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Gallbladder Disease among Obese Patients in Taiwan

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Background: Obesity is a risk factor for gallbladder disease. The authors analyze the prevalence and clinicopathology of gallbladder disease among obese patients in Taiwan.

Methods: Prevalence and various clinical factors associated with cholelithiasis were studied in 199 patients who were undergoing bariatric surgery for obesity. Clinical data (gender, age, BMI and associated diseases), laboratory evaluation and immunoglobulin G antibodies against *Helicobacter pylori* were obtained from the patient records. The histopathologic findings of the gallbladder were also examined retrospectively. The degree of acute inflammation, chronic inflammation, cholesterolosis, cholesterol polyp and gastric metaplasia was determined and scored.

Results: Of the patients, 91% (n=181) were females and 9% (n=18) were males, age 34.26 ± 8.41 years, with mean BMI 35.28 ± 6.11 kg/m^2. The prevalence of cholelithiasis was 10.1%. Increased diastolic blood pressure and HBsAg carrier were the only significant factors associated with cholelithiasis. All obese patients in our study presented with variable degrees of chronic mononuclear cell infiltration in the gallbladder mucosa. Cholesterolosis was present in 100 patients (50.3%), followed by gastric metaplasia (27.1%), cholesterol polyp (16.1%) and acute inflammation (9.5%). Multivariate analysis showed an association between cholelithiasis and acute and chronic inflammation. The predictors of cholesterolosis were BMI, waist circumference and high-sensitivity C-reactive protein. The seroprevalence of *H. pylori* was 42.2%. Older age, abnormal liver function tests, calcium and HBsAg carrier were significantly different between *H. pylori*-seropositive and *H. pylori*-seronegative obese patients. However, we could rarely find *H. pylori* within the gallbladder mucosa.

Conclusion: Cholelithiasis in Asian obese patients is significantly associated with increased diastolic blood pressure and hepatitis B surface antigen carriers. Because chronic liver disease seems to be a risk factor for cholelithiasis in both non-obese and obese populations, prophylactic cholecystectomy can be considered in obese patients with HBsAg positivity. We did not find evidence that *H. pylori* has a role in the pathogenesis of gallbladder disease and gallstone by histologic and serologic examinations. Furthermore, mucosal abnormalities of acute and chronic inflammatory cell infiltration are common in obese patients, which related to cholelithiasis.

Key words: Morbid obesity, gallbladder disease, *Helicobacter pylori*, histopathology

Abbreviations:
BMI, body mass index; *H. pylori*, Helicobacter pylori; HBsAg, hepatitis B surface antigen; GGT, γ-glutamyltransferase; HOMA-IR, homeostatic model assessment method - insulin resistance; ALT, alanine transaminase; AST, aspartate transaminase

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Introduction

Obesity is a pan-endemic health problem in both Western and Eastern countries. Gallstones are a common problem and even a greater problem in the obese population. The prevalence rate for gallstone varies among different populations in the world. Prevalence of gallbladder disease has ranged from 2-15% in various non-obese populations as measured by ultrasonography.[1] Prevalence of gallbladder disease in obese patients undergoing bariatric sur-

gery has been found to range as 60-95% when evaluated by gross and histologic examination after cholecystectomy.[2-7] Dittrick et al[8] concluded that obese patients have an increased incidence of benign gallbladder disease, and the relative risk was correlated with increase in the BMI. Two prospective studies by Csendes et al[9,10] suggested that chronic inflammatory changes could occur prior to the appearance of stones. Morbidly obese patients not only have a high frequency of gallstones, but also a high proportion of abnormal histologic findings in the gallbladder mucosa and a high probability of developing stones after bariatric surgery. Taiwan is a newly industrialized country and the incidence of obesity is accelerating. The prevalence of gallstones for Chinese people in Taiwan was 4.3%, and was associated with age and diabetes mellitus.[11] The prevalence, multiple risk factor analysis and histologic change of gallbladder disease and gallstones in the Eastern Asian obese population have rarely been investigated.

Helicobacter pylori is a gram-negative spiral-shaped bacillus. Recently, *Helicobacter* species and *H. pylori* DNA have been identified in resected gallbladder tissue with chronic cholecystitis and in the bile samples.[12] *Helicobacter* species associated with the pathogenesis of human cholelithiasis and cholecystitis was hypothesized.[13,14] However, controversial results exist, and whether *H. pylori* infection plays a role remains to be determined.[15-18] A large-scale study[19] failed to identify the presence of *H. pylori* in areas of gastric metaplasia of resected gallbladders, suggesting that *Helicobacter* species rarely colonize the gallbladder epithelium. Lack of histological correlation associating *Helicobacter* species with hepatobiliary diseases was also noted.[18,20] *H. pylori* infection is prevalent in Taiwan. As reported by Wu M-S et al,[21] the seroprevalence of *H. pylori* was 43.7% for morbidly obese patients and 60.0% for controls.[21] The relationship of the association of obese patients with gallbladder disease and *H. pylori* remains unclear.

The aim of this study was to retrospectively investigate the clinicopathologic features of gallbladder disease and the association with seroprevalence of *H. pylori* among obese patients in Taiwan.

Materials and Methods

Study Design, Patient Selection and Preoperative Assessment

The retrospective study was performed with approval of the ethics committee of the En-Chu Kong Hospital. From February 1999 to October 2005, extensive preoperative and perioperative data collection on 199 obese patients who underwent concomitant cholecystectomy during weight reduction surgery was evaluated. The inclusion criteria were a history of obesity of >5 years duration, BMI >37 kg/m^2 or BMI >32 kg/m^2 in the presence of diabetes alone or two other significant obesity-related co-morbidities,[22] documented weight-loss attempts in the past, and good motivation for surgery. Written informed consent was obtained from all patients who agreed to undergo weight reduction surgery. Ultrasound of the gallbladder was performed if the patients had symptoms that were suggestive of biliary disease.

The preoperative assessment included a clinical and familial assessment, a psychiatric assessment, anthropometric measurements and laboratory tests. Laboratory tests included blood count tests, liver function tests, fasting lipid profiles, fasting glucose profile, fasting insulin, C-peptide, high-sensitivity C-reactive protein, HbA1c, HOMA-IR= (insulin x glucose)/ 22.5, hepatitis B and C serology (HBsAg and antibody to Hepatitis C virus). Venous blood samples were obtained from the patients and the sera were stored at -70C until tested. A commercially available enzyme-linked immunosorbent assay (ELISA) kit (IBL, Hamburg, Germany) with reported sensitivity and specificity of >95% was used to investigate the prevalence of *H. pylori* infection. All assays were performed in duplicate and interpreted by a single laboratory investigator unaware of the sample status. Western blot assay for IgG was performed if an equivocal result was noted for ELISA.

Pathological Assessment

Sections of gallbladder specimens were examined and histologic parameters graded using hematoxylin-eosin stain. Each specimen was blindly interpreted by one pathologist (P-L L). Parameters included (a) degree of acute inflammation (i.e. epithelial and stromal neutrophil infiltration), (b) chronic inflammation

(mononuclear cell infiltration), (c) cholesterosis, (d) presence of cholesterol polyp and (e) gastric metaplasia. Acute inflammation was graded on a 0 to 3 semi-quantitative scale: (0) no polymorphonuclear (PMN) infiltration, (1) focal mild neutrophil infiltration (<10PMN/high-powered field (HPF)), (2) focal dense neutrophil infiltration (10-20 PMN/HPF), (3) diffuse and dense neutrophil infiltration (>20 PMN/HPF). Mononuclear cell infiltration was scored on a 0 to 3 semi-quantitative scale: (0) no inflammation, (1) mild inflammation (slight increase in mononuclear cells without lymphoid follicles), (2) moderate inflammation (dense but focal mononuclear inflammatory cell infiltrate without lymphoid follicles) and (3) severe inflammation (dense and diffuse mononuclear inflammatory cell infiltration with or without lymphoid follicles). Cholesterolosis was scored on a 0 to 2 semi-quantitative scale: (0) none, (1) mild cholesterolosis and (2) prominent cholesterolosis. Cholesterol polyp was assessed on a 0 to 2 semi-quantitative scale: (0) none, (1) few polyps and (2) many polyps. Gastric metaplasia was assessed on a 0 to 3 semi-quantitative scale: (0) no metaplasia, (1) <10% of mucosa, (2) 10-50% of mucosa, (3) >50% of mucosa. The modified Giemsa stain was used for identification of *H. pylori* in cases of interest.

Statistical Analysis

Data were expressed as median ± interquartile range, mean ± SD and percentages. Statistical analyses were performed using Chi-square test and Mann-Whitney U tests. Multivariate analysis was done on factors that were significant in the univariate analysis. Stepwise selection method, logistic regression and Spearman rank correlation were used to assess the significance of associations between ordinal or continuous predictors' variables. A P-value of <0.05 was considered statistically significant. The SPSS statistical software (SPSS, Inc., Chicago, IL) was used for statistical analysis.

Results

We studied 199 patients consisting of 18 men and 181 women. The mean age was 34.26 ± 8.41 years, and the mean BMI was 35.28 ± 6.11 kg/m^2. Gallstones were detected in 20 patients. The prevalence rate was 10.1% (20/199). Table 1 demonstrates the comparison of demographic and clinical characteristics between patients with cholelithiasis and without cholelithiasis. The diastolic blood pressure (P=0.019) and HBsAg carrier (P=0.036) were significantly different. Further logistic regression analysis showed that only increased diastolic blood pressure (P=0.021) was independently associated with cholelithaisis.

On pathological examination, all obese patients presented with chronic inflammatory cell infiltration in their resected gallbladder specimens (Figure 1). Cholesterolosis (Figure 2) was present in 100 patients (50.3%), gastric metaplasia was present in 54 patients (27.1%), cholesterol polyp was present in 32 patients (16.1%), and 19 patients (9.5%) had acute inflammation. Clinical and laboratory correlations with scored histological features on gallbladder specimen are shown in Table 2. Predictors of the degree of acute inflammation were best correlated with diastolic blood pressure and cholelithiasis. Inverse relationship was noted between acute inflammation and albumin, total protein and high-density lipoprotein cholesterol. Predictors of chronic inflammation were serum ALT, high-sensitivity C-reactive protein and cholelithiasis. The best predictors of cholesterolosis were BMI, waist circumference, hip circumference, waist/hip ratio and high-sensitivity C-reactive protein. Alkaline phosphatase was inversely related to cholesterol polyp. BMI, hip circumference and high-density lipoprotein cholesterol were found to be inversely related to gastric metaplasia.

Serologic testing for *H. pylori* was done in 154 patients, and the seroprevalence of *H. pylori* was 42.2 % (65/154). Clinical characteristics including age (P=0.009), AST (P=0.007), ALT (P=0.001), calcium (P=0.032) and HBsAg carrier (P =0.041) were different between *H. pylori*-positive and *H. pylori*-negative patients. After recheck with logistic regression, only serum calcium showed a significant difference (P=0.042).

Discussion

In this study, we demonstrated that the prevalence of gallstones was 10.1% in our obese patients. The risk factors associated with gallstone formation were diastolic blood pressure and hepatitis B surface anti-

Table 1. Comparison of demographic and clinical characteristics between patients with cholelithiasis and without cholelithiasis

	No Cholelithiasis	Cholelithiasis	All Patients	*P*-value†
Total number (n)	179	20	199	
Age (years)	34.03±8.27	36.30±9.54	34.26±8.41	0.309
Gender (n)[F/M]	164/15	17/3	181/18	0.328
BMI (kg/m^2)	35.20±5.81	36.03±8.48	35.28±6.11	0.789
Waist circumference (cm)	106.91±14.78	107.33±17.61	106.95±15.04	0.971
Hip circumference (cm)	117.99±13.29	117.53±18.68	117.95±13.86	0.993
Waist/hip ratio	0.91±0.08	0.92±0.12	0.91±0.09	0.915
Systolic blood pressure (mmHg)	128.78±14.64	133.15±20.52	129.22±15.33	0.386
Diastolic blood pressure (mmHg)	81.61±10.01	88.55±12.95	82.31±10.52	0.019*
Fasting blood sugar (mg/dl)	105.12±36.04	101.15±38.88	104.72±36.25	0.187
Total cholesterol (mg/dl)	199.96±34.14	199.25±28.10	199.89±33.52	0.941
Triglyceride (mg/dl)	169.55±138.55	165.55±+95.32	169.15±134.65	0.462
UA (mg/dl)	6.93±1.92	6.78±1.70	6.92±1.90	0.910
AST (IU/L)	36.08±33.77	37.05±21.78	36.18±32.72	0.325
ALT (IU/L)	49.84±47.93	55.75±42.06	50.43±47.31	0.344
Albumin (g/dl)	4.46±0.38	4.32±0.28	4.45±0.37	0.063
Alkaline phosphatase (IU/L)	70.50±18.27	62.30±8.81	69.48±17.55	0.113
WBC (1000/μl)	8.03±2.19	8.18±2.20	8.05±2.18	0.454
Hemoglobin (g/dL)	13.18±1.34	13.36±1.62	13.20±1.37	0.317
MCV (fl)	85.83±8.58	89.10±6.37	86.16±8.43	0.080
Insulin (μU/ml)	25.61±41.20	24.72±40.15	25.53±40.96	0.584
hsCRP (mg/L)	0.66±0.76	0.46±0.34	0.64±0.73	0.833
HDL-C (mmol/l)	47.29±11.77	43.92±11.34	46.97±11.73	0.105
HbA1C (%)	6.14±4.93	5.87±1.11	6.11±4.70	0.980
C-peptide (ng/ml)	3.67±2.54	3.87±2.71	3.69±2.54	0.817
Calcium (mg/dL)	8.85±0.25	10.82±4.02	9.24±1.84	0.085
γGT(IU/L)	31.36±18.87	42.80±28.12	33.27±20.56	0.468
HOMA – IR (%)	9.32±262.55	7.07±168.69	9.10±254.45	0.616
HBsAg**	0±0	0±0	0±0	0.036*
Anti-HCV**	0±0	0±0	0±0	0.254
H. Pylori	18.02±22.4	12.07±11.42	17.58±21.81	0.347

NOTE. For continuous demographics and anthropometric: mean ± SD, *P*-value Mann-Whitney U test. Gender, HBsAg and Anti-HCV, *P*-value chi-square test.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; WBC, white blood cell.
*$P<0.05$
**Data are given as median ± interquartile range.
†Data given for the comparison between no cholelithiasis and cholelithiasis groups.

gen (HBsAg) carriers. However, gender, age, BMI, hyperlipidemia, and diabetes mellitus were not significantly associated with gallstones. Further logistic regression analysis revealed that only increased diastolic blood pressure was independently associated with cholelithiasis. Obesity is a chronic inflammatory condition and is strongly linked to raised levels of pro-inflammatory factors.[23] Visceral fat and adipocytes are key regulator sites for the process of inflammation, and atherosclerotic lesions are essentially an inflammatory response. Endothelial activation correlates with visceral body fat, possibly through inappropriate secretion of cytokines.[24] A previous study[25] concluded that subjects with gallstone disease had an increased risk of having coronary heart disease, which is frequently a part of the metabolic syndrome.[26] This study provided evidence of an important role between cholelithiasis, inflam-

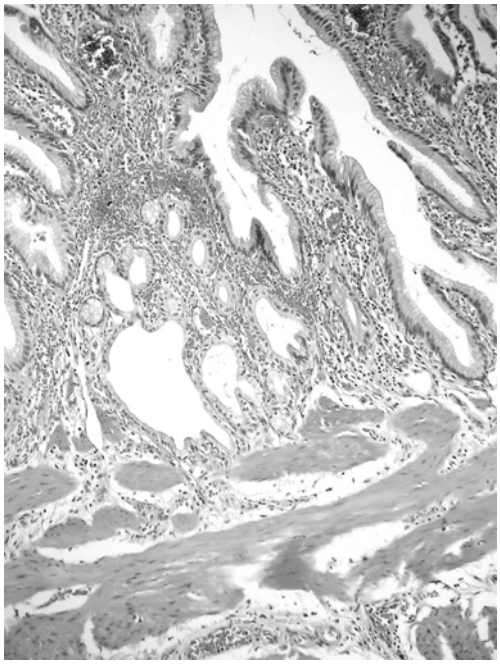

Figure 1. Chronic cholecystitis with inflammatory infiltrate and gastric metaplasia composed of mucin-secreting antral-type glands in the mucosa. (Hematoxylin and eosin; original magnification X 100).

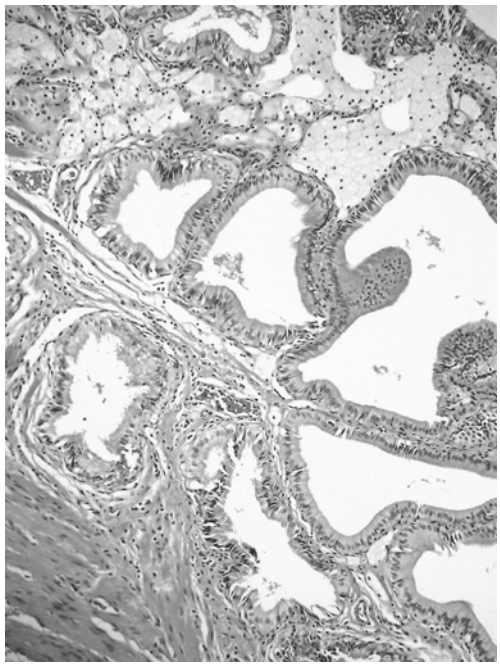

Figure 2. Cholesterolosis with foamy macrophages within the lamina propria. (Hematoxylin and eosin; original magnification X 100).

mation, endothelial dysfunction and increased diastolic blood pressure in the obese population. A prospective study reported by Sheen I-S et al[27] suggested that chronic liver disease, particularly liver cirrhosis, was a risk factor for cholecystolithiasis. This is an interesting issue because Taiwan is an endemic area for hepatitis B virus (HBV) infection, with 15-20% of its population being hepatitis B surface antigen (HBsAg) carriers, including many with chronic hepatitis and liver cirrhosis. Besides, Taiwan has a relative lower prevalence of gallstones[11] than in Western populations. The true prevalence of gallbladder disease and gallstones in obese patients with chronic liver disease is undetermined. It is a unique opportunity to examine the prevalence of gallstones in this particular obese population. In our study, HBsAg was positive in 13.4% of 199 obese patients; further studies between the roles for virology factor of hepatitis B in gallstone formation with the progression of liver disease are needed in a larger cohort with a control non-obese population.

It has been well known that the prevalence of cholelithiasis increased along with the increasing duration and severity of chronic liver disease. The prevalence of cholelithiasis in liver cirrhotic patients was 4 to 5.5 times higher than that of the healthy population. Steatosis was the basic liver cell injury and was common in morbidly obese patients. The prevalence of nonalcoholic fatty liver disease is 74-98%, while that of nonalcoholic steatohepatitis (NASH) is up to 37% in the obese.[28] About 15-20% of patients with NASH develop cirrhosis. A previous study in Taiwan demonstrated the relative risk for fatty liver was 1.77 (0.86-3.62, 95% confidence interval; *P* value 0.08) among gallstone cases in the normal control population.[11] The prevalence and associated factors of gallstone disease in non-alcoholic fatty liver have been studied, both sharing insulin resistance as the common pathogenic mechanism.[29] Further studies are needed to clarify the relationship of cholelithiasis among chronic hepatitis B carriers concurrent with steatohepatitis and liver cirrhosis in obese patients.

The present study is the first report assessing the histological findings using a scoring system comprised of acute inflammation, chronic inflammation, cholesterolosis, cholesterol polyp and gastric metaplasia in gallbladder tissue in obese patients. Our results agree with the previous reports that histological changes in the gallbladder could occur prior to

Table 2. Analysis of the association between clinical and laboratory data and histological features (n=199)

	Acute Inflammation [0-3]	Chronic Inflammation [0-3]	Cholesterolosis [0-2]	Cholesterol Polyp [0-1]	Gastric Metaplasia [0-3]
Age (years)	NS	NS	NS	NS	NS
Gender (n)[F/M]	NS	NS	NS	NS	NS
BMI (kg/m^2)	NS	NS	0.255**	NS	-0.172*
Waist circumference (cm)	NS	NS	0.252**	NS	NS
Hip circumference (cm)	NS	NS	0.176*	NS	-0.169*
Waist/hip ratio	NS	NS	0.191*	NS	NS
Systolic blood pressure (mmHg)	NS	NS	NS	NS	NS
Diastolic blood pressure (mmHg)	0.152*	NS	NS	NS	NS
Fasting blood sugar (mg/dl)	NS	NS	NS	NS	NS
Total cholesterol (mg/dl)	NS	NS	NS	NS	NS
Triglyceride (mg/dl)	NS	NS	NS	NS	NS
AST (IU/L)	NS	NS	NS	NS	NS
ALT (IU/L)	NS	0.152*	NS	NS	NS
Albumin (g/dl)	-0.156*	NS	NS	NS	NS
Alkaline phosphatase (IU/L)	NS	NS	NS	-0.235*	NS
Insulin (μU/ml)	NS	NS	NS	NS	NS
hsCRP (mg/L)	NS	0.183*	0.256**	NS	NS
Total protein (g/dL)	-0.203*	NS	NS	NS	NS
HDL-C (mmol/l)	-0.226*	NS	NS	NS	NS
HOMA – IR (%)	NS	NS	NS	NS	-0.163*
HBsAg	NS	NS	NS	NS	NS
Anti-HCV	NS	NS	NS	NS	NS
H. Pylori	NS	NS	NS	NS	NS
Cholelithiasis	0.271**	0.275**	NS	NS	NS

NOTE. Spearman correlation coefficients used for continuous clinical and laboratory variables.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
**Correlation is significant at 0.01 level (2-tail).
*Correlation is significant at 0.05 level (2-tail).

the appearance of gallstones.[8-10] Nearly all obese patients in our study presented with variable degrees of chronic mononuclear cell infiltration in the gallbladder mucosa, and 50.3% presented with cholesterolosis. The best predictors of chronic inflammation were serum ALT, high-sensitivity C-reactive protein and cholelithiasis. In addition, cholesterolosis was best correlated with body weight, BMI, waist and hip circumferences, waist/hip ratio and high-sensitivity C-reactive protein. It was interesting to find that both acute and chronic inflammation were significantly associated with gallstone formation. The significance of pathological findings of inflammatory cell infiltration and cholesterolosis with respect to the development of gallbladder disease and gallstone is not clear.

A pathological role of *H. pylori* with respect to the development of gallstone was not found in our study. We could rarely find *H. pylori*-like microorganism on histopathologic examination. A previous study from Korea concluded that *H. pylori* DNA may be present in the bile but did not colonize the bile duct epithelium.[18] The incidence of *H. pylori* seroprevalence in our obese patients undergoing cholecystectomy was 42.2%. Our obese patients positive for *H. pylori* were associated with older age, decreased liver function tests, increased serum calcium and HBsAg carrier. We did not investigate *H. pylori* DNA determined by polymerase chain reaction and sequence analysis from the resected gallbladder. Our results do not exclude the possibility of *Helicobacter* infection as a cofactor in the development of gallstones.

Obesity and rapid weight loss induced by bariatric surgical procedures are both risk factors for the development of cholelithiasis.[30-32] Preoperative ultrasonography[33] or intraoperative findings other than palpable gallstones were inaccurate at predicting those patients who would benefit from concomitant cholecystectomy. A review of the current standard care for cholecystectomy for patients undergoing bariatric surgery was conducted.[34] A study indicated that a noninterventionist approach to the gallbladder was appropriate for patients undergoing adjustable gastric banding surgery.[35] Our study did not examine the prevalence and risk factors of gallstone formation after bariatric operations. Further study is warranted to estimate the risk for developing gallstone and gallbladder disease after bariatric surgery in the Asian obese population.

In conclusion, the prevalence of cholelithiasis is lower in Asian than in Western obese patients and is significantly associated with increased diastolic blood pressure and hepatitis B surface antigen carriers. Chronic liver disease seems to be a risk factor for cholelithiasis in both non-obese and obese populations. Prophylactic cholecystectomy can be considered in HBsAg positive obese patients. *H. pylori* has no role in the pathogenesis of gallbladder disease and gallstones by histologic and serologic examinations. Furthermore, mucosal abnormalities of acute and chronic inflammatory cell infiltration are common in obese patients, which related to cholelithiasis.

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