

# Gallstones and Liver Disease: an Overview

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Gallstones (GS) may form as a result of many different disorders. Two main categories of gallstones can be identified according to their predominant chemical composition: cholesterol and pigment stones.

Unphysiological biliary supersaturation from hypersecretion of cholesterol, gallbladder hypomotility and the accumulation of mucin gel contribute to the formation of cholesterol GS, while black pigment stones derive from the precipitation of calcium hydrogen bilirubinate where pigment supersaturation and deposition of inorganic salts, phosphate and calcium bicarbonate accelerate the nucleation. Pigment supersaturation is common in hemolytic disorders, enterohepatic cycling of unconjugated bilirubin and ileal disorders and/or surgery [1].

There is also a third main type of GS, very common in East Asia: brown pigment stones, which form in the bile ducts due to bile stasis, parasites, uncomplete polymerization of calcium hydrogen bilirubinate, saturated fatty acids and bacterial infection with enzymatic hydrolysis of biliary lipids.

In the general population, one of the main risk factors for developing GS is the sex: GS are more common in women than in men. Other factors are age, genes, race - the burden of GS disease is epidemic in American Indians (60-70%), decreases in Hispanics of mixed Indian origin and is further reduced in Black Americans [2]. Additional factors are obesity, rapid weight loss, glucose intolerance, insulin resistance, high dietary glycemic load, alcohol use, diabetes mellitus, hypertriglyceridemia, drugs, pregnancy. Nowadays, there is much interest in discovering the relationship between GS and liver disease and in the last issue Coelho and colleagues [3] decided to assess the prevalence of cholelithiasis in patients undergoing liver transplantation

for end stage liver disease. Their study deals with a really interesting and new issue. In fact, whereas many studies observed a higher prevalence of GS in chronic liver disease, up to now none have assessed GS prevalence in the subset of patients subjected to liver transplantation. In addition, this article evaluates this particular issue in Latin America, a geographical area from which few data are available in current literature. The reference standard to detect GS was represented not only by the ultrasonographic scan of the gallbladder but also on the direct examination of the explanted liver.

The results of the study by Coelho and colleagues deserve some considerations that could be summarized by answering three main questions:

a) How did we get here? b) What is the reason for the increased frequency of gallstones in cirrhosis? c) Do gallstones worsen the course of liver cirrhosis?

a) How did we get here? Different groups conducted follow up of patients with liver cirrhosis in order to assess gallstone incidence. Table I summarizes the main results of these studies.

All the published series confirm that cirrhosis represents a relevant risk factor for gallstones. Regarding the sex, despite the higher absolute frequency of GS in females with cirrhosis, the risk of cholelithiasis in cirrhotic males is much higher than in the healthy population. Fornari et al [4] claimed that cirrhosis is a risk factor for GS in males and suggested that a high level of estrogens could play a role by an impairment of gallbladder emptying as observed also in pregnant women. Age, sex and BMI, relevant factors for GS development in general population, are much less important in patients affected by cirrhosis, where the main factor to be considered is the degree of impairment of underlying liver disease [5].

One study discussed also the different prevalence of GS in cirrhosis and acute or subacute liver necrosis [6], and found that patients who died from acute or subacute liver failure did not have an increased tendency to form GS, probably because of the lack of time to develop this complication. This could be related to the evidence that the severity of cirrhosis, graded according to the Child Pugh

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**Table I.** Gallstone prevalence in different series comparing cirrhotics to controls, according to sex

Authors	Patients (No.)	Controls (No.)	Ref. Standard	Gallstone prevalence					
				Cirrhotics (%)	Controls (%)	Cirrhotics Women (%)	Cirrhotics Men (%)	Controls Women (%)	Controls Men (%)
Acalovschi et al [20]	140	140	US	29.2	13.6	48.8	20.6	15.1	12.1
Goebell et al [21]	11143	697	Necropsy	21.5	16.5	35.2	16.2	26.3	10.8
Conte et al [22]	1110	-	US	29.5	10	32	28	15	10
Fornari et al [23]	410	414	US	31.9	20.7	-	30.2	-	16.5
Bouchier et al [6]	235	3282	Necropsy	29.4	12.8	30.8	28.2	18.5	8.4
Genzini et al [7]	110	-	US	27.3	-	33.3	25.3	-	-

scoring system, could be strictly related to the risk of GS development [7], which resulted in significance only for Child class B and C, reflecting the long lasting underlying disease (Table II) with a significant linear trend ( $p < 0.001$ ). The only data available from Brazil until now [8] did not find a correlation between liver function defined by Child's classification, and GS.

Considering patients with decompensated cirrhosis, the cumulative incidence of GS among those with ascites was

**Table II** Gallstone prevalence (%) in cirrhotics according to Child-Pugh's class

Authors	Patients (No.)	Child A	Child B	Child C
Conte et al (22)	1110	16.7	29	43
Fornari et al (23)	165	6.4	24	49.3
Elzouki et al (24)	413	16	-	56.2

found to be five times higher than in compensated liver disease. In addition, taking into account portal hypertension, GS seemed to be more than two times more common when compared with the control population [9].

Also the etiology of liver disease could play a role in increasing the prevalence and incidence of gallstones, probably higher in HBsAg-negative as compared with HBsAg-positive cases and in patients with previous alcohol abuse [10], a factor which may occur independently of cirrhosis, although not all the series have been able to confirm these data. Hepatitis C virus infection, investigated in patients affected by chronic infection without cirrhosis, seems also to be a risk factor for GS formation especially when concomitant to diabetes mellitus [11-13].

b) What is the reason for the increased frequency of gallstones in cirrhosis? The reason is still uncertain [14], but chronic hemolysis secondary to hypersplenism, hyperestrogenism as mentioned before, changes in the proportion of biliary lipids, reduced hepatic synthesis and transport of bile salts and unconjugated bilirubin leading to an impaired binding and polymerization of calcium ions,

could in part explain the higher GS frequency in cirrhosis. Furthermore, a significant factor in GS formation could be the impairment in the gallbladder postprandial refilling [15].

All these factors could support the evidence that in liver cirrhosis pigment stones are much more common than cholesterol ones and suggest that selective precipitation of calcium bilirubinate and phosphate is much more relevant than the precipitation of calcium carbonate [16].

c) Do gallstones worsen the course of liver cirrhosis? Some studies, such as that conducted by Grassi et al [17] found that the incidence of complications such as digestive hemorrhage, coma and hepato-renal syndrome was similar in cirrhotics with and without GS; a fatal outcome was less common in cirrhotic patients with GS than in those without. They conclude that biliary lithiasis does not aggravate the course of liver cirrhosis.

Also Acalovschi et al in a necroptic study on the prevalence of coledithiasis in liver cirrhosis [18] suggested that the average age of death was lower, but without statistical significance, in cirrhotic patients without GS than in those with. In detail, considering 133 patients and 1187 controls, they observed a prevalence of 24.8% in cirrhotics versus 17.8% in controls with a ratio of 0.8 in cirrhotic women and 1 in men, versus 1.6 in control women and 1 in men.

In cirrhotic patients, GS are more frequently asymptomatic and surgery is rarely required but, when surgery is mandatory, these patients carry a higher risk of morbidity than the general population undergoing cholecystectomy. Female gender, advanced age and viral etiology of cirrhosis are relevant risk factors for the development of symptoms [19].

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