Prevalence of Cholelithiasis in Patients Subjected to Liver Transplantation for Cirrhosis

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Abstract

Background and Aims: The prevalence of cholelithiasis in patients subjected to liver transplantation has not been evaluated yet. This study examines the prevalence of cholelithiasis in patients subjected to liver transplantation due to cirrhosis compared to an age- and sex-matched control group. **Methods**: The electronic study protocols of 400 consecutive cirrhotic patients aged between 20 and 69 years who had undergone liver transplantation for cirrhosis were evaluated to determine the presence of gallstones. **Results**: The overall prevalence of cholelithiasis was higher in transplant recipients (96 patients; 24%) than in controls (38 patients; 9.5%) ($p<0.001$). There was no increase in the prevalence of cholelithiasis with age in the transplant recipients ($p=0.332$). Conversely, the prevalence of cholelithiasis increased with age in the control group ($p<0.001$). There was no difference in the gallstone prevalence between sexes in the transplant recipient group ($p=0.102$). However, the gallstone prevalence was 2.2 times higher in females (14.8%) than in males (6.8%) in the control group ($p=0.009$). **Conclusion**: Prevalence of cholelithiasis is higher in patients subjected to liver transplantation for cirrhosis. In contrast with the general population, the prevalence of cholelithiasis in cirrhotic patients is similar in both sexes and does not increase with age.

Key words

Cholelithiasis – pigment gallstones – alcoholic liver cirrhosis – chronic liver disease – viral cirrhosis – liver transplantation.

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Introduction

Cholelithiasis is a major public health problem and its prevalence is about 10% of the general population of Europe, United States and most South American countries, including Brazil [1,2]. Although most patients with gallstones are asymptomatic, some may have severe morbidity and mortality, mainly patients with associated diseases such as diabetes and liver cirrhosis [3,4]. Some autopsy and ultrasonographic studies have shown an increased prevalence of gallstones in patients with liver cirrhosis [5-11]. Moreover, the prevalence of cholelithiasis has been reported to vary according to the severity of cirrhosis, with the highest prevalence in advanced cirrhosis [10, 11].

To the best of our knowledge, the prevalence of cholelithiasis in patients subjected to liver transplantation has not been evaluated yet. In addition, there are no studies in Latin America on the prevalence of gallstones in cirrhotics. The purpose of this study is to assess the prevalence of cholelithiasis in patients subjected to liver transplantation due to cirrhosis compared to an age- and sex-matched control group.

Patients and methods

A total of 400 consecutive cirrhotic patients aged between 20 and 69 years who underwent liver transplantation for cirrhosis at the Nossa Senhora das Graças Hospital and Clinical Hospital of the Federal University of Parana, Brazil was included in the present study (Transplant Recipient Group). The transplants were performed from September 1991 to March 2009.

The electronic study protocols of all patients were reviewed to determine the demographics, etiology of cirrhosis, abdominal ultrasonography, and results of pathologic examination of the explanted liver.

A total of 400 volunteers were selected from visitors of two shopping centers of our city (General Population Group). The individuals were recruited by interviewers of a research institute to match the age and sex of the transplanted patients. Afterwards, a questionnaire was presented by medical

residents to all volunteers. Information about age, sex, race, family and personal medical history, dietary habits, past and current use of medications, and number of pregnancies were obtained. The results of a physical examination were also recorded. After the interview, the individuals were subjected to an ultrasonographic examination of the upper abdomen, performed by two experienced ultrasonographers using a high-resolution real-time equipment with a convex transducer of 3.5 MHz (SSD 500, Aloka Co., Japan).

Ultrasonographic diagnosis of gallstones was established by the presence of movable echogenic structure(s) within the gallbladder lumen that caused a posterior acoustic shadow. Pathologic diagnosis of cholelithiasis in the transplant recipients was based on the finding of gallstones on the gallbladder examination of the explanted liver. Patients who had undergone cholecystectomy for calculous cholecystitis previously both in the transplant group (n=12) and in the control group (n=10) were considered as having gallstones.

The type of gallstones was also determined in the transplant recipients based on the macroscopic aspect of the stones on pathologic gallbladder examination. The stones were classified as either cholesterol stones or pigment stones. Cholesterol stones were single or multiple, of variable size, shape, and color. Pigment stones were multiple, black, small, and sometimes spiculated.

The protocol of this study was approved by the Research Committee of the Clinical Hospital of the Federal University of Paraná. Values were expressed as mean ± SD (standard deviation). Statistical analysis was performed using the Excel Microsoft software and the Statistica version 9 software (StatSoft Inc., Tulsa, OK, USA). The Student´s t-test was employed to determine the difference between the means and chi-square test with Yates' correction to assess the difference between the expected frequencies and the observed frequencies of the two groups. Logistic regression analysis was used to assess the association between age and sex with gallstones. Results were considered statistically significant when $p \leq 0.05$.

Results

Demographic characteristics of liver transplant recipients and controls are shown in Table I. Mean age, sex distribution, and number of pregnancies of the two groups were similar.

The indications of liver transplantation are shown in Table II. The most common indications were hepatitis C (33%), alcoholic cirrhosis (12.8%) and hepatitis B (8.8%). There was no evidence of liver cirrhosis in the medical history and ultrasonography of all individuals of the control group.

The overall prevalence of cholelithiasis was higher in transplant recipients (96 patients; 24.0%) than in controls (38 patients; 9.5%) ($p<0.001$) (Table III). The prevalence was higher both in males (57 patients; 21.5% vs 18 patients; 6.8%; $p<0.001$) and females (39 patients; 28.9% vs 20 patients; 14.8%; $p<0.01$) (Table IV). This higher prevalence was also observed in all age groups, except in the 60-69 year-old-group, in which the overall prevalence was similar ($p=0.201$) (Table III).

Table I. Demographic characteristics of liver transplant recipients and controls

Characteristics	Transplant	Controls
Number of patients	400	400
Age (years)		
Mean± SD	47.0± 11.9	45.3± 11,5
Range	20-69	20-69
Gender		
Male	265	265
Female	135	135
Pregnancy		
None	53	44
1 to 2	38	48
≥3	44	43

Table II. Etiology of cirrhosis in 400 patients receiving OLT

Etiology	N	%
Chronic HCV infection	132	33.0
ETOH chronic abuse	51	12.8
Chronic HBV infection	35	8.8
ETOH plus HCV/HBV	18	4.5
Primary sclerosing cholangitis	23	5.8
Primary biliary cirrhosis	21	5.3
Autoimmune cirrhosis	16	4.0
Metabolic disease	12	3.0
Cryptogenic	43	14.3
Others	49	12.3

ETOH: ethanol consumption

There was no association between gallstone prevalence and age in the transplant group ($p=0.332$). In the control group, the prevalence of cholelithiasis increased with age in both sexes. The overall prevalence in the control group increased from 2.1% in the 20-29 year-old group to 18.4% in the 60-69 year-old group ($p<0.001$). There was no difference in the gallstone prevalence between sexes in the transplant group ($p=0.13$) (Table IV). However, the gallstone prevalence was 2.2 times higher in females (14.8%) than in males (6.8%) in the control group ($p=0.01$). The prevalence in the control group was higher in females in all age groups, except in the 60-69 year-old group ($p<0.01$).

Logistic regression analysis showed that the prevalence of gallstones was associated with older age (OR= 1.06; 95% CI= 1.02 – 1.09; $p < 0.001$) and female sex (OR=0.41; 95% CI= 0.20 – 0.82; $p < 0.01$) in the control group. The prevalence of gallstones was not associated with older age (OR= 1.01; 95% CI= 0.99 – 1.03; $p = 0.20$) and female sex (OR= 0.63; 95% CI= 0.39 – 1.03; $p = 0.07$) in the transplant group.

On gallbladder pathological examination of cirrhotic patients, the prevalence of cholelithiasis was the same as

Table III. Prevalence of cholelithiasis in liver transplant recipients and controls, according to sex and age

Age (years)	Transplant recipients									Controls									
	Male			Female			Overall			Male			Female			Overall			
	N	Gallstone N	%	N	Gallstone N	%	N	Gallstone N	%	N	Gallstone N	%	N	Gallstone N	%	N	Gallstone N	%	p
20-29	22	4	18.2	23	5	21.7	45	9	20.0	25	0	0	23	1	4.3	48	1	2.1	0.005
30-39	38	8	21.1	21	6	28.6	59	14	23.7	57	2	3.5	22	2	9.1	79	4	5.1	0.001
40-49	81	15	18.5	46	12	26.1	127	27	21.3	80	5	6.3	47	6	12.8	127	11	8.7	0.005
50-59	80	19	23.7	34	11	32.3	114	30	26.3	64	5	7.8	33	8	24.2	97	13	13.4	0.020
60-69	44	11	25.0	11	5	45.5	55	16	29.1	39	6	15.4	10	3	30.0	49	9	18.4	0.201
Total	265	57	21.5	135	39	29.0	400	96	24.0	265	18	6.8	135	20	14.8	400	38	9.5	<0.001

Table IV. Gallstone prevalence according to sex in 400 OLT recipients and 400 controls

	Controls (400)		OLT recipients (400)	
Gallstone	M (265)	F (135)	M (265)	F (135)
Present N (%)	18 (6.8)	20 (14.8)	57 (21.5)*	39 (28.9)*
Absent N (%)	247 (93.2)	115 (85.2)	208 (78.5)	96 (71.1)

*P< 0.01 versus controls. M: males; F: females

that observed on pre-transplant ultrasonography. Type of gallstones was determined in 369 transplant recipients. Pigment stones were identified in 318 patients (86.2%) and cholesterol stones in 51 (13.8%). In the 31 remaining patients, type of stones was not determined due to either a previous cholecystectomy (n=12) or absence of stone classification on the electronic protocol (n=19).

Discussion

Autopsy and ultrasonographic studies have shown an increased prevalence of gallstones in patients with liver cirrhosis, which ranged from 21.5% to 30.8% [12-14]. Our study was the first to assess the prevalence of cholelithiasis in patients subjected to liver transplantation for cirrhosis. It is also the first study to evaluate the prevalence of gallstones in patients with cirrhosis in Latin America. Diagnosis of cholelithiasis was based on the finding of gallstones both on ultrasonographic and on gallbladder examination of the explanted liver. Our findings confirm that the prevalence of cholelithiasis is higher in patients with liver cirrhosis. The overall prevalence of cholelithiasis was 24%, similar to that observed in the studies mentioned previously [10-14]. The higher prevalence in patients with cirrhosis compared to the general population was noted in both sexes and all age groups, except in the 60-69 year-old group. The lack of higher prevalence in this age group is possibly due to the small number of transplants performed in this group in our series.

It is well known that gallstone prevalence increases with age in the general population [1, 2]. However, the results are controversial in patients with liver cirrhosis. Acalovschi et al [8] and Del Olmo et al [15] have reported an increase in gallstone prevalence with age in cirrhotics. Conversely, three other studies observed no prevalence change with age [10, 12, 16]. In our series, we have also observed no increase in the prevalence of cholelithiasis with age in the transplant recipients, as seen in the general population.

Cholelithiasis is 2 to 4 times more common in females than in males in the general population [2, 16, 17]. There is no consensus in the literature whether gallstone prevalence is higher in females than in males with liver cirrhosis. In accordance with Conte et al [16], but in disagreement with other authors [11, 15], cholelithiasis prevalence was similar in both sexes in our study.

The findings of our study suggest that sex and age, important risk factors associated with cholelithiasis in the general population, are far less important in patients with cirrhosis. The differences in gallstone prevalence according to age and sex in patients with cirrhosis vs general population may be due to distinct risk factors for gallstone formation in these two groups. In the general population, most stones are of cholesterol and the primary event in the formation of stones is usually cholesterol supersaturation of bile [1, 18]. Other factors, such as gallbladder hypomotility and excess secretion of mucus into the gallbladder are also important [1, 18]. The factors responsible for cholesterol stone formation are age- and sex-dependent and they explain why gallstone prevalence increases with age and in females in the general population.

Conversely, the mechanisms related to gallstone formation in patients with liver cirrhosis are different. These factors are possibly not age- or sex-dependent. Therefore, gallstones may develop in a cirrhotic independent of age or sex. In patients with cirrhosis, most gallstones are black pigment stones and they are formed by supersaturation of calcium bilirubinate in bile [1,18]. The findings of our study confirm that pigment stones are by far the most common type of gallstones in patients with liver cirrhosis.

Gallstone formation in patients with liver cirrhosis is possibly multifactorial [19]. The proposed mechanisms include chronic hemolysis secondary to hypersplenism, changes in bile constituents, and increase in estrogen levels [16, 19, 20]. Alvaro et al [14] have reported that a low

ratio of bile salt to unconjugated bilirubin and high levels of monoconjugated bilirubin represent two independent physico-chemical factors predisposing cirrhotic patients to pigmentary cholelithiasis. Gallbladder dysmotility due to autonomic neuropathy and/or increased gallbladder wall thickness may also be a contributory factor to stone formation in cirrhotics [5, 11].

It is concluded from the present study that the prevalence of cholelithiasis is higher in patients with liver cirrhosis who have undergone liver transplantation. In contrast with the general population, the prevalence of cholelithiasis in patients with cirrhosis is similar in both sexes and does not increase with age.

Conflicts of interest

None to declare.

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