World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i23.3015

World J Gastroenterol 2012 June 21; 18(23): 3015-3019
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Analysis of risk factors for polypoid lesions of gallbladder among health examinees

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Received: January 28, 2012 Revised: March 20, 2012
Accepted: April 9, 2012
Published online: June 21, 2012

Abstract

AIM: To investigate the prevalence and risk factors of polypoid lesions of gallbladder (PLG) among the health examinees in the Shanghai region, China.

METHODS: A total of 11 816 subjects who underwent health examinations in our hospital between August 2010 and February 2011 were analyzed retrospectively. Among them, there were 7174 men and 4642 women. PLG was diagnosed by the real-time ultrasonography. Those with the body mass index (BMI) $\geqslant$ 28 were considered to be obese. Blood biochemical indices were detected with the fully automatic biochemical analyzer and hepatitis B surface antigen (HBsAg) was tested by the automated enzyme immunoassay. The correlations between the prevalence of PLG and age, sex, BMI, serum cholesterol (T-Cho), triglycerides (TG), blood sugar, HBsAg, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), gallstone and fatty liver were investigated. After univariate analysis of 11 variables, stepwise logistic regression analysis was performed to explore the risk factors of PLG.

RESULTS: There was a significant difference in sex, T-Cho, HBsAg, HDL-C, LDL-C and fatty liver between the PLG-positive group and the PLG-negative group (332/163 *vs* 6842/4479, P = 0.003; 22/473 *vs* 295/11 026, P =0.013; 92/403 *vs* 993/10 328, P = 0.001; 47/448 *vs* 332/10 989, P = 0.001; 32/463 *vs* 381/10 940, P = 0.001; 83/412 *vs* 3260/8061, P = 0.001). No significant difference was found in the age, BMI, TG, blood sugar and gallstone between the two groups (47.3 ± 26 *vs* 45.1 ± 33, P = 0.173; 59/436 *vs* 1097/10 224, P = 0.102; 52/443 *vs* 982/10 339, P = 0.158; 17/478 *vs* 295/11 026, P = 0.26; 24/471 *vs* 395/10 926, P = 0.109). Logistic regression analysis showed that the sex, HBsAg and HDL-C were independent risk factors for the development of PLG in a descending order of HDL-C > HBsAg > sex.

CONCLUSION: In healthy people, the male gender, positive HBsAg, and low HDL-C confer higher risks of PLG development.

Key words: Polypoid; Gallbladder; Risk factors; Ultrasonography; Health examination

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Yang HL, Kong L, Hou LL, Shen HF, Wang Y, Gu XG, Qin JM, Yin PH, Li Q. Analysis of risk factors for polypoid lesions of gallbladder among health examinees. *World J Gastroenterol*

2012; 18(23): 3015-3019 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i23/3015.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i23.3015

INTRODUCTION

The prevalence of polypoid lesions of gallbladder (PLG), a common clinical gallbladder disease, is about 3%, with an increasing trend[1,2]. PLG is the general term of the limited abnormal accumulations of mucous membrane tissue of the gallbladder or the limited lesion projecting into the lumen of the gallbladder. Clinically, the types of polypoid growth of the gallbladder mainly includes cholesterol polypoid/cholesterosis, inflammatory polyp, cholesterosis with fibrous dysplasia of gallbladder, adenomyomatosis, hyperplastic cholecystosis and adenocarcinoma. Ultrasonography (US) is a convenient and non-traumatic modality used to profile the gallbladder and the position of the lesion. The application of US has improved significantly the detection rate of PLG. It is of great clinical significance to analyze the risk factors of PLG in an attempt to improve its prevention and diagnosis. This study retrospectively analyzed the prevalence and risk factors of PLG among 11 816 health examinees in our clinical center. Through the univariate and multivariate analyses, this study aimed to provide the first-hand evidences for the primary prevention of PLG.

MATERIALS AND METHODS

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The study protocol was approved ethically by Putuo Hospital. All patients provided informed written consent.

Subjects

A total of 11 816 subjects, including 7174 men and 4642 women with an average age of 48.6 ± 31 years (range, 15-86 years) who underwent health examinations in our health center between August 2010 and February 2011, were included in this study.

Diagnosis of polypoid lesions of gallbladder

The subjects were examined with ultrasonography using a real-time scanner with a 3.5 MHz array transducer (Philips En Visor and Philips-iU22) in the early morning after fasting for about 8-12 h. They were required to stay supine or change the position when it is necessary. The gallbladder was observed through multiple cross sections to detect the size, shape, number, location, internal echo, basal part, local cyst wall and the movement of lesions with the position change.

The diagnosis of gallbladder polyps was established according to the following criteria: (1) Spherical, mulberry-like or papillary projections, derived from either pedunculated or narrow bases, and no change after position change; (2) Multiple echogenic spots which could be found in any part of the gallbladder, e.g., the gallbladder neck, body or bottom, especially in the body and bottom of the gallbladder; (3) Small echogenic spots, usually less than 10 mm; and (4) Hyperechoic (more visible) or medium echoic structures without acoustic shadow.

Measurement of body weight

We measured the body mass index (BMI) of the subjects following "The Prevention and Control Guideline for Overweight and Obesity among Chinese Adults"[3], and BMI was calculated by dividing the mean weight by the mean height squared (kg/m^2). BMI $\geqslant$ 28 was defined as obesity.

Determination of blood biochemical indices and hepatitis B surface antigen

Blood serum samples of 5 mL were routinely collected intravenously in the morning before breakfast. Cholesterol (T-Cho), triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) and blood glucose levels were detected and analyzed using a Hitachi 7020 Automatic Biochemical Analyzer. Hepatitis B surface antigen (HBsAg) was detected with an Italy RB 138 Automated Enzyme Immunoassay Analyzer. The reagents used were offered by the Shanghai Kehua Bioengineering Co., Ltd, Shanghai, China. The tests were undertaken strictly according to the instructions of the manufacturers.

Statistical analysis

Results were expressed as mean ± SD. We analyzed 11 variables with univariate analysis to compare the differences between the two groups. Variables (age, sex, BMI, T-Cho, TG, HDL-C, LDL-C, glucose, HBsAg, gallstones and fatty liver) were defined as independent variables and the PLG was defined as a dependent variable. They were examined in a multivariate model using forward stepwise maximum likelihood logistic regression to identify the risk factors of PLG ($\alpha = 0.05$). The variable assignment is shown in Table 1. Data were analyzed using the SPSS version 13.0 statistical software and significance was set at $P < 0.05$.

RESULTS

General data of patients with PLG

The overall prevalence of PLG found among the health examinees was 4.2% (495/11 816). The incidence of PLG was 4.6% (332/7174) in men and 3.5% (163/4642) in women. Overall, males had a significantly higher prevalence of PLG than females (4.6% *vs* 3.5%, $P = 0.003$). In this group, the incidence of obesity was 9.8% (1156/11 816); the rates of increased T-Cho, TG and LDL-C were 2.7% (317/11 816), 8.8% (1034/11 816) and 3.5% (413/11 816), respectively; the rate of high blood sugar was 2.6% (312/11 816), and the incidence of low

Table 1 Instructions of assignment of variables for polypoid lesions of gallbladder

	Female = 0	Male = 1
BMI	(< 28) = 0	(≥ 28) = 1
T-Cho	Normal or decreased = 0	Increased = 1
TG	Normal or decreased = 0	Increased = 1
HDL-C	Normal or increased = 0	Decreased = 1
LDL-C	Normal or decreased = 0	Increased = 1
Blood glucose	Normal or decreased = 0	Increased = 1
HBsAg	(-) = 0	(+) = 1
Gallstones	(-) = 0	(+) = 1
Fatty liver	(-) = 0	(+) = 1

BMI: Body mass index; T-Cho: Cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein; LDL-C; Low density lipoprotein; HBsAg: Hepatitis B surface antigen.

Table 2 Results of univariate analysis of the relevant factors of polypoid lesions of gallbladder

	PLG positive	PLG negative
Age (yr)	47.3 ± 26	45.1 ± 33
Sex, male/female	332/163[a]	6842/4479
BMI, ≥ 28/< 28	59/436	1097/10 224
T-Cho, increased/normal or decreased	22/473[a]	295/11 026
TG, increased/normal or decreased	52/443	982/10 339
Glucose, increased/normal or decreased	17/478	295/11 026
HBsAg, +/-	92/403[a]	993/10 328
HDL-C, decreased/normal or increase	47/448[a]	332/10 989
LDL-C, increased/normal or decreased	32/463[a]	381/10 940
Gallstones, +/-	24/471	395/10 926
Fatty liver, +/-	83/412[a]	3260/8061

[a]$P < 0.05$ *vs* negative PLG. PLG: Polypoid lesions of gallbladder; BMI: Body mass index; T-Cho: Cholesterol; TG: Triglyceride; HBsAg: Hepatitis B surface antigen; HDL-C: High density lipoprotein; LDL-C; Low density lipoprotein.

HDL-C was 3.2% (379/11 816); and the incidence of gallstone, the fatty liver and HBsAg (+) was 3.5% (419/11 816), 28.3% (3343/11 816) and 9.2% (1085/11 816), respectively. There were significant differences in sex, T-Cho, HBsAg, HDL-C, LDL-C and fatty liver between the PLG-positive group and the PLG-negative group (332/163 *vs* 6842/4479, $P = 0.003$; 22/473 *vs* 295/11 026, $P = 0.013$; 92/403 *vs* 993/10 328, $P = 0.001$; 47/448 *vs* 332/10 989, $P = 0.001$; 32/463 *vs* 381/10 940, $P = 0.001$; 83/412 *vs* 3260/8061, $P = 0.001$). No significant difference was found in the age, BMI, TG, blood sugar and gallstone, between the two groups (47.3 ± 26 *vs* 45.1 ± 33, $P = 0.173$; 59/436 *vs* 1097/10 224, $P = 0.102$; 52/443 *vs* 982/10 339, $P = 0.158$; 17/478 *vs* 295/11 026, $P = 0.26$; 24/471 *vs* 395/10 926, $P = 0.109$) (Table 2).

Logistic regression analysis of relevant risk factors for PLG

Logistic regression analysis showed that sex, HBsAg and HDL-C were independent risk factors for PLG, in a descending order of HDL-C > HBsAg > sex. The subjects with lower HDL-C had a 3.346 times higher risk of PLG than those who had normal or higher HDL-C. The risk of PLG was 2.563 times higher in HBsAg-positive subjects than in HBsAg-negative ones. Men had a 1.843 times higher risk of PLG than women (Table 3).

Table 3 Logistic regression analysis of multiple relevant factors of polypoid lesions of gallbladder

Variables	OR	95% CI	*P* value
Sex	1.843	1.245-2.789	0.0035
HBsAg	2.563	1.875-3.418	< 0.001
HDL-C	3.346	2.932-4.133	< 0.001

OR: Odds ratio; HBsAg: Hepatitis B surface antigen; HDL-C: High density lipoprotein.

DISCUSSION

PLG, which is often neglected due to lack of significant clinical signs or symptoms, is a common disease found in the ultrasound examinations. In recent years, with changes of diet, acceleration of the pace of life, increasing health awareness and the popularity of ultrasonography, the detection rate of PLG tends to increase, and nearly 85% of PLG are detected in a routine physical examination. It is reported that the prevalence of PLG in the Western society is 1.0%-6.9%[4-6], which is significantly lower than in the Asians. Park *et al*[7] reported that PLG prevalence in the South Korea was about 6.1%. Lin *et al*[8] reported a prevalence of 9.5% in Taiwan. After the logistic regression analysis of 34 669 cases, Lin *et al*[8] showed that the male gender was an independent risk factor of PLG. The domestic studies showed a prevalence of 3% in healthy adults in our country[1,2]. The Logistic regression analysis in this study showed that the gender was an independent risk factor for PLG and males bear a significantly higher risk of PLG than females. The risk of PLG in men was 1.843 times higher than in women.

In China, hepatitis B virus carriers account for 7.2% of the population. HBsAg infection may lead to acute or chronic hepatitis. In acute hepatitis, gallbladder wall thickening, volume change and abnormal bile composition can occur and the normal systolic and diastolic functions may be disrupted[9]. Cholesterol polyp is the most common type among PLGs. Compared with non-hepatitis B patients, chronic hepatitis B patients are prone to PLG and the possible causes include: (1) Liver cell cholesterol metabolic disorders may lead to the alteration of the bile composition and quantity, and increased cholesterol in the bile of the gallbladder may easily crystallize and precipitate on the gallbladder wall, resulting in abnormal deposition; (2) Hepatitis B virus activates the immune system to produce autoimmune inflammation, leading to an increased activity of the gallbladder macrophages for cholesterol phagocytosis; (3) Gastrointestinal hormone secretion and metabolic disorder may cause tension adjustment disorder of the sphincter of Oddi, causing increased bile viscosity and poor drainage; and (4) Damages of the liver Kupffer cells may compromise the

detoxification of microbial toxins and phagocytic functions. Together with the small bile ducts and capillary damage, microorganisms and toxins can invade the gallbladder[10]. Our data showed that compared with PLG-negative group, PLG-positive group had a significantly higher incidence of hepatitis B virus infection. The logistic regression analysis showed that positive HBsAg was a risk factor for PLG. Lin *et al*[8] also reported that positive HBsAg was an independent risk factor for PLG. But there are some contrary reports[11]. The inconsistent findings may be related to the number of cases, sex ratio, ethnic differences and other factors. The role of hepatitis B virus in PLG still deserves further studies.

PLG formation mechanisms are very complicated, involving many interacting factors. The mechanisms for cholesterol polyps, the main type of PLG, have been most frequently reported. It has been reported that cholesterol polyps are related to the metabolism of cholesterol in bile. Khairy *et al*[12] found that in 74 patients with cholesterol polyps, 63 (85.1%) patients had elevated plasma cholesterol levels. However, other studies showed that higher plasma T-Cho and TG levels and the incidence of PLG were not necessarily correlated with PLG[13,14]. Ivanchenkova *et al*[15] and Zák *et al*[16] found that plasma HDL-C levels in patients with cholesterol polyps were significantly lower than in the control group, while LDL-C levels were significantly increased. Our data showed that compared with PLG-negative group, T-Cho and LDL-C levels were significantly higher in PLG-positive group while HDL-C levels were significantly lower. The TG level showed no significant difference between the two groups. Consistent with the report by Cantürk *et al*[17], our study showed that low HDL-C level was a risk factor for PLG. Currently, whether the cholesterol deposited in the gallbladder is from the plasma and the relevance between plasma TG level and PLG still remain unclear. Most studies have focused on the mechanisms of absorption and excretion of cholesterol by the mucosa of the gallbladder[18].

Although PLG is an independent disease, it is closely related to the occurrence of the gallbladder stone, which is commonly seen in PLG patients. Studies showed that PLG was often accompanied with stones, and Ito *et al*[19] reported that the rate of PLG with stones was 12%. Colecchia *et al*[20] believed that metabolic disorders of cholesterol existed in both PLG and gallbladder stones, which shared the common pathogenesis. However, these two diseases were not necessarily correlated. Our study showed that the incidence of the gallbladder stone was not significantly different between PLG-positive and PLG-negative groups.

In recent years, the prevalence of diabetes, fatty liver and obesity has been increasing year by year, affecting more and more people at younger ages. These three morbidities all belong to metabolic disorders and their roles in PLG are not consistent among previous reports[11,21,22]. Our study demonstrated that the incidences of fatty liver were not statistically different between PLG-positive and PLG-negative groups, nor the plasma glucose and obesity. The logistic regression analysis showed that diabetes, fatty liver and obesity were not risk factors of PLG.

The exact mechanisms underlying PLG pathogenesis are still not clear. This retrospective analysis has demonstrated that low HDL-C level, male gender and positive HBsAg are the risk factors for PLG, and these findings will provide the related evidence and guidance for health education, and prevention and treatment of PLG.

COMMENTS

Background

Polypoid lesions of gallbladder (PLG) are tumor or tumor-like projections, referring to any mucosal projection into the lumen of the gallbladder which is usually non-neoplastic (> 95%), but may infrequently be neoplastic (< 5%) in nature. The diagnosis of gallbladder polyps is relatively easy by ultrasonography. Although numerous studies have focused on gallbladder polyps, little has been known about factors associated with the occurrence of PLG. The authors aimed to investigate the prevalence and possible risk factors of PLG in a health screening population of Shanghai region.

Research frontiers

The incidence of PLG has an increasing tendency in recent years. The reports and analysis on the risk factors of PLG were not consistent. The literatures mostly focus on gender, lipid metabolism disorders, gallstones, hepatitis B, glucose metabolism disorders, gallbladder local inflammation and so on. Inconsistencies may be related to race, lifestyle, culture, geographic characteristics worldwide, as well as experimental design and other factors.

Innovations and breakthroughs

In China, especially in the Shanghai region, there have been few larger sample analyses on the risk factors of PLG. In this study, the authors reported that the male gender, positive hepatitis B surface antigen, and low high-density lipoprotein are high-risk factors for developing PLG in healthy people.

Applications

The study is conducive to the prevention and treatment of PLG. The relationship between gender, hepatitis B and high-density lipoprotein and PLG is worthy of further studies.

Peer review

It is an interesting topic. The authors analyzed the risk factors for polypoid lesions of gallbladder in a population of health examinees in the Shanghai region.

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