common pathology with a high global prevalence of approximately 10–20%; it occurs mainly in patients with excess body weight [1]. The main risk factor associated with the development of this disease is the presence of central obesity [2–4] and with the rising prevalence of overweight and obesity around the world the prevalence of GD is expected to continue to increase. GD has been reported to carry a high medical burden due to its treatment, which is principally surgical, as well as its association with cardiovascular diseases, metabolic dysfunction, and bladder cancer [5]. Even though its mortality is low, it is important to seek methods for a better control of its associated risk factors such as obesity, diet, physical inactivity, and medications and thus reduce the costs of morbidity [6].

Obesity has been consistently established as the main risk factor for the development of gallstones, but this disease has also been described in non-obese patients [7]. Therefore, it should be considered that GD development is determined by the sum of the different modifiable risk factors such as physical inactivity, diet, medications, and body mass index (BMI), and non-modifiable risk factors such as age, ethnicity, genetics, sex, and parity [8]. The most common type of stones formed in obese and non-obese patients are from cholesterol (>90%), due to cholesterol metabolism products, as well as cholesterol bile supersaturation [9]. However, there are other processes involved in the pathophysiology of this disease [10, 11].

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The development of GD is caused by the imbalance between the liver-gallbladder-intestine system, in which cholesterol synthesis processes are carried out. The alterations in these processes are due to the disbalance in the bile lipids transport, in the cholesterol esterification enzymes, and in the regulatory signaling pathways as well as in the gallbladder motility [12]. This has led the scientific community to delve into the type of altered pathogenic pathway in the formation of lithiasis and the main risk factors involved in each one of them. In this review, we analyze the current knowledge of the association of excess body weight and the development of gallstones, along with the role of other associated molecules such as bile lipids and intestinal hormones, which share pathophysiology with other metabolic diseases of important clinical impact.

Epidemiology

The global prevalence of GD ranges between 10 and 20% [13]; however, this distribution varies between populations. The highest prevalence is present in America, affecting approximately 25% of the United States population [14, 15]. In Chile, the prevalence of GD has been described to be higher among Chilean Machupes with 35% compared to Hispanics with 27% or Maoris Chileans with 21% [16]. In Europe 20% of the adult population has the disease [17]. Asian countries have documented a moderate prevalence between 3 and 10%; specifically, China oscillates at 6.9% [18] and the lowest prevalence has been found in Africans [19]. This diversity in prevalence highlights ethnicity as an important risk factor. It has been reported that there is a higher prevalence in Mexicans and Mexican-Americans, even at younger age, compared to non-Hispanic whites [20, 21]. An increase in HLA-B alleles expression has also been documented, which proposes a genetic association that confers a higher risk of developing the disease in this population [22]. An increased hazard of gallstones has also been reported in the female gender [23].

In contrast with the possible genetic association and the development of GD, one meta- analysis of genetic predisposition in Chinese population calculates a risk ratio of 1.42 (95% CI 1.22–1.64) for gallbladder disease. Associations between BMI were also documented with liver enzymes, steatosis, and fibrosis scores, consistent with observational associations [24].

The presence of multiple risk factors in common with other diseases makes it possible to associate the GD with other cardiovascular diseases such as atherosclerosis carotid disease, and metabolic dysfunction. Although GD does not report a high mortality, it is a high medical burden disease [25, 26].

Risk Factors

Diet

In Europe, Asia, and the United States, diet consumption is hypercaloric and low in fiber. With this type of diet, the development of cholesterol stones is increased [10]. A study showed that overnutrition contributes to obesity and stone formation due to an increased cholesterol secretion [27, 28]. In contrast, a high fiber diet accelerates intestinal transit and reduces the accumulation of bile acids (BA) and the saturation of bile with cholesterol [29].

Alcohol intake has been associated with the inhibition of cholesterol gallstone development, because it reduces the cholesterol supersaturation in the bile, with a protective association (OR 0.42, 95% CI 0.23–0.78, $p < 0.05$) when there is an intake of more than 60 g of alcohol per day [30]. However, the risk of pigmentary stone formation is increased, due to chronic liver damage and to BA system dysfunction [31].

It has been proposed that coffee might exert a beneficial effect on the circulation of BA, which may probably reduce the risk of gallstone formation, but the evidence is not conclusive [32].

Medications

Total parenteral nutrition, which weakens gastrointestinal stimulation and predisposes to biliary sludge by a range from 20 to 75%, induces the development of gallstones, although this might be reduced with a concomitant oral intake [33]. Some drugs have also been associated with biliary stasis, by decreasing intestinal transit, among them octreotide and somatostatin analogues [34]. In contrast, ezetimibe exerts a beneficial effect because it prevents the formation of stones by reducing the absorption of cholesterol from the intestine [35]. Statins also decrease liver cholesterol biosynthesis, which appear to have a protective effect on the risk of gallstones [36].

Metabolic Disease

Hyperinsulinemia is associated with increased hepatic cholesterol uptake, biliary secretion, and hyposecretion of biliary BA. In addition, insulin resistance and type 2 diabetes mellitus act as independent factors that are associated with cholesterol gallstones and GD [37]. Among the excess of body weight, abdominal adiposity, abdominal circumference, and waist-hip index predict the probability to develop gallstones, more than BMI itself [38]. A study carried out by Kim et al. [39] showed the correlation of GD with obesity-related factors as waist and thigh circumference, cholesterol levels, and BMI. Obesity has broadly been described as the main risk factor of GD; mainly women with a BMI higher than 30 have twice the risk of developing gallstones. Plasmatic insulin levels are higher in patients with GD, showing that insulin resis-

tance is a risk factor for GD development. A study performed by Méndez-Sánchez et al. [27] revealed that patients with GD had 26.2% higher insulin levels compared to controls (OR 2.3; 95% CI 1.14–4.66, $p = 0.03$), regardless of the plasmatic triglyceride concentration. They also highlighted that the high levels of plasmatic insulin provoke an increased bile cholesterol saturation index (CSI), promoting GD; this could be explained by the rise of the hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and by increasing the bile leakage. This group also showed the potential "lithogenic effect" of leptin reduction in overweight patients, provoking gallbladder hypomotility contributing to cholesterol gallstones.

Physical Inactivity

Physical activity improves intestinal motility and increases BA excretion. Some studies have reported a protective factor to physical activity with RR 0.72 (95% CI 0.58–0.89, $p < 0.001$) [40]. In a study performed by Hou et al. [3], they showed that physical inactivity represents an important risk factor for GD. Physical inactivity was determined by the cumulative occupational sitting time, which has a strong positive association with GD increasing by 30% the risk of suffering from GD; the energy expenditure reduces in 20% the risk of developing GD.

Rapid Weight Loss

Rapid weight loss, defined as reduction of ≥1.5 kg of weight per week, by a very low-calorie diet or after bariatric surgery causes the formation of gallstones due to an accelerated metabolism for the elimination of cholesterol, which supersaturates the bile and increases the CSI [8].

Pregnancy

Importantly, pregnancy is a well-recognized risk factor for gallstone formation. Interestingly, gallstones can disappear postpartum, indicating that pregnancy can be a transient lithogenic state [22, 41].

Genetics

Genetic variants have been identified in the cholesterol transporter (ABCG5\8 p.D19H) located in the canalicular cell, which generate increased secretion of cholesterol esters. This mutation is present in 20–25% of the population with gallstones [10, 42].

Many other genes have been identified to have a relationship in gallstone formation, among them cholecystokinin (CCK) A or cholecystokinin 1 receptor (CCK-1R) gene or *Lith 13* has been described to be related to the expression of CCK-1R, which is directly responsible of cholesterol absorption and gallbladder motility. Variants of this gene are associated with gallstone formation. Knockout mice have a reduced gallbladder contraction and emptying, along with an augmentation of cholesterol absorption in the small intestine, causing cholesterol stone formation [43].

Another study, by Méndez-Sánchez et al. [23] demonstrated gene frequencies of HLA-B in patients with GD, predominantly HLAB39. It has also been described in mice that there is a reduction in genes involved in cholesterol metabolism as HMG-CoA reductase, cholesterol 7-a-hydroxilase (CYP7a1), sterol 27-hydroxylase (CYP27), oxysterol 7 a hydroxylase (CYP7b1), and a probable dysfunction in ABCB4 [44].

Gut Microbiota

It has been reported that there is an association between certain bacteria of the microbiome and gallstone formation. One of the mechanisms involved in GD related to microbiota is the expression of mucin genes (MUC1, MUC3, and MUC4); another mechanism is the participation of the microbiome in oxidation of BA promoting gallstone formation. Among the bacteria that have been related to GD are Clostridium, Bifidobacterium, Peptostreptococcus, Bacteroides, Eubacteria, Salmonella, and *E. coli*. Another bacteria that has been involved is *H. pylori*, but the mechanism by which this infection promotes GD is not completely clear [45, 46]. An additional mechanism of bacterial role in the development of gallstones is that some bacteria provoke the formation of betaglucuronidase, phospholipase, and slime, promoting pigment and mixed stone formation [47].

Central Role of Obesity in Gallstone Formation

The BMI is an estimate of the general obesity of each individual [7]. In multiple studies, the association between elevated BMI figures as an independent risk factor for the development of gallstones has been consistent [4, 48]. For example, it has been estimated that an increase of more than 5 points in the BMI value increases the risk of gallstone formation by 1.63 times [49]. However, this association has been positive for females, while for males it has been so to a lesser degree [50]. Attempts have been made to justify this variability due to the greater composition of lean mass in males [50]. But it must be taken into account that there are other predominant factors in the female sex such as estrogen levels, which increase the secretion and synthesis of hepatic cholesterol, with greater CSI and formation of crystals, which make it a more prevalent disease in this group of patients [10].

It has been established that one of the pathophysiological mechanisms by which obesity increases the risk of developing GD is due to the increase in plasma insulin levels [52], because higher levels of plasma insulin stimulate activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase causing a cholesterol hypersecretion [53].

Table 1. Comparison of impact variables in multivariate analysis and results of analytical studies with anthropometric measurements for estimating the risk of developing gallstones [4, 35, 39]

Author/year	Study design	Population/origin	Statistical variables, adjusted for cofounding factors	Association measure OR or RR or HR or PR (95% confidence interval)	Outcome
Tsai et al. [38], 2004	Cohort	29,847 American male	AP (M) >102.6 cm	RR 2.29 (1.69–3.11)	AP + WHI increased indices of central adiposity; increases the risk of developing gallstones with statistical significance
			WHI >0.99	RR 1.78 (1.38–2.28)	
Liu et al. [4], 2018	Cohort	88,947 Male and female Chinese	BMI (M) AP (M) WHI (M)	HR 1.63 (1.47–1.79) HR 1.53 (1.40–1.68) HR 1.44 (1.31–1.58)	BMI + AP indices that together increase the predictive value to determine the development of lithiasis in M with statistical significance
			BMI (F) AP (F) WHI (F)	HR 2.11 (1.79–2.49) HR 1.84 (1.55–2.19) HR 1.84 (1.55–2.19)	BMI + WHI indices that together increase the predictive value to determine the development of lithiasis in F with statistical significance
Kim et al. [39], 2019	Cross-sectional	724,114 Subgroup analysis 20–39 years *n* = 154,463 young adults Male and female Korean	HDL (M)	OR 0.858 (0.741–0.994)	Low HDL in M, independent risk factor for the development of lithiasis with statistical significance
			BMI (F) HDL (F)	OR 1.512 (1.17–1.955) OR 0.747 (0.573–0.972)	High BMI and low HDL in F, independent risk factors for the development of stones with statistical significance

M, male; F, female; OR, odds ratio; RR, relative risk; HR, hazard ratio; PR, prevalence risk; BMI, body mass index; AP, abdominal perimeter; WHI, waist-hip index.

Several analytical studies have directed their research to define which anthropometric measurements may most accurately estimate the risk of developing gallstones (Table 1) [4, 35, 39].

Liu et al. [4] in a prospective cohort study, carried out in a Chinese population, compared different ways of measuring the degree of obesity and analyzed which one of these measurements was associated with an increased risk of developing GD. They evaluated 88,947 patients with no history of gallstones; measurements of BMI, waist circumference, and abdominal perimeter were made. Different combinations were established between the anthropometric measurements taken and it was evaluated which of the different models best predicts the development of the disease. At the end of the adjustment for possible confounding variables, they found that the increase in BMI, waist circumference, and abdominal perimeter was associated with a greater risk of developing gallstones in both sexes, but with different predictive models for each group.

Although obesity and overweight have been established as an independent risk factor for the development of GD [54], other authors have sought to establish whether this association is present or not in patients with normal weight. This could be explained by genetic mutations that increase the risk of developing stones in patients with normal BMI [7].

Another factor involved in the pathogenesis of gallstones is leptin, a hormone released by the adipocytes. The leptin receptor gene influences the type of fat distribution. Some studies in murine models have observed a decrease in cholesterol crystals when there is resistance to leptin action [55]. In the Mexican population, elevated levels of leptin have been associated with a higher diagnosis of GD, contrasted with the effects of leptin injection in murine models, where they observed that leptin stimulates cholesterol elimination [56].

Biliary Lipids and Gut Hormones in Gallstone Formation

Biliary Lipids

Biliary lipids (BL) are secreted into the canalicular lumen through the ATP-dependent membrane transporter ABC. BL are made up of a relatively higher proportion of BA, then from lecithin phospholipids, cholesterol, and in a lesser quantity by conjugated bilirubin. They can be in conjugated or unconjugated forms and are divided in 2 groups: primary BA, cholic and chenodeoxycholic acids that are synthesized from cholesterol in the hepatocyte and secreted into the lumen by the ABCB11 transporter; and secondary BA, deoxycholic and lithocholic acids that result from the action of gut microbiota in primary BA. BL proceed to an enterohepatic circuit, and after their reabsorption in the distal ileum, they regulate their own synthesis and play a role in energetic homeostasis and glucose and lipid metabolism [57, 58].

Cholesterol and phospholipids are not hydrophilic; they must form micelles and/or vesicles to travel intraluminally. These micelles are thermostable and soluble when the proportion of their composition does not present a supersaturated bile. The lower the proportion of biliary acids, the higher the saturation of the bile by cholesterol; therefore, an alteration in the secretion of bile salts

Table 2. Influence of nuclear receptors on bile acid metabolism, lipogenesis, insulin sensitivity, and gallstone formation [57, 64, 71–81]

Characteristic	TGR5	FXR	PPARs	LXR	HNF
Location	• Liver cells (Kupffer, endothelial) • Gallbladder • Bile ducts • Adipose tissue • Other organ cells	• Liver cells (Kupffer, stellate, and endothelial cells) • Ileal cells	• PPARs liver, heart, kidney, intestine, and adipose tissue • PPARγ adipocytes (brown and white)	• LXRa: liver, intestine, adipose tissue, macrophages • LXRb: ubiquitous	Liver, intestine, pancreas, others
Subtypes	None	None	PPARα, γ, β/δ, α/δ	LXRa (encoded by Nrlh3) and LXRb (encoded by Nrlh2)	Hepatocyte nuclear factor-1 alpha (HNF1A), Hepatocyte nuclear factor-4 alpha (HNF4A), Hepatocyte nuclear factor-1 beta (HNF1B)
Bile acids	• Reduce PBA synthesis • Increase BA circulation and export	Increase bile acid pool	Control BA synthesis and transport by transcriptional regulation and by crosstalk with FXR signaling	• Conversion of cholesterol to bile acids in the liver • Activates bile acid excretion	• Controls bile acid uptake • Bile acids regulate the expression of HNF1α • HNF4α central role in regulation of bile acid metabolism
Lipid metabolism and lipogenesis	• Reduce VLDL clearance • Increase free fatty acids beta oxidation • Reduce lipogenesis through inhibition of Cyp7a1 and Cyp8b1 expression	• Mechanism TGR5/GLP1 signaling improves lipid metabolism • Promotes adipose tissue browning	• PPARα: fatty acid catabolism, regulate B-oxidative enzymes, raise plasma HDL-c by induction of ApoA, ketogenesis • PPARβ/δ: increase free fatty acid oxidation, increase FFAs uptake • PPARγ: reduction of triglycerides, induction of expression of lipoprotein lipase, adipogenesis	• Maintain cholesterol homeostasis • Regulates lipogenic transcription factor sterol regulatory element-binding protein 1c • Incorporation of polyunsaturated fatty acids into phospholipids by lysophosphatidylcholine acyltransferase 3 (LCAT3) • Induce lipogenesis • Activate de novo fatty acid synthesis by SREBP-1c • Elevation of plasmatic triglycerides	• Protects against hepatic steatosis and dyslipidemia • Its ablation causes alterations in HDL structure causing dyslipidemia
Glucose and insulin sensitivity	Increase insulin sensitivity	• Improves hepatic glucose sensitivity • Increase insulin sensitivity and secretion through GLP1 stimulation • Increase energy expenditure through thermogenesis	• PPARa: control glucose metabolism, induce pyruvate dehydrogenase kinase 4 (PDK4) expression • PPARg: hypoglycemic, improve insulin activity, facilitates energy storage by suppressing leptin expression	• Downregulate FGF21 expression • Upregulate the expression of glycolytic enzymes (GK) • Activated upon insulin and glucose signaling	Mutation of HNF1a and 4a causes diabetes in young
Effect on gallstone formation	Prevents gallstone formation	Stimulates gallbladder refilling	PPARg prevents gallstone formation	LXRα agonist aggravates lithogenic diet-induced gallstone formation (in mice)	Its suppression induces formation of cholesterol gallstones in mice

has been established as one of the mechanisms of stone formation [2].

The expression of ABCG5/ABCG8 transporters in murine models has been associated with higher cholesterol secretion. Finally, presenting a cholesterol-supersaturated bile provokes its crystallization [59].

BA can cause inflammation, apoptosis, and necrosis of liver cells; for this reason, the body has protective mechanisms that are responsible for keeping the concentrations and production of BA under control [11]. Initially, the accumulation of the BA pool derived from the enterohepatic circulation stimulates the bile canaliculi to continue the formation of bile, prevents cholesterol from crystallizing in the gallbladder and in the intestinal lumen, and facilitates the absorption of fat and fat-soluble vitamins [60]. It is currently known that BA act as ligands for the Farnesoid X receptor (FXR), a member of the superfamily of nuclear receptor transcription factors [61]. The stimulated receptor modulates the expression of metabolic genes that regulate the release of BA. Activated FXR in hepatocytes decreases CYP7A1 levels, with a consequent decrease in synthesis of primary BA [62]. It also promotes the release of circulating fibroblast growth factor (FGF119) in the ileum and contributes to the regulation of hepatic BA synthesis [63]. Nuclear receptors, related to BA metabolism that might have a role on gallstone formation are FXR, peroxisome proliferator activated receptors (PPARs), liver X receptors (LXR), Takeda G protein-coupled receptor 5 (TGR5), and hepatocyte nuclear factor 4a (HNF4a) [64] (Table 2).

Gut Hormones

CCK is the main gut hormone involved in gallbladder emptying; it is secreted by the stimulus of fat and protein

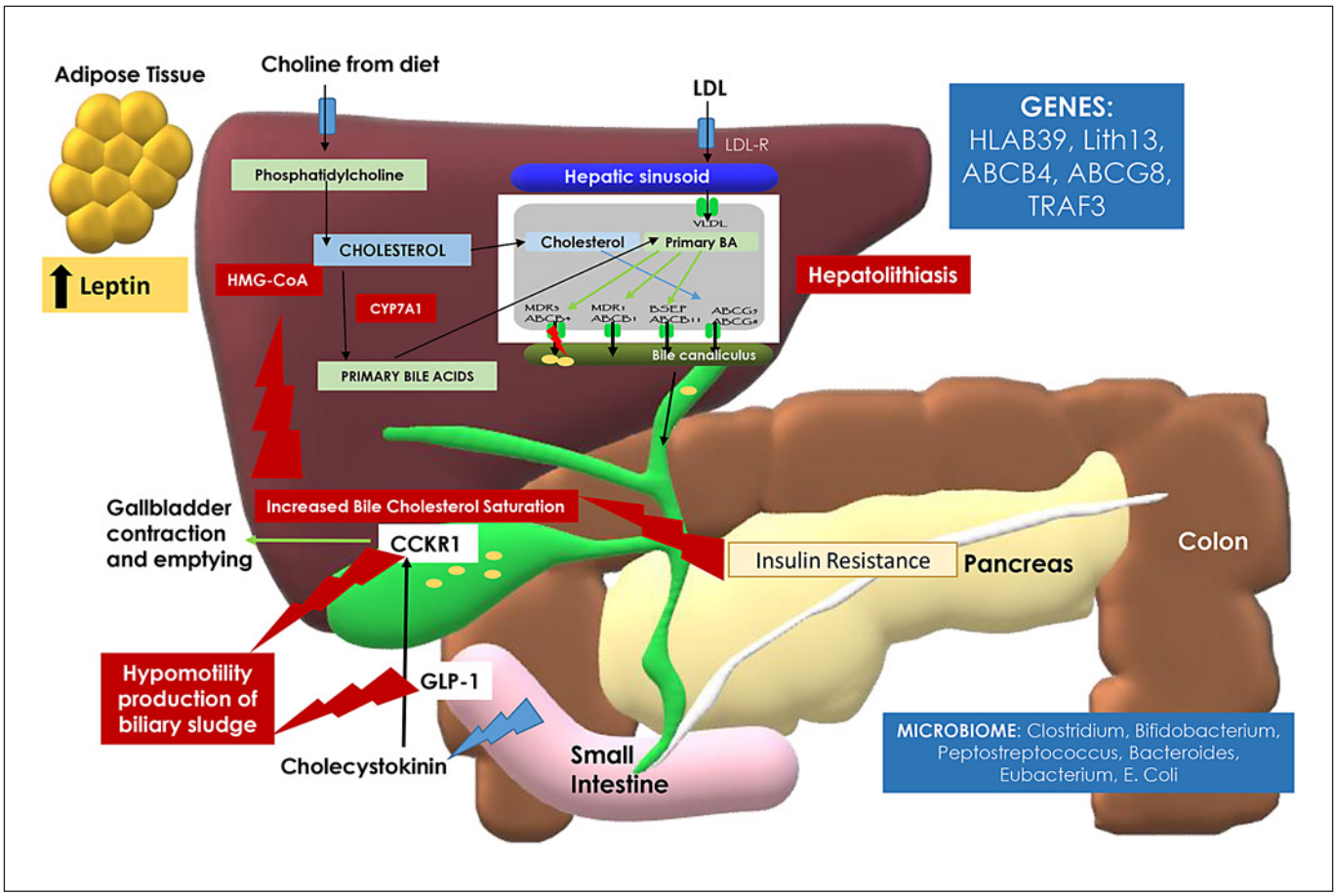

Fig. 1. Pathophysiology of gallstone disease. (1) Gut hormones. Cholecystokinin is secreted in the small intestine and through its receptor CCKR1 causes gallbladder contraction and emptying; the dysfunction of this receptor causes hypomotility of the gallbladder and the formation of biliary sludge. (2) Genetics. Genes involved in HLAB39, ABCB4, and Lith13. Microbiota has also shown a role in gallstone formation. (3) Microbiome. Several bacteria have been associated with GD; colon microbiota: Clostridium, Bifidobacterium, Peptostreptococcus, Bacteroides, Eubacteria, *E. coli*, and gastric bacteria: *H. pylori*. (4) Metabolic syndrome. Insulin resistance increases the bile cholesterol saturation index (CSI) by increasing the activity of HMG-CoA. Leptin has also been described as "lithogenic" stimulating an abnormal gallbladder emptying.

food ingestion mainly, and is produced by the initial part of the small intestine. CCK triggers gallbladder contraction and small intestine motility through CCK-1R regulating cholesterol metabolism along with its absorption [65]. CCK-1R is mainly expressed in gallbladder, pancreas, and small intestine, and is responsible of cholesterol absorption. The dysfunction of this receptor causes gallbladder hypomotility with the consequent production of biliary sludge as wells as small intestine delayed transit generating an increase in cholesterol absorption and its accumulation in the gallbladder [43, 66]. Hence, an interesting study in mice made by Shahid et al. [67] showed that the stimulation of CCK secretion by exogenous pancreatic secretory trypsin inhibitor-I increases the endogenous production of CCK, but this does not protect the animal from gallstone formation if they are fed with a lithogenic diet. These findings suggest that lithogenic diet alters bile salt composition and demonstrate that high level of CCK causes a desensitization of this hormone to its receptor, causing decrease in gallbladder contraction with a consequent cholesterol accumulation and crystallization. This discovery showed the importance of the lithogenic diet in gallstone formation (Fig. 1).

Gallstones and Metabolic Associated Fatty Liver Disease

Metabolic associated fatty liver disease (MAFLD) is defined for accumulation of more than 5% of fat in the hepatocytes, without another associated cause such as alcohol, medications, hepatitis, or deposit diseases [68]. The behavior of this disease varies from simple steatosis to metabolic steatohepatitis and can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma [69]. The coexistence of MAFLD and GD has been observed, main-

ly because it shares several risk factors such as obesity, age, ethnicity, insulin resistance, and metabolic syndrome [6]. A study demonstrated an increased prevalence of GD in patients with MAFLD of 47% versus patients without MAFLD of 26% ($p < 0.0001$) [70].

The molecular association between insulin resistance, hepatic steatosis, and GD remains largely unclear. The observation that high plasma leptin is associated with MAFLD subjects and GD is not completely clear. Adiponectin levels that have a protective effect on MAFLD are reduced in obese subjects compared to lean ones but no data have revealed its effect on GD [12].

Regarding the main worry in patients with overweight in the presence of fatty liver disease, a Turkish study by Yilmaz et al. [71] found that patients with gallstones and MAFLD were older, had higher BMI, had metabolic syndrome, and were mostly females, but they did not find an association between the presence of gallstones and the severity of MAFLD fibrosis or inflammation.

Conclusion

GD continues to be worrisome all around the world; its prevalence will continue to increase due to the augmentation of obesity rates. Although obesity has been established as the main risk factor for the development of the disease, several metabolic pathways are linked to stone formation. The principal mechanism involved is an increased cholesterol metabolism with its consequent hypersecretion, which is intimately linked to excess of body weight. Other processes involved in GD are gallbladder hypomotility and the disturbance in the signaling pathways that modulate the gene's expression for the synthesis of BA. It is crucial to clarify several pathophysiological mechanisms that are still unknown to better understand and control the development of this disease that represents a high medical burden all over the world.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.M.P.-L., J.C.-G., and N.M.-S. contributed to the conceptualization and the writing of the manuscript.

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