REVIEW ARTICLE

Cholecystectomy as a risk factor for non-alcoholic fatty liver disease development

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Abstract

Background: Hepatic steatosis and gallstone disease are highly prevalent in the general population; the shared risk factors are age, ethnicity, obesity, insulin resistance, metabolic syndrome, atherosclerosis, risk of cardiovascular disease, and mortality. The presence of insulin resistance is the critical element in this association because it represents a crucial link between metabolic syndrome and non-alcoholic fatty liver disease, as well as a higher susceptibility to gallstone formation.

Methods: An exhaustive search engine investigation of gallstone disease, cholecystectomy, and liver steatosis latest literature was made.

Results: Clinical studies and systematic reviews suggest an association between gallstone disease, cholecystectomy, and hepatic steatosis.

Conclusion: The bidirectional relationship between liver steatosis and gallstone disease and cholecystectomy is summarized in the role of insulin resistance, lipid metabolism, bile acids signaling pathways regulated by transcription factors expression, and to the gallbladder physiological role; however, more epidemiological and experimental studies should be complemented.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to liver fat accumulation, which exceeds 5–10% of the organ total weight, without the cause being chronic alcohol consumption. The disease includes a broad spectrum of liver conditions ranging from pure fatty liver (simple steatosis), usually a benign and non-progressive condition, to non-alcoholic steatohepatitis, which may eventually progress to cirrhosis and hepatocellular carcinoma.[1]

The pathophysiology and natural evolution are still under study and are inconclusive; however, approximately 10% of NAFLD carriers will evolve to steatohepatitis, and 20–25% of these patients will develop fibrosis that will evolve to cirrhosis and 5% to hepatocarcinoma.[2] NAFLD is observed worldwide and is the most common hepatic disorder in western industrialized countries, with one or more risk factors: central obesity, systemic hypertension, dyslipidemia, insulin resistance (IR), metabolic syndrome and type 2 diabetes mellitus (T2D). The number of patients with NAFLD is increasing globally, with a prevalence in the adult population of approximately 30%.[3,4]

NAFLD definition is about the infiltration of fat in the liver on radiological examination or biopsy, without significant alcohol intake ($\leq$210 g/week for males and $\leq$140 g/week for females), medication intake causing fatty liver, or other causes (eg, autoimmune hepatitis, or hepatitis B antigen or hepatitis C virus antibody positivity).[5]

The paper is not based on a previous communication to a society or meeting.

In the USA, NAFLD prevalence has increased over time, as evidenced by the National Survey of Health and Nutrition Examination three-cycle comparison, which shows that in 1988 and 1994, NAFLD prevalence was 5.5%, between 1999 and 2004 it was 9.8% and between 2005 and 2008 it was 11%, representing an increment of 47, 63 and 75% respectively. Also, in these same three periods, obesity, T2D and high blood pressure increased.[6] Another study estimated that the prevalence of NAFLD between 2011 and 2012 was 30% with ultrasound, taking into account fasting insulin and triglyceride concentrations, body mass index, sex and gamma-glutamyl transferase activity.[7] Patients diagnosed with NAFLD have a higher risk of death compared to the general population, and increasing rates of obesity and T2D will be directly associated with NAFLD mortality escalation in the next years.[8]

IR produces relevant changes in lipid metabolism, including increased peripheral lipolysis, hepatic fatty acid uptake, and triglyceride synthesis, which contributes to fatty acid β oxidation, the accumulation of lipids in the liver and therefore oxidative stress.[9] On the other hand, liver iron, leptin, antioxidant deficiency, and intestinal bacteria have been proposed as possible oxidative stressors, improving insulin sensitivity and reducing iron-mediated oxidative stress, which decreases hepatocyte substrate burden, lipid peroxidation, hepatocellular injury and serum ALT activity. Although it is speculative, some studies support that diminished iron chelation and increased iron load decrease oxidative stress and lipid peroxidation, improving NAFLD.[10] As well, increased bacteria growth in the small intestine and hence intestinal permeability markers are closely related to NAFLD.[11]

Adiponectin is a hormone secreted exclusively by adipose tissue that produces beneficial effects on lipid metabolism, but also has direct anti-inflammatory effects that suppress tumor necrosis alpha factor production in the liver. Therefore, low serum adiponectin levels are associated with metabolic syndrome, which correlate with NAFLD presence and liver fibrosis.[12]

Besides, NAFLD is a complex disorder that involves environmental and genetic factors. Studies in twins have shown an active hereditary component (approximately 50 percent) in both liver fat content and liver fibrosis. Different PNPLA3 genetic variants, studied in homozygous twins are responsible for coding the proteins that regulate lipid metabolism in the liver, which are associated with NAFLD development and progression.[11]

On the other hand, in Western societies, cholesterol gallstones account for 80–90% of the gallstones found at cholecystectomy. Excess cholesterol precipitation in bile as solid crystals is a prerequisite for cholesterol gallstone formation; these gallstones are composed mainly of cholesterol crystals (70%) held together in a glycoproteins organic matrix, calcium salts, and bile pigments. Several risk factors are involved in gallstone formation,[13] such as having given birth, estrogen replacement therapy, oral contraceptive use, and rapid weight loss. Similar to atherosclerosis, the risk of gallstone disease (GSD) increases with age, obesity, T2D, dyslipidemia, hypertriglyceridemia, poor high-density lipoprotein (HDL), elevated serum cholesterol, hyperinsulinemia, and sedentary lifestyle. All these conditions are risk factors for metabolic syndrome, with cholesterol gallstones being another complication.[13]

If biliary cholesterol concentration increases or bile salt and phosphatidylcholine concentrations drop, cholesterol supersaturation occurs, and cholesterol crystals and stones precipitate. The most common severe mutation p.E342K ('PiZ') might interfere with hepatic lipid metabolism and contribute to fatty liver disease, and promote cholesterol crystallization in bile. GSD is a complex trait resulting from an interaction between genetic predisposition and environmental risk factors. In recent years, large cohorts of patient's analyses, using different approaches, have helped to detect the predisposing variants that might increase or decrease gallstones development risk. The first genome-wide association study for a hepatobiliary disease, identified the hepatic cholesterol transporter ABCG8 as a susceptibility gene for human GSD.[14]

NAFLD and cholelithiasis are chronic diseases with a multifactorial evolution that involve alterations in genetic and epigenetic regulation. During the last decade, the role of epigenetic mechanisms in NAFLD pathogenesis has become relevant, although they have not yet been fully described; several studies suggest that epigenetic regulation, mainly by microRNAs is mediated by post-transcriptional modifications that can alter cell signaling pathways by modifying physiological functions without changes in the DNA sequence.[15]

As well, some data suggest that NAFLD is associated with cholecystectomy, using a group of 12,232 participants in a United States population survey; controlling factors such as age, sex, body mass index, T2D and cholesterol levels. Patients who underwent a cholecystectomy were more than twice as likely to suffer from NAFLD than those who did not have the surgery (OR 2.4, 95% CI: 1.8–3.3). NAFLD prevalence in patients with gallstones who did not undergo cholecystectomy did not increase.[7]

Although NAFLD treatment is mainly based on promoting lifestyle changes with relatively poor results due to the patient's low adherence, the best and most effective approach for GSD is cholecystectomy, which is the most frequent surgical procedure worldwide.[16]

Gallstones as a risk factor for NAFLD

GSD currently represents a significant public health problem that affects approximately 20% of the general population in Europe; Hispanics have the highest prevalence rates with more than 50%, mainly in Central and South America.[17]

Cholesterol gallstone formation involves an abnormal bile composition, with supersaturated cholesterol high concentrations, coupled with proteins that promote cholesterol crystals nucleation, as well as gallbladder malfunction due to decreased contractility and impaired epithelial secretion.[18]

From 5 to 30% of the laparoscopic cholecystectomies performed annually are for acalculous vesicular disease diagnosis; however, this surgical procedure is recommended for gallbladder diseases, such as vesicular polyps, tumors, GSD, cholecystitis, and biliary dyskinesia.[19,20] This technique is currently one of the most frequently performed surgical procedures worldwide.[21]

NAFLD as a risk factor for gallstones

NAFLD and GSD are diseases derived from cholesterol deposition, which are associated with increased mortality from chronic liver disease, cardiovascular disease, and cancer, representing a significant impact on public health.[22,23] Both diseases have very high prevalence rates; similar in North and South America, as well as in Europe, which represent between 10 and 50% of the adult population.[24,25] GSD and NAFLD often coexist, and their association is determined by the presence of shared risk factors such as age, ethnicity, obesity, IR, metabolic syndrome, atherosclerosis and cardiovascular disease risk.[23,26–28] (Fig. 1).

There is convincing evidence based on retrospective epidemiological studies showing that cholecystectomy can be an independent risk factor in the progression of NAFLD[29,30] and metabolic syndrome.[31] This association is explained by metabolic alterations related to the gallbladder baseline physiological function, the recognition of bile acids (BAs) as key signaling molecules and endocrine imbalance, which support reciprocal influences between the trinomial disease gallstones-cholecystectomy-NAFLD. A recent study showed a significant relationship between NAFLD and GSD grade. Participants with GSD are more likely to have dyslipidemia, hyperglycemia, obesity, and metabolic syndrome that are also associated with NAFLD.[5,32]

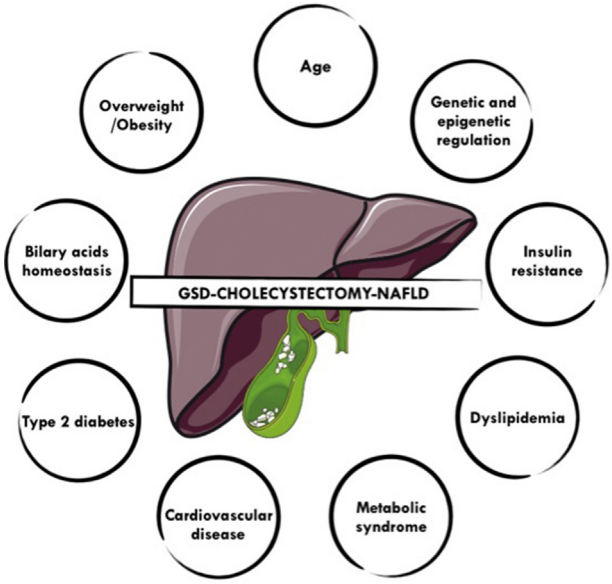

Figure 1 Associated risk factors in GSD-Cholecystectomy-NAFLD

Clinical studies and systematic reviews have supported the link between NAFLD and GSD, highlighting that NAFLD is an independent risk factor for developing GSD. Besides, cholecystectomy itself can be a metabolic risk factor for NAFLD progression, which forces us to analyze gallbladder ablation consequences. Koller *et al.* have evaluated the existing evidence between the GSD-cholecystectomy-NAFLD trinomial, founding a higher prevalence of GSD among patients with NAFLD versus those without NAFLD (47 vs. 26%, respectively; $P < 0.0001$) where NAFLD is an independent risk factor for developing cholelithiasis.[33]

The finding was also reported by Loria *et al.*[34] in a cohort of 161 patients with NAFLD, defined by ultrasound, where GSD prevalence was higher than the reported in the general population. On the other hand, an Asian study with large-scale longitudinal cohort found NAFLD as an independent risk factor for GSD development, especially in women.[35]

In contrast to these results, another study by Yilmaz *et al.* did not demonstrate this association; a population of 441 turkish patients with a confirmatory biopsy for NAFLD and an adjustment for metabolic variables, did not show an association between GSD and hepatic fibrosis [OR = 1.06; 95% confidence interval (95% CI) 0.5–2.1] or a definitive non-alcoholic steatohepatitis diagnosis (OR = 1.03; 95% CI 0.5–2.1).[36]

Therefore, it is relevant to analyze GSD and its possible association with cholecystectomy history; Ruhl and Everhart demonstrated that NAFLD prevalence is different among individuals with gallstones compared to previously cholecystectomized subjects.[29] The collection of the National Survey of Health and Nutrition Examination III data prevents bias that occurs in studies with selected patients and allows a better understanding between the trinomial GSD, cholecystectomy, and NAFLD.[36]

The results of an adjusted multivariate analysis showed that NAFLD is associated with cholecystectomy (OR = 2.4; 95% CI 1.8–3.3), but not with gallstones (OR = 1.1; 95% CI 0.84–1.4). This study grouped subjects with cholecystectomy separated from patients with gallstones, showing a stronger association between NAFLD and cholecystectomized subjects compared to patients with gallstones; being stronger in men than in women, approximately two-thirds of cholecystectomized men had NAFLD.[29] Therefore, cholecystectomy itself increases NAFLD risk, in addition to increasing other diseases associated with metabolic syndrome.[16]

The data available so far, only show association, not causality between NAFLD and GSD, which corresponds to a bidirectional association where NAFLD appears to be an independent risk factor for GSD and the latter represents an independent risk factor for NAFLD, the metabolic disorder commonly present in these two entities can be considered as the liver risk factor.[37]

Cholecystectomy as a risk factor for NAFLD

Most of the studies include patients with cholecystectomy and cholelithiasis within the same group, a relationship that seems logical because the vast majority of cholecystectomized patients have a GSD history. However, recent studies analyze groups with prior cholecystectomy, finding an independent association with NAFLD, which is even stronger than reported for the association with GSD.[37]

In the National Survey of Health and Nutrition Examination database analysis, the cholecystectomy presented an increased risk for NAFLD (OR 2.4; 95% CI, 1.8–3.3). The independent association between NAFLD and cholecystectomy was reported, but not between NAFLD and gallstones, indicating that cholecystectomy could be a risk factor for NAFLD in the United States.[29] Another study conducted at the Seoul University Hospital between January 2010 and December 2010 with a large Asian population (N = 17,612 subjects) confirms the independent association between cholecystectomy and NAFLD, but not with gallstones. This study supports the idea that cholecystectomy has some effect on NAFLD development.[30]

Two cross-sectional studies of different populations are the basis for establishing that NAFLD risk increases significantly with a cholecystectomy compared to patients with GSD who preserve the gallbladder and control patients, even after making adjustments in the shared metabolic risk factors.[30,38] Therefore, this association was mainly attributable to a previous cholecystectomy history, not to gallstones presence, establishing cholecystectomy as a risk factor for NAFLD development.[39] Recent information on the endocrine functions of the gallbladder makes it possible to assume that its ablation represents critical metabolic consequences in NAFLD.[40]

Consistent with the previous findings, a two-year follow-up pilot study evaluated liver fat content by MRI in patients who underwent a cholecystectomy, showing a significant increase in liver fat in non-obese patients undergoing the surgical procedure compared with patients without surgery.[41]

Potential consequences of cholecystectomy: physiopathological relationship

The pathophysiology between NAFLD and GSD has not been fully understood; however, IR provides a critical link, that increases GSD susceptibility; therefore, hepatic IR is a determinant for cholesterol gallstones formation[42] and a fundamental phenomenon in NAFLD development and progression.[43] As well, the association between NAFLD and cholecystectomy persisted with only a minimal change after an additional adjustment for IR.[30] The relationship between IR and the development of GSD is not unidirectional since some evidence suggests that gallbladder dysfunction may also initiate or aggravate IR in individuals with susceptibility.[40,41] It has been seen that after 24 months of a cholecystectomy, apoB levels can be raised, which suggests systemic and hepatic IR, since insulin increases apoB secretion and decreases its clearance.[44]

IR is a fundamental pathogenic factor that alters triglycerides regulation in the liver by increasing hepatic lipogenesis and adipocyte lipolysis, decreasing the activity of peripheral lipoprotein lipase, thus, producing an increase in chylomicrons and VLDL, which result in triglycerides accumulation in the organ.[45] The increase in de novo lipogenesis is an essential factor of hepatic steatosis in IR due to lipogenic branch excessive activation of the insulin-signaling pathway in the hepatocyte.[46–48]

The gallbladder participates in the regulation of lipid metabolism, glucose, and energy by controlling both BA enterohepatic cycle and FGF15/19 secretion. Possibly, decreased levels of circulating FGF19, either by cholecystectomy OR GSD, favor the alteration of glucose homeostasis, IR and liver lipid content, which promote complications such as diabetes and NAFLD.[49]

Cholecystectomy is associated with increased manifestations of IR, including NAFLD, which has led to the proposal that the gallbladder may have physiological functions that regulate the action of insulin. It should be noted that gallbladder ablation in mice causes an increase in bile cholesterol and energy expenditure, as well as an increase in BAs secretion.[50] A prospective pilot study showed that 24 months after cholecystectomy, fat levels, apoB, insulin, and HOMA-IR index increased significantly in a cohort of non-obese hispanic subjects. These findings support the claim that while cholecystectomy ameliorates GSD and eliminates the gallbladder cancer risk, it can have substantial negative metabolic consequences, which contributes to IR development or worsening.[41] This result is consistent with NAFLD higher prevalence in patients who have undergone cholecystectomy reported in two extensive population-based retrospective studies in North America[29] and Asian populations. The increase observed in the liver fat and HOMA-IR index 24 months after a cholecystectomy supports the hypothesis that NAFLD and IR could develop after surgery due to the recently discovered metabolic roles of the gallbladder.[30]

However, these studies do not explain the difference between patients with cholecystectomy and those with gallstones who have either mild symptoms or no symptoms at all. It is possible that cholecystectomy may simply be a surrogate marker for individuals with greater risk of NAFLD, dyslipidaemia and IR rather than a true causal risk factor.

Role of the gallbladder in the biliary acids homeostasis: FGF 15/19

The gallbladder function is integrated with the "liver-gallbladder-intestine" axis, responsible for maintaining the homeostasis of triglycerides, non-esterified fatty acids, BAs and cholesterol throughout the body.[51] Over the past decade, a series of studies have reported that BAs are signaling molecules that modulate complex enterohepatic and systemic metabolic functions, as well as the gallbladder motility.[52]

Changes in the gallbladder motor function can not only contribute to GSD but can also protect in multiple pathological situations through BA sequestration and changes in its composition. It is suggested that the gallbladder regulates IR sensitivity, as it regulates signaling factors secreted by its mucosa, which indirectly control enterohepatic BAs flow through systemic circulation during rapid feeding cycles. One of the factors derived from the gallbladder that plays a vital role in this configuration is the fibroblast growth factor (FGF) 15/19 (FGF15, mouse ortholog; FGF19, human ortholog).[51]

BAs induce the synthesis and release of FGF15/19 from enterocytes through the farnesoid X receptor (FXR) activation; this hormone reaches the portal circulation and reduces hepatic BA synthesis by decreasing CYP7A1 via transcriptional mechanisms.[41] Also, the gallbladder mucosa highly expresses FGF15/19, which regulates the filling and bile secretion.[40] This ileal hormone is a versatile regulator of several metabolic pathways; it is involved in homeostatic control of BAs, carbohydrates and lipid metabolism in multiple target organs, such as the liver, adipose tissue, and brain.[53] Consequently, the growing evidence suggests that FGF15/19 abnormalities related to a dysfunctional gallbladder or a cholecystectomy could contribute to a series of metabolic disorders such as fatty liver disease, the development of IR, T2D, as well as different gastrointestinal dysfunctions.[53,54] In fact, FGF15/19 regulates energy expenditure and insulin sensitivity in diabetic mice due to the activation of adipose tissue thermogenesis.[55,56] Another *in vitro* studies have demonstrated the inhibitory effect of FGF-19 on the synthesis of hepatic fatty acids, as well as the decrease in FGF19 serum levels after cholecystectomy can alter metabolic regulation, favoring the accumulation of triglycerides in the liver.[57] It was found that a lower serum level of FGF19 was associated with an increased risk of NAFLD.[58]

The altered circulation of BAs exerts effects on liver lipids and modulate glucose metabolism through BA receptors activity, such as FXR and the G5 protein-coupled BA receptor (TGR5), which generates changes in liver gene expression that can lead to the development of NAFLD.[59–61] On the other hand, cholecystectomy increases the rates of BAs enterohepatic recirculation, which produces metabolic effects and an increased NAFLD risk development, cirrhosis, and small bowel cancer, regardless of cholelithiasis.[62]

Biliary acids and nuclear receptors: liver receiver X, farnesoid receiver X, and TGR5

BAs, through the activation of liver X receptor (LXR), FXR, and TGR5, are involved in the regulation of lipid and glucose metabolism, being responsible for hepatic, intestinal, and adipose tissue homeostasis. On this basis, cholecystectomy determines a high exposure of BAs to nuclear and cell membrane receptors, which lead to pathological effects on triglycerides and glucose balance.[40,63]

Several transcription factors regulate hepatic lipogenesis, including LXR, a member of the heterodimeric nuclear receptor superfamily, which is activated with oxysterols. It is involved in biliary cholesterol secretion as it regulates the expression of ABCG5/ABCG8 transporters, is also responsible for de novo fatty acid synthesis, cholesterol esterification, and canalicular excretion and critically related to the formation of gallstones and NAFLD.[64,65] In mice, LXR has been shown to promote lithogenesis in an LDL receptor-dependent manner.[66] NAFLD severity correlates with hepatic LXR expression in humans.[65]

Another transcription factor in GSD and NAFLD association is FXR, a highly expressed nuclear BA receptor in the liver and the intestine that functions as a critical metabolic regulator of cholesterol and triglycerides synthesis pathways, but also in glucose homeostasis. FXR regulates the expression of ABCB11 and ABCB4 canalicular transporters, as well as is responsible for BAs and phosphatidylcholine transport; having a high impact on bile cholesterol solubilization. FXR-deficient mice are more likely to develop GSD after a high-fat diet, as well as rapid supersaturation of bile with cholesterol, precipitation of gallbladder crystals, increased hydrophobia and inflammation of the gallbladder; therefore, deregulation of FXR can promote both GSD and NAFLD.[67]

LXR act as cholesterol sensor, which activate genes involved in cholesterol metabolism and transport, while FXR is a key regulator of BA homeostasis. LXR and FXR work together to preserve an adequate metabolism of cholesterol and bile acids in the enterohepatic system. The limiting enzyme in the biosynthesis of BAs cholesterol 7α-hydroxylase transcription, is positively regulated by LXR, while FXR modulates it negatively. Thus, CYP7A1 activity increases the transformation of cholesterol into BAs and therefore increases the cholesterol gallstones.[67] Cholecystectomized patients are frequently readmitted for biliary pancreatomicrolithiasis. Nowadays, ursodeoxycholate therapy delays cholesterol crystallization with a reduced risk of biliary pain and acute cholecystitis; however, cholesterol GSD is not completely prevented, so FXR could be a new therapeutic objective for this disease.[68]

Although, more recent data suggests that long-term direct activation of FXR also reduces BA pool size, which consequently causes a decrease in energy expenditure and augments IR. Conversely, glucose and insulin are associated as major postprandial factors that increased BAs synthesis, but it has been determined that it is in an FXR independent manner.[69]

TGR5 mediates another relevant BA dependent signaling pathway; its activation is through BAs, which induce smooth muscle relaxation and stimulates the filling of the gallbladder with hepatic bile and FGF15/19.[70] Besides, TGR5 activation modulates glucose and lipid homeostasis through stimulation of the glucagon-1-like incretin peptide hormone.[71]

The effects of cholecystectomy on energy consumption were considered dependent on TGR5 because the decrease in the activation of TGR5 by BAs in adipose tissue and skeletal muscle

could diminish the oxidation of fatty acids and increase their availability for the accumulation of hepatic triglycerides that enhance NAFLD, as were demonstrated in mice deficient in TGR5.[50]

Together, the data mentioned above strongly support that the role of the gallbladder is critical to control BA homeostasis within the enterohepatic circulation and metabolic homeostasis of the entire body.

Conclusion

Clinical studies and systematic reviews have demonstrated the association between GSD, cholecystectomy, and NAFLD, underlining that NAFLD is an independent risk factor for GSD, and conversely, when performing separation of GSD in gallstones in situ and previous history of cholecystectomy, it is confirmed that cholecystectomy but not gallstones appear as a risk factor for complications associated with metabolic syndrome, particularly NAFLD. Also, elective cholecystectomy increases the liver fat content index, HOMA-IR, and serum apoB concentration. These results support the idea that cholecystectomy is a risk factor for NAFLD and other conditions associated with IR.

Cholecystectomy or gallbladder dysfunction increases the cycle of BAs through the liver and intestine, which has repercussions on metabolic regulation regarding the hepatic triglycerides accumulation, favoring the appearance of NAFLD. The bidirectional relationship between NAFLD and GSD is summarized in the role of central and peripheral IR, the importance of endocrine pathways regulated by BAs with change in the expression of transcription factors LXR, FXR and TGR5, in addition of the physiological role of the gallbladder in the signaling of insulin through the secretion of FGF19, however more epidemiological and experimental studies should be complemented (Fig. 2).

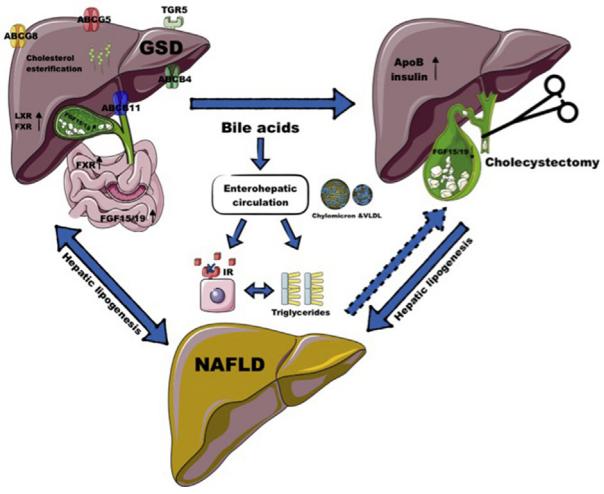

Figure 2 Relationship between GSD-Cholecystectomy-NAFLD. The relationship between NAFLD, GSD and cholecystectomy is summarized in the role of insulin resistance, the altered transport of bile acids in enterohepatic circulation, insulin resistance, increased triglycerides as well as chylomicrons and VLDL. In GSD, bile acids transport through ABCB11, ABCB4 ABCG5/8 is altered, with changes in the expression of transcription factors LXR, FXR and TGR5, in addition of insulin signaling through the secretion of FGF15/19. Cholecystectomy increases bile acids through the liver and intestine, which has repercussions on metabolic regulation regarding the hepatic triglycerides accumulation, favoring the appearance of NAFLD. Nonalcoholic fatty liver disease (NAFLD), gallstone disease (GSD), insulin resistance (IR), apolipoprotein B (ApoB), very low density lipoprotein (VLDL), farnesoid X receptor (FXR), protein-coupled bile acid receptor (TGR5), liver X receptor (LXR), Cassette type conveyors ATP binding (ABCG5/8, ABCB11, ABCB4)

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Conflict of interest statement

We confirm that this work is original and has not been published nor is it currently under consideration for publication elsewhere, in whole or in part, and we have not had any competing financial interests or commercial relationships that might pose a conflict of interest in connection with the submitted manuscript. In case of acceptance, the copyright is transferred to HPB.

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