World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i23.7277

World J Gastroenterol 2014 June 21; 20(23): 7277-7285
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (11): Cirrhosis

Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects

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Received: October 26, 2013 Revised: January 19, 2014
Accepted: April 1, 2014
Published online: June 21, 2014

Abstract

Gallstones occur in about one third of the patients having liver cirrhosis. Pigment gallstones are the most frequent type, while cholesterol stones represent about 15% of all stones in cirrhotics. Increased secretion of unconjugated bilirubin, increased hydrolysis of conjugated bilirubin in the bile, reduced secretion of bile acids and phospholipds in bile favor pigment lithogenesis in cirrhotics. Gallbladder hypomotility also contributes to lithogenesis. The most recent data regarding risk factors for gallstones are presented. Gallstone prevalence increases with age, with a ratio male/female higher than in the general population. Chronic alcoholism, viral C cirrhosis, and non-alcoholic fatty liver disease are the underlying liver diseases most often associated with gallstones. Gallstones are often asymptomatic, and discovered incidentally. If asymptomatic, expectant management is recommended, as for asymptomatic gallstones in the general population. However, a closer follow-up of these patients is necessary in order to earlier treat symptoms or complications. For symptomatic stones, laparoscopic cholecystectomy has become the therapy of choice. Child-Pugh class and MELD score are the best predictors of outcome after cholecystectomy. Patients with severe liver disease are at highest surgical risk, therefore gallstone complications should be treated using noninvasive or minimally invasive procedures, until stabilization of the patient condition.

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Key words: Liver cirrhosis; Pigment gallstones; Cholesterol gallstones; Lithogenesis; Risk factors; Asymptomatic gallstones; Laparoscopic cholecystectomy

Core tip: Gallstones often occur in patients with liver cirrhosis. Their prevalence increases with age and with disease severity. In most cases, stones are of pigment type; in about 15% of cases, they are cholesterol stones. This review presents new data on pathogenesis and risk factors for gallstones in patients with liver cirrhosis. An evidence-based approach to gallstones in these patients is described. Patients with liver cirrhosis and asymptomatic gallstones should be followed-up closely and offered laparoscopic cholecystectomy once symptoms develop. In patients with advanced liver disease, noninvasive or mini-invasive procedures should be used to treat the complications of gallstones.

Acalovschi M. Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects. *World J Gastroenterol* 2014; 20(23): 7277-7285 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i23/7277.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i23.7277

INTRODUCTION

Gallstone disease (GD) is a common disease in many parts of the world: gallstones are present in 10%-15% of the population in developed countries. There are two main types of gallstones with regard to the chemical composition: cholesterol and pigment type. Cholesterol gallstones represent the major type of gallstones in developed countries. In many cases, gallstones are mixed,

with the predominance of one or the other component. Pigment gallstones might be black stones (metabolic), in patients with hemolytic conditions, or brown stones (infectious), in patients with biliary infections/infestations.

Liver cirrhosis develops as the end-stage of chronic liver diseases. It is a quite common disease, with a rising prevalence in Western countries[1,2]. This is due to the growing epidemics of obesity and metabolic syndrome, having fatty liver as hepatic expression, and also to the fact that the spread of hepatitis C virus (HCV) infection in the United States and Europe occurred after the 1970s and a long duration of infection is necessary for cirrhosis to develop.

Among the many liver disorders that can lead to cirrhosis, some progress rapidly (years) and others more slowly (decades). Gallstones usually develop after a longer duration of cirrhosis. Gallstone prevalence in patients with liver cirrhosis ranges between 25% and 30%, being at least twice that in the general population.

In this paper we have reviewed the current literature in order to present the mechanisms responsible for the development of GD in patients with liver cirrhosis, as well as the clinical and therapeutical aspects of gallstones formed in this setting.

PREVALENCE AND INCIDENCE

The first data indicating a higher prevalence of gallstones in cirrhotics were derived from necroptic studies[3-7]. Prospective ultrasound studies have later confirmed the higher prevalence[8-13] and incidence[9,14-17] of gallstones in cirrhotic patients. The global cumulative incidence of gallstones was first evaluated in 72 patients followed-up for a mean of 2 years: 12 patients (16.6%) developed gallstones. The cumulative incidence was 5.5 cases/100 cirrhotics/year, and it was higher in advanced (decompensated) cirrhosis, irrespective of etiology[15]. Conte *et al*[17] followed-up 618 cirrhotic patients for almost 4 years, and found that 141 (22.8%) developed gallstones in this period, with an estimated cumulative probability of 6.5%, 18.6%, 28.2%, and 40.9% at 2, 4, 6, and 8 years, respectively. The multivariate analysis confirmed that advanced cirrhosis (Child class B and C) was associated with a greater risk for gallstones in these patients.

Although a number of risk factors for lithogenesis in liver cirrhosis have been identified, there are still aspects insufficiently elucidated. This is why cohort and case-control studies continue to be published[16,18-22], trying to better define the risk factors and the pathogenesis of gallstones in the cirrhotic patients.

GALLSTONE PATHOGENESIS

In most patients with liver cirrhosis, gallstones are of black pigment type[21,23-25]. Liver cirrhosis is considered as the major risk factor for pigment lithogenesis in adults. Only a small proportion of cirrhotic patients harbour cholesterol stones.

The major abnormalities leading to gallstone formation are the changes in bile composition (supersaturation of the bile in calcium bilirubinate for pigment stones, or supersaturation in cholesterol for cholesterol stones), enhanced crystal nucleation in the presence of mucin and its congeners, and gallbladder hypomotility (stasis) that allows crystals to grow into gallstones.

Changes in bile composition

Pathogenesis of black pigment stones: Pigment gallstones invariably contain a mucin glycoprotein matrix ("scaffolding")[26]. Black pigment stones develop in the sterile bile supersaturated in calcium bilirubinate. Supersaturation occurs in the presence of an increased concentration of unconjugated bilirubin or of an increased concentration of free ionized Ca^{2+} in the bile[27-30]. The unconjugated bilirubin fraction represents in physiological conditions less than 1% of the total amount of bilirubin in bile. It increases significantly in case of: (1) increased excretion of unconjugated bilirubin due to defective conjugation or hemolysis; (2) increased hydrolysis of conjugated bilirubin in bile due to enhanced beta-glucuronidase activity; (3) defective acidification of the bile due to mucin hypersecretion, resulting in increased ionization of unconjugated bilirubin and precipitation of Ca^{2+}; (4) decreased solubilization of bilirubinate anions in the presence of reduced bile salt concentration; and (5) induced enterohepatic cycling of unconjugated bilirubin.

Increased hemolysis and/or hydrolysis of conjugated bilirubin in bile lead to a shift in the ratio of bilirubin conjugates in the bile of cirrhotic patients in favour of bilirubin monoconjugates, especially monoglucuronides[24]. Bilirubin monoglucuronide is more easily deconjugated in bile by the β-glucuronidase secreted by hepatic parenchymal[31] or biliary epithelial cells, or is deconjugated through non-enzymatic hydrolysis.

Most mechanisms involved in pigment lithogenesis are also present in liver cirrhosis. A higher prevalence of hypersplenism and hemolysis was found in cirrhotics with gallstones than in those without gallstones[10,25]. Hemolysis could be promoted in advanced liver disease by hypersplenism, Kupffer cell destruction and altered membrane lipid composition.

The very low bile salt/unconjugated bilirubin molar ratio found in cirrhotic patients as compared to controls is an independent physico-chemical factor predisposing to pigment gallstone formation[24]. The reduction of the global bile acid pool size in cirrhotic patients is due to the impaired bile acid synthesis in the liver. Solubilization of the unconjugated bilirubin in bile, which is dependent on its interaction with bile salts, is reduced in liver cirrhosis. Vlahcevic *et al*[32] found a decreased cholic acid, but relatively preserved chenodeoxycholic acid synthesis in cirrhotic patients. They explained the fact that cirrhotic patients form rather pigment than cholesterol stones by demonstrating a reduced secretion of phospholipids and especially of cholesterol in their bile[33].

The decreased biliary secretion of phosphatidylcho-

line and cholesterol diminishes the detergent effect on membranes of the bile salts, potentially leading to bile salt-induced injury of the gallbladder mucosa. This favors pigment lithogenesis not only by production of mucosal β-glucuronidase from the biliary epithelial cells, but also by mucin glycoprotein hypersecretion and possibly by reactive oxygen species (ROS) production[34].

An induced enterohepatic cycling of unconjugated bilirubin, favored by alcohol abuse and low-protein diets[35] might contribute to gallstone formation in liver cirrhosis.

Pathogenesis of cholesterol stones in liver cirrhosis: Cholesterol gallstones occur more rarely in cirrhotic patients. Coelho *et al*[21] in their study on 369 transplant recipients with liver cirrhosis and gallstones observed on direct examination of the explanted livers that 318 patients (86.2%) had pigment stones, and 51 patients (13.8%) had cholesterol stones. The type of gallstones was not evaluated in relation to the etiology of liver cirrhosis. Viral C infection was in 132 patients (33% of the transplanted patients) the cause of liver cirrhosis[21].

Cholesterol gallstones occur in liver cirrhosis mainly in patients with viral C and non-alcoholic fatty liver disease (NAFLD) cirrhosis, and are due to the cholesterol supersaturated bile. Chronic HCV infection seems to be a risk factor for GD in patients with liver cirrhosis: gallstones are more frequent in patients with viral C as compared with viral B or alcoholic cirrhosis[20,36]. An increased incidence of gallstones in subjects with chronic HCV infection was found not only in cirrhosis, but also in the stage of chronic viral C hepatitis[37].

Non-alcoholic fatty liver diseases is associated with an increased prevalence of gallstones[38-40] due to obesity and increased insulin resistance. The risk of GD increases with the severity of liver disease; the highest prevalence of gallstones was found in the more advanced stages of fibrosis (cirrhosis) in NAFLD patients[39].

Enhanced nucleation in bile

Both cholesterol and pigment stones form on a matrix of mixed mucin glycoproteins secreted by the epithelial cells lining the biliary tree. Mucin hypersecretion, favored by gallbladder wall inflammation, accounts for the enhanced nucleation in cirrhotic patients.

Advanced liver disease is associated with a reduced apolipoprotein (apo) A1 and apoAII secretion in alcoholic patients with liver disease[41,42] and also in cirrhosis of other etiology. This might contribute to the enhanced crystal nucleation in cirrhotics' bile, as apo A-I and A-II act as antinucleating factors.

Gallbladder hypomotility

Unlike its contribution to the formation of cholesterol gallstones, the role of gallbladder hypomotility in pigment lithogenesis has longtime been controversial. However, larger fasting gallbladder volumes in patients with liver cirrhosis have been unanimously found[43-45]. Some earlier studies revealed a normal gallbladder emptying in patients with liver cirrhosis[43,44], but later most ultrasonographic[45-49] and scintigraphic[50] studies documented the reduced gallbladder contractility in these patients. The contradictory findings were mainly due to the different test meals used in these studies for evaluating gallbladder emptying.

Changes in the neurohormonal control of gallbladder motility and the structural changes of the gallbladder wall (edema caused by hypoalbuminemia and venous congestion in the context of portal hypertension) might account for the impaired gallbladder emptying in cirrhotics.

The level of circulating CCK is higher in cirrhotic patients than in controls[44,51,52]. This was explained by the impaired hepatic degradation in cirrhosis, as CCK-8 is normally metabolized on its first passage through the liver[53]. In spite of the higher levels of circulating CCK, gallbladder motility is diminished in liver cirrhosis, possibly due to a higher resistance of the gallbladder at the receptor site. Increased plasma concentrations of intestinal peptide hormones that have an inhibitory influence on gallbladder smooth muscle, such as VIP, somatostatin[54], glucagon[55] and pancreatic polypeptide were also detected in liver cirrhosis, as a consequence of their impaired degradation in the liver. The increased levels of relaxing peptides might explain the earlier cessation of the humoral stimulation of gallbladder emptying in cirrhotics: refilling of the gallbladder is more important and starts before complete emptying of the stomach in cirrhotics as compared to controls[45].

Hypocontractility of the gallbladder in patients with liver cirrhosis is proportional with the severity of liver disease, and is more important in cirrhotics with gallstones than in those without gallstones[56]. This suggests that gallbladder stasis might be a contributor to gallstone formation in the advanced stages of cirrhosis.

RISK FACTORS FOR LITHOGENESIS

Age and gender

Diehl *et al*[25], in a clinical study on 551 patients undergoing cholecystectomy, found that patients with pigment stones were older than those with cholesterol stones: most subjects older than 70 years had pigment stones ($P < 0.00001$), and cirrhosis was strongly associated with pigment gallstones. Other studies also found that gallstone prevalence increased with age in cirrhotics[5,10,17,20]. Advanced age was shown to represent also an independent risk factor for gallstone symptom development in patients with liver cirrhosis[57].

Necroptic studies, as well as clinical and ultrasound surveys resulted in contradictory data regarding the gender influence on gallstone formation in cirrhosis. Some studies indicated a higher prevalence in men[3,4,12-14,19], up to a 1/1 female/male ratio. The increased estrogen level in cirrhotic males was suggested to favor gallstone formation[12], but no correlation between presence of clinical signs of hyperestrogenemia in men and the incidence of

gallstones could be demonstrated[3]. In other studies, the female/male ratio was comparable with that of gallstone carriers in the general population[9,10,57]. Even if the prevalence in these studies was higher in cirrhotic females, gallstones were considerably more frequent in the cirrhotic males when compared with control males. Regarding development of symptoms, males seem to have a lower risk (OR = 0.20, P = 0.0049) than female patients with cirrhosis[57].

Family history of GD

GD is a complex disease, resulting from the interaction between environmental factors and numerous genetic influences. The familial aggregation of gallstones supporting the genetic influence on gallstone formation has been known since decades. A large family study, comprising 358 families with 1038 subjects having symptomatic gallstones, suggested that the genetic factors account for at least 30% of the etiology of symptomatic GD[58].

The first human susceptibility genes for cholesterol gallstone formation were recently identified. A genome-wide association study (GWAS) detected a highly significant association of GD with the DH19 polymorphism in the *ABCG8* gene, the gene controlling the cholesterol transporter in the bile[59]. This variant of the *ABCG8* gene was found to be associated with GD in a linkage and association study in siblings with gallstones[60], and it was later confirmed in many populations. An update inventory of human gallstone genes can be found in two recent reviews[61,62].

The Gilbert syndrome variant rs6742078 in the promoter of the *UGT1A1* gene, the gene encoding uridine 5'-diphosphate (UDP)-glucuronyltransferase 1A1 (UGT1A1), that is responsible for bilirubin conjugation, was identified as a candidate gene for GD in a genome-wide association study of Sardinian subjects having increased serum bilirubin levels[63]. This variant promotes formation of pigment gallstones. It was confirmed as a candidate gene for pigment stones in German and Chilean patients[64], especially in men, and was shown to increase the risk not only for pigment gallstones, but for all types of gallstones. The association of the variant of *UGT1A1* not only with the stone bilirubin content but also with the global risk for gallstones confirms the presence of common factors in the pathogenesis of cholesterol and pigment gallstones[64]. An increased gallstone risk was later found in Swedish twins carriers of this variant[65], supporting also the nucleation in the bilirubin supersaturated bile as an initial step in cholelithogenesis. Buch *et al*[64] calculated that the population-attributable fraction of the common *ABCG8* and *UGT1A1* variants in men was 21.2%. If estimated for all European gallstone carriers, this fraction was between 15% and 20%[62].

It would be of interest to evaluate the presence of these variants in patients with liver cirrhosis and gallstones. A genetic susceptibility might represent an independent risk factor for the occurrence of gallstones in cirrhotic patients. It has been already demonstrated that a positive family history of GD increases the risk of developing symptoms in cirrhotic gallstone carriers[57].

Etiology of liver cirrhosis

All prevalence studies agree that the lithogenetic risk in patients with liver cirrhosis is related to the cirrhotic change of the liver, which develops as the end stage of chronic liver diseases of any etiology. However, for some liver diseases, the lithogenetic risk was demonstrated to be higher.

Chronic alcoholism: Friedman *et al*[66] did not find an association between chronic alcoholism and lithogenesis. Trotman and Soloway[67] observed that a history of alcoholism in cholecystectomized patients did not influence gallstone type, cholesterol or pigment. Some clinical studies found a protective effect of alcohol in moderate consumers (39 g/d), suggesting a reduced bile lithogenicity as responsible for this effect[68]. Other studies noted an association between pigment stones and chronic alcoholism without cirrhosis[69], which was explained by the direct effect of chronic alcohol consumption on the liver, bile and red blood cells (macrocytosis) leading to an increased proportion and decreased solubilization of unconjugated bilirubin in the bile. Alcohol consumption was shown in one study to reduce the risk of symptoms in noncirrhotic women with gallstones[70]. In summary, epidemiological studies have been contradictory regarding the protective/favoring effect of alcohol for gallstone formation in patients without liver cirrhosis.

But all studies agree that alcohol-related liver cirrhosis is associated with an increased prevalence of gallstones. And previous alcohol abuse was found to be an independent risk factor for gallstone formation in a prospective follow-up of cirrhotic patients of all etiologies[16]. Regarding the risk for gallstone symptoms, this is significantly lower in patients with alcoholic versus viral cirrhosis (OR = 0.23, P = 0.0116)[57].

Chronic HCV infection: HCV infection represents a major cause of liver cirrhosis in the developed countries, where its prevalence is rising[1]. Some prospective[71] and retrospective[19,72] studies evidenced a higher gallstone risk in patients with chronic HCV infection in the stage of liver cirrhosis. A study derived from a populational survey in the United States (NHANES Ⅲ) found that anti-HCV positive men had a higher prevalence of gallstones than the HCV-negative, and that gallstone prevalence was higher in those with severe disease[35]. Stroffolini *et al*[20] noted a significantly higher prevalence of GD in viral C versus viral B or alcohol-related cirrhosis.

A study performed on 453 patients with chronic HCV-infection (cirrhotics excluded) demonstrated that HCV infection represented an independent risk factor for gallstone formation[37]. Prevalence of GD was higher in patients than in controls, gallstones occurred at a younger age and central obesity and fatty liver (steatosis) were the significant risk factors for their occurrence. A causal

link between chronic HCV infection and GD was thus proved, at least for the subgroup of obese subjects with liver steatosis.

The increased insulin resistance, commonly present in obese subjects and in those with fatty liver disease, could represent the link between chronic HCV infection and cholesterol GD. Increased insulin resistance favors cholesterol lithogenesis *via* increased biliary saturation in cholesterol. Although gallstone composition has not been evaluated in these patients, one can presume that cholesterol stones are the prevalent type in patients with viral C liver disease.

NAFLD: NAFLD is characterized by the fat accumulation in the liver in the absence of alcohol abuse and includes a large spectrum of liver changes, from simple fatty liver to non-alcoholic steatohepatitis (NASH) and liver cirrhosis. Cholesterol GD and NAFLD share many common risk factors, such as insulin resistance, type 2 diabetes mellitus, central obesity, hypertriglyceridemia and metabolic syndrome. These common factors account for the higher prevalence of cholesterol GD in patients with NAFLD[38-40]. Given this frequent association, it was even suggested that routine liver biopsy for diagnosing and staging NAFLD might be justified during cholecystectomy[73].

A recent study by Fracanzani *et al*[39] showed a progressive increase of gallstone prevalence with the severity of fibrosis in NAFLD (P for trend = 0.0001): from a gallstone prevalence of 15% in fibrosis stages 0-2, to 29% in stage 3 and 56% in stage 4 (cirrhosis). Female gender, prediabetes/diabetes, central obesity, older age and metabolic syndrome were significantly more frequent in NAFLD patients with gallstones than in NAFLD patients without gallstones.

Obesity and type 2 diabetes mellitus

Abdominal (central) obesity, type 2 diabetes mellitus and hypertriglyceridemia are risk factors for cholesterol gallstones in the general population, and have also been found to be independent risk factors for GD in patients with liver cirrhosis[13,17,22]. Increased insulin resistance represents the link between these disorders, being also responsible for NAFLD development. The increased gallstone risk in cirrhotics with obesity and type 2 diabetes mellitus might thus mainly refer to patients with NAFLD-induced liver cirrhosis, but to date, no study has evaluated this aspect.

Duration/severity of liver disease

The main determinant for gallstone formation in patients with cirrhosis of the liver appears to be the severity of liver disease. Advanced liver cirrhosis indicates a long duration of the disease. Most authors have shown that prevalence of gallstones was higher in the advanced stages of the disease: in decompensated versus compensated, or in Child C *vs* Child A patients, respectively[4,9,11,12,14,15]. This was confirmed in patients with NAFLD, in whom gallstone prevalence significantly correlated with the severity of liver fibrosis[39].

CLINICAL ASPECTS

Asymptomatic (silent) stones

In most patients, gallstones remain asymptomatic (silent) during the entire life. Gallstones are asymptomatic even if accompanied by dyspeptic symptoms, provided biliary pain is absent. They are often discovered incidentally at abdominal ultrasonography performed for various indications. Epidemiological studies suggest that about 70%-80% of gallstones in the general population are/remain asymptomatic and about 20% will eventually develop symptoms and complications within 5 and 20 years after diagnosis[74,75]. However, a recent large epidemiological study[76] found that in the general population, a significant proportion of cholecystectomies (41.3%) are still performed in asymptomatic patients.

In patients with liver cirrhosis, gallstones are also usually asymptomatic and have more chances to be detected at the periodical check-ups of liver disease by ultrasonography. A higher percentage of cholecystectomies used to be found in cirrhotic patients than in the normal population in the same area[8,18]. In his retrospective study, Maggi *et al*[18] found that only 62% of the cholecystectomized cirrhotics had a history of biliary pain. This could be due either to the detection of unknown latent cirrhosis during cholecystectomy, or because cholecystectomy is more readily recommended in case of altered liver function tests in these patients, presumed erroneously to indicate symptomatic or complicated lithiasis.

The risk of developing symptoms and complications is also low for patients with liver cirrhosis, but it was evaluated only in a few studies.

Symptomatic stones

Gallstones are symptomatic when pain occurs: pain is either colicky or continuous, steady. The simplest definition of biliary pain is that of pain located in the right hypocondrium or epigastrium, which irradiates to the back, occurs (usually, but not always) postprandially, is intense and lasts more than 15-30 min.

In the era before the introduction of laparoscopic cholecystectomy (LC), a small study found that out of 64 patients hospitalized with the diagnosis of liver cirrhosis and having gallstones, 14 (22%) developed biliary complications necessitating cholecystectomy[77]. Fifty patients (78%) remained asymptomatic at a 2-year follow-up. It was concluded that complications of gallstones do not occur more frequently than in gallstone carriers in the general population. In those patients with asymptomatic gallstones who were later submitted to elective surgical treatment for porto-systemic shunt, morbidity and mortality of the associated cholecystectomy did not differ from the rates observed in a group of 170 patients who underwent only portal surgery during the same period. But if complications occurred, emergency operation car-

ried a higher risk in cirrhotic patients. According to this study, the proportion of symptomatic versus asymptomatic gallstones seems to be similar in cirrhotic patients with that in the general population.

In a case-control study of 140 patients with liver cirrhosis and gallstones, both symptomatic and asymptomatic, the univariate analysis showed that advanced age, female gender, positive family history of gallstones, viral etiology of cirrhosis and duration of cirrhosis were significantly associated with the symptomatic stones[57]. In the multivariate analysis, only family history of gallstones and advanced age were independent risk factors for symptom development. Male gender and alcoholic etiology of cirrhosis negatively correlated with symptom presence, suggesting their protective effect on symptom development.

Recognizing the risk factors for symptoms is a very important issue for the medical decision. Once symptoms appear, patients are at risk for pain recurrence and complications. When symptoms do occur, morbidity and mortality are higher than in noncirrhotic patients. Early cholecystectomy in patients with surgical risk, as soon as the first symptoms occur, could avoid emergency surgery for complications in a more advance stage of liver disease.

TREATMENT

Expectant management for asymptomatic stones

Expectant management (observation alone) is the appropriate recommendation for patients with asymptomatic gallstones in the general population, due to the low risk to develop symptoms and/or complications. Cholecystectomy is not only an expensive procedure, but it carries a risk, even low, of morbidity and mortality in patients who might otherwise never develop symptoms or complications.

The same recommendation should be made for the cirrhotic patients with silent gallstones. Asymptomatic gallstones in cirrhotic patients are best managed conservatively, with close monitoring and surgery if symptoms or complications occur. Given the higher risk for surgery in the presence of advanced liver disease, the management options should be discussed with the patients when gallstones are diagnosed, and they should be actively involved in the process of therapeutic decision.

Prophylactic cholecystectomy

For the time being, there are no published randomized trials to evaluate the better approach for patients with silent gallstones: cholecystectomy or expectant management[78]. Prophylactic cholecystectomy is generally not recommended for gallstone carriers in the general population, except for some special situations. It should be also not recommended in cirrhotic patients given their higher surgical risk as compared to patients without liver disease. The management of asymptomatic gallstones found incidentally in these patients during abdominal surgery for another indication is controversial. Concomitant cholecystectomy might be a reasonable option for patients with well compensated cirrhosis undergoing elective abdominal surgery for other conditions[77]. However, in a small study on 34 patients with liver cirrhosis, all patients, even those in Child A or B class, who underwent additional cholecystectomy during the non-shunting operation for esophageal varices required blood transfusion[79].

Laparoscopic or open conventional cholecystectomy

Before the introduction of laparoscopic cholecystectomy (LC), the postoperative mortality in patients with cirrhosis undergoing conventional open cholecystectomy (OC) was between 7.5% and 25.5%[77,80-82]. As expected, patients with the most severe liver disease were at the highest risk. And although at the beginning of the 1990s it was already documented that LC had important advantages over OC when considering hospital stay and morbidity of gallstone patients, a consensus statement on LC in 1992 stipulated that patients with end-stage cirrhosis of the liver and with portal hypertension were not candidates for LC.

One year later, a first study was published regarding the outcome of LC in cirrhotic patients[83]. Lacy *et al*[84] reported a 9% conversion rate, no morbidity and an average hospital stay of patients of less than 2 d. Case series, case-control studies[85] and meta-analyses[86-90] were thereafter published. The first meta-analysis published in 2003 by Puggioni *et al*[86] showed that LC offered the advantages of less blood loss, shorter operative time, and shorter length of hospitalization in patients with cirrhosis. Further meta-analyses and randomized controlled trials (RCTs) confirmed that shorter operative time, reduced hospital stay, rapid recovery, reduced complications rate[86,89,90] and earlier resumption of a normal diet[90] were the most important advantages of LC in patients appropriately selected. The Child-Pugh classes and especially the MELD score were established as the best predictors of a better outcome after LC[88,91].

Patients with advanced cirrhosis (Child-Pugh class C) remain at significantly higher risk of complications and mortality for cholecystectomy. Progress in the surgical equipment, better therapy for liver failure, and multiplication of surgical options, including laparoscopic cholecystostomy and percutaneous transhepatic cholecystostomy have increased the safety of the intervention also for these patients. A recent systematic review and meta-analysis comparing LC and OC, which included all published RCTs and a total of 2005 cirrhotic patients undergoing cholecystectomy, showed that the mortality rates reported for both LC and OC were "substantially lower than those reported for OC in the 1980s"[89], acknowledging the progress in the management of these patients in the last two decades. Laparoscopic cholecystectomy *per se* did not entirely account for the lower mortality in cirrhotics. A rigorous selection of patients for surgery, based on imaging techniques with higher diagnostic accuracy and

a better control of the underlying liver disease, as well as the availability of less invasive techniques for temporary management-surgical or endoscopic-in those with advanced liver cirrhosis have substantially contributed to the improved outcome of these patients.

CONCLUSION

Gallstones occur often in patients with liver cirrhosis. Their prevalence increases with age and with the severity (*i.e.*, duration) of disease. They are in most patients pigment stones, while about 15% of cirrhotics have cholesterol stones. Lithogenesis is induced in these patients by the metabolic changes in the liver, involving bilirubin and biliary lipid secretion, and is favored by gallbladder hypomotility. Gallstones develop in cirrhosis of all etiologies, but more frequently in alcoholic, viral C and fatty liver disease. Asymptomatic gallstones should not be operated in cirrhotic patients, but patients should be followed-up closely and offered LC once symptoms develop. In patients with advanced liver disease, noninvasive or minimally-invasive procedures should be used to treat the complications of gallstones.

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P- Reviewers: Cheng NS, Codoner-Franch P, Xu Z
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ISSN 1007-9327

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