

Retrospective Study

Cholecystectomy does not significantly increase the risk of fatty liver disease

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Abstract

AIM: To investigate the relationship between cholecystectomy and fatty liver disease (FLD) in a Chinese population.

METHODS: A total of 32428 subjects who had voluntarily undergone annual health checkups in the Second Affiliated Hospital of Nanjing Medical University from January 2011 to May 2013 were included in this study. Basic data collection, physical examination, laboratory examination, and abdominal ultrasound examination were performed.

RESULTS: Subjects undergoing cholecystectomy were associated with greater age, female sex, higher body mass index, and higher levels of systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, and triglycerides. However, no significant differences were found in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, albumin, and serum uric acid. The overall prevalence of FLD diagnosed by ultrasonography was high at 38.4%. The prevalence of FLD was significantly higher for subjects who had undergone cholecystectomy (46.9%) than those who had not undergone cholecystectomy (38.1%; χ^2 test, $P < 0.001$). Cholecystectomy was positively associated with FLD (OR = 1.433, 95%CI: 1.259-1.631). However, after adjusting for possible factors associated with

FLD, multivariate regression analysis showed that the association between cholecystectomy and FLD was not statistically significant (OR = 1.096; 95%CI: 0.939-1.279).

CONCLUSION: According to our study results, cholecystectomy may not be a significant risk factor for FLD.

Key words: Cholecystectomy; Fatty liver disease; Relationship; Cross-sectional study

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Core tip: The prevalence of fatty liver disease (FLD) without cholecystectomy was 38.1%, and was up to 46.9% with cholecystectomy, showing an increase in the prevalence of FLD after cholecystectomy. However, no significant association was found between cholecystectomy and FLD after adjusting for multiple related factors. To the best of our knowledge, this is the first study on the correlation between cholecystectomy and FLD in a large Chinese population.

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INTRODUCTION

Fatty liver disease (FLD) is a leading cause of chronic liver disease in China^[1], and is classified as nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease according to etiology^[2,3]. Recent population-based epidemiological studies indicate that the median prevalence of FLD in China is 17% (12.5%-27.3%), and approximately 90% of cases appear to be nonalcoholic^[4-8]. FLD may progress to end-stage liver disease and then to steatohepatitis, advanced fibrosis, cirrhosis, and hepatocellular carcinoma^[1,2,8-10]. Although it is not a direct cause of death, FLD is considered a preclinical condition related to cardiovascular disease and other metabolic diseases^[2,9,11,12].

Cholecystectomy is one of the most common surgical procedures due to its curative effect. However, there are many long-term complications associated with this procedure. Whether cholecystectomy is a risk factor for FLD requires further study. According to a recent report^[13], the prevalence of NAFLD has increased possibly due to the metabolic effects of the absence of the gallbladder after cholecystectomy. Cholecystectomy in mice also led to FLD by changing triglyceride metabolism^[14]. This may be interpreted as an alteration in the enterohepatic circulation of

bile acids^[15] and the loss of metabolic activity of the gallbladder mucosa^[16]. However, these reports are not enough to confirm this conclusion. Whether cholecystectomy increases the prevalence of FLD requires more research. In this study, we attempted to determine the association between cholecystectomy and FLD in a large population-based study.

MATERIALS AND METHODS

All participants were informed about the purpose and general procedures of the examination. The Ethics Committee of Nanjing Medical University approved the study protocol and manner of consent.

Study subjects were recruited from participants who had voluntarily undergone annual health checkups at the Second Affiliated Hospital of Nanjing Medical University between January 2011 and May 2013. The analyses were limited to the subjects who underwent abdominal ultrasonography, and those who had full records of anthropometric and biochemical data. The subjects were included if they complied with the following criteria: (1) absence of markers of hepatitis B virus infection (hepatitis B surface antigen) and hepatitis C virus (HCV) infection (anti-HCV antibody); (2) no previous history of liver disease, including fatty liver; and (3) the absence of other factors inducing fatty changes in the liver, including the use of liver damaging drugs, and autoimmune diseases. Finally, a total of 32428 subjects (22463 men and 9965 women) were enrolled.

Clinical examinations were performed by trained staff using standardized procedures. Height and weight were measured using an automatic digital stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After resting for at least ten minutes, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured. Venous blood samples were also obtained from subjects following an overnight fast of more than eight hours and alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), fasting plasma glucose (FPG), albumin, and serum uric acid (SUA) levels were measured using standard techniques. All subjects received abdominal ultrasonography to determine FLD and cholecystectomy combined with a surgical history.

Statistical analyses were performed using SPSS 18.0 software for Windows (SPSS Inc., Chicago, IL, United States). Due to non-normal distribution, continuous variables were expressed as median and interquartile range (25%-75%) due to abnormal distribution of the data. Comparisons between the independent groups were conducted using the Mann-Whitney *U* test. Categorical variables were compared

Table 1 Demographics and clinical characteristics of the subjects according to cholecystectomy

	With cholecystectomy (<i>n</i> = 949)	Without cholecystectomy (<i>n</i> = 31479)	<i>P</i> value
Age (yr)	63 (54-73)	49 (36-59)	< 0.001
Sex (male/female)	447/502	22016/9463	< 0.001
BMI (kg/m ²)	24.26 (22.55-26.65)	23.92 (21.71-26.09)	< 0.001
SBP (mmHg)	131 (121-141)	125 (116-135)	< 0.001
DBP (mmHg)	80 (72-88)	77 (69-86)	< 0.001
FPG (mmol/L)	5.41 (4.97-5.99)	5.04 (4.68-5.47)	< 0.001
TC (mmol/L)	5.07 (4.43-5.74)	4.93 (4.34-5.57)	< 0.001
TG (mmol/L)	1.28 (0.92-1.74)	1.14 (0.82-1.67)	< 0.001
HDL cholesterol (mmol/L)	1.28 (1.10-1.51)	1.28 (1.09-1.50)	0.240
LDL cholesterol (mmol/L)	2.88 (2.37-3.42)	2.88 (2.39-3.40)	0.987
ALT (U/L)	19 (14-26)	19 (14-27)	0.132
AST (U/L)	20 (17-24)	20 (17-24)	0.237
GGT (U/L)	22 (16-33)	22 (15-36)	0.243
Albumin (g/L)	47.7 (45.8-49.3)	47.7 (45.6-49.6)	0.835
SUA (mmol/L)	327 (265-379)	329 (275-386)	0.070
FLD (yes/no)	445/504	12003/19476	< 0.001

The data are expressed as the median (IQR) due to abnormal distribution. Mann-Whitney *U* and χ^2 test were performed. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; SUA: Serum uric acid; FLD: Fatty liver disease.

Table 2 Logistic regression analysis of odds ratios for fatty liver disease relative to cholecystectomy

	Multivariate regression analysis		
	OR	95%CI	<i>P</i> value
Cholecystectomy (not adjusted)	1.433	1.259-1.631	< 0.001
Cholecystectomy (adjusted ¹)	1.096	0.939-1.279	0.245

¹Data were adjusted for age, gender, BMI, SBP, DBP, FPG, TC, TG, HDL cholesterol, LDL cholesterol, ALT, AST, GGT, albumin, and SUA. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; SUA: Serum uric acid.

using the χ^2 test. Multivariate logistic regression analyses were conducted to assess the odds ratio (OR) for FLD, comparing subjects with cholecystectomy to those without cholecystectomy. *P* < 0.05 (2-tailed) was considered statistically significant.

RESULTS

Of 32428 subjects enrolled in this study, 949 subjects had a history of cholecystectomy. Compared with subjects without cholecystectomy, cholecystectomy was associated with higher age, female sex, higher BMI, and higher levels of SBP, DBP, FPG, TC, and TG. However, between the two groups, no significant differences were found in HDL cholesterol, LDL cholesterol, ALT, AST, GGT, albumin, and SUA (Table 1). These results indicate that cholecystectomized subjects may not have more metabolic abnormalities than those without cholecystectomy, particularly serum lipids and liver function abnormalities.

In this study, the overall prevalence of FLD diagnosed by ultrasonography was high at 38.4%. Using the χ^2 test, the prevalence of FLD was significantly higher for cholecystectomized subjects (46.9%) than those without cholecystectomy (38.1%; χ^2 test, *P* < 0.001). In addition, logistic regression analysis, not considering other risk factors, showed that cholecystectomy was positively associated with FLD (OR = 1.433, 95%CI: 1.259-1.631) (Table 2). In order to avoid the influence of other relevant factors, multiple logistic regression analysis was further performed to investigate the ORs for FLD with cholecystectomy. After adjusting for possible factors associated with FLD, multivariate regression analysis showed that the association between cholecystectomy and FLD was not statistically significant (OR = 1.096; 95%CI: 0.939-1.279). These results may indicate that there is no significant association between cholecystectomy and FLD.

DISCUSSION

Several studies have investigated the positive association between cholecystectomy and FLD^[13,14]. However, in our study, the results indicated that cholecystectomy may not be associated with FLD. Although the prevalence of FLD in the cholecystectomized subjects was higher than those without cholecystectomy, no significant association was found between cholecystectomy and FLD after adjusting for multiple related factors.

In a population from the United States, the prevalence of NAFLD with cholecystectomy was 48.4%. In addition, the prevalence was higher than that in subjects with (34.4%) or without gallstone disease (17.9%). Controlling for numerous factors associated with both NAFLD and gallstone disease, multivariate-adjusted analysis confirmed the association between

NAFLD and cholecystectomy (OR = 2.4; 95%CI: 1.8-3.3), indicating that cholecystectomy may be a risk factor for NAFLD^[13]. In our study, the prevalence of FLD without cholecystectomy was 38.1%, and was up to 46.9% with cholecystectomy, showing an increase in the prevalence of FLD after cholecystectomy. However, no significant association was found when adjusted by age, gender, BMI, SBP, DBP, FPG, TC, TG, HDL cholesterol, LDL cholesterol, ALT, AST, GGT, albumin, and SUA. These metabolic factors are closely related to FLD. Therefore, to study the relationship between cholecystectomy and FLD, these metabolic factors should be considered.

The previous study from the United States^[17] found that subjects with cholecystectomy were more likely to have elevated serum ALT and GGT, and was associated with the development of cirrhosis. However, the levels of serum liver enzymes, including ALT, AST and GGT, were not changed after cholecystectomy in our study. There is no reasonable explanation for this, although different eating habits and different BMI between subjects in the United States and China may play a part. In addition, several possible biological mechanisms were analyzed. Following cholecystectomy, bile is continuously secreted into the duodenum, and the bile acid pool circulates more quickly, exposing the liver to a greater flux of bile acids^[18-20]. The gallbladder mucosa is metabolically active, secreting and absorbing compounds to and from the bile and loss of the gallbladder provides another possible mechanism for the increased risk of NAFLD following cholecystectomy^[13].

However, our results are not entirely consistent with other studies, which might be due to the following shortcomings. First, information regarding smoking and drinking status, physical activity, and the surgical approach for cholecystectomy (open or laparoscopic) were not available, and these factors may act as confounding variables in the association between cholecystectomy and FLD. Further longitudinal studies should consider these confounding factors. Second, the causal relationship between cholecystectomy and FLD might not be reliable using a cross-sectional analysis, although we ensured all cholecystectomy subjects had no FLD before cholecystectomy. Thus, a prospective cohort study may be more convincing. Finally, the study subjects were recruited at one provincial hospital and therefore may not represent the entire community. Fortunately, these limitations may be partly balanced by the benefits of using a large population-based sample, particularly the avoidance of ascertainment bias which occurs in studies of selected patients.

In conclusion, in 32428 Chinese subjects, cholecystectomy might not be a significant risk factor for FLD according to our findings. Further studies should be performed to verify these results due to the limitations of our study.

COMMENTS

Background

Fatty liver disease (FLD) is considered a preclinical condition related to cardiovascular disease and other metabolic diseases. It has been reported that the prevalence of nonalcoholic fatty liver disease (NAFLD) has increased possibly due to the metabolic effects of the absence of the gallbladder after cholecystectomy. However, whether cholecystectomy is a risk factor for FLD remains to be further studied.

Research frontiers

In a population from the United States, the prevalence of NAFLD with cholecystectomy was 48.4%. The prevalence was higher than that in subjects with (34.4%) or without gallstone disease (17.9%). Controlling for numerous factors associated with both NAFLD and gallstone disease, multivariate-adjusted analysis confirmed the association between NAFLD and cholecystectomy (OR = 2.4; 95%CI: 1.8-3.3), indicating that cholecystectomy may be a risk factor for NAFLD.

Innovations and breakthroughs

In this study, the prevalence of FLD without cholecystectomy was 38.1%, and was up to 46.9% with cholecystectomy, showing an increase in the prevalence of FLD after cholecystectomy. However, no significant association was found between cholecystectomy and FLD after adjusting for multiple related factors.

Applications

In this study, cholecystectomy may not be a significant risk factor for FLD in our 32428 Chinese subjects. Further studies should be performed to verify the results due to the limitations of our study.

Peer-review

As the manuscript point out, FLD was classified as NAFLD and alcoholic liver disease. The author analysis the data by combining the two types, and concluded that cholecystectomy does significantly increase the risk of FLD.

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