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BRIEF ARTICLES

Gender and metabolic differences of gallstone diseases

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Abstract

AIM: To investigate the risk factors for gallstone disease in the general population of Chengdu, China.

METHODS: This study was conducted at the West China Hospital. Subjects who received a physical examination at this hospital between January and December 2007 were included. Body mass index, blood pressure, fasting plasma glucose, serum lipid and lipoproteins concentrations were analyzed. Gallstone disease was diagnosed by ultrasound or on the basis of a history of cholecystectomy because of gallstone disease. Unconditional logistic regression analysis was used to investigate the risk factors for gallstone disease, and the Chi-square test was used to analyze differences in the incidence of metabolic disorders between subjects with and without gallstone disease.

RESULTS: A total of 3573 people were included, 10.7% (384/3573) of whom had gallstone diseases. Multiple logistic regression analysis indicated that the incidence of gallstone disease in subjects aged 40-64 or ⩾ 65 years was significantly different from that in those aged 18-39 years ($P < 0.05$); the incidence was higher in women than in men ($P < 0.05$). In men, a high level of fasting plasma glucose was obvious in gallstone disease ($P < 0.05$), and in women, hypertriglyceridemia or obesity were significant in gallstone disease ($P < 0.05$).

CONCLUSION: We assume that age and sex are profoundly associated with the incidence of gallstone disease; the metabolic risk factors for gallstone disease were different between men and women.

Key words: Gallstone disease; Metabolic disorder; Risk factor; Sex; Age

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INTRODUCTION

Gallstone disease is prevalent worldwide; however, its prevalence varies by region. In Western countries, the prevalence of gallstone disease reportedly ranges from approximately 7.9% in men to 16.6% in women[1]. In Asians it ranges from approximately 3% to 15%, is nearly non-existent (less than 5%) in Africans[2,3], and ranges from 4.21% to 11% in China[4]. The prevalence of gallstone disease is also high in some ethnic groups, e.g. 73% in Pima Indian women; 29.5% and 64.1% of American Indian men and women, respectively; and 8.9% and 26.7% of Mexican American men and women, respectively[1,5,6]. From a medical economic perspective, gallstone disease is the most common reason for hospitalization and creates a high burden in the United States[7] and other Western countries[8]. Many recent studies have shown that gallstone disease is related to age, sex, and metabolic disorders, such as obesity, dyslipidemia (hypertriglyceridemia), and type 2 diabetes[9-11]. The pathogenesis of gallstone disease is suggested to be multifactorial and probably develops from complex interactions between many genetic and

environmental factors[12,13].

Because of an increase in the Westernization of dietary habits and a decrease in physical activity, the prevalence of gallstone disease has increased in the Chinese population in recent years. From a public health standpoint, it is not only important to study the background prevalence of gallstone disease regionally, but to also explore the demographic and biological markers related to the development of gallstone disease. Meanwhile, gallstone disease can result in serious outcomes, such as acute gallstone pancreatitis and gallbladder cancer. If we can predict which factors contribute to the development of gallstone disease, we can prevent it by controlling these factors. The present study was designed to explore the potential risk factors for gallstone disease and to improve the understanding of the overall pathogenesis of this disease.

MATERIALS AND METHODS

Data resource and data collection

This study was conducted at the physical examination center of West-China Hospital at Sichuan University. This hospital provides medical care mainly for middle- and high-income individuals from Chengdu City and the surrounding metropolitan areas. Our sample population consisted of consecutive subjects who were referred to the physical examination center by their companies as an annual requirement. Data collection, including age, sex, demographic data, history of systemic diseases and gastrointestinal surgery, and a complete physical examination were done by the doctors at the physical examination center. Ultrasonography of the abdomen was conducted by ultrasonographers using a scanner equipped with a 3.5-MHz transducer (Philips Medical Systems, Bothell, USA). Blood samples were drawn *via* venipuncture from the study participants, after they had fasted overnight, by clinical nurses for laboratory examination. Fasting plasma glucose (FPG), triglyceride, total cholesterol, high-density-lipoprotein cholesterol (HDL-C), and low-density-lipoprotein cholesterol (LDL-C) concentrations were measured using Hitachi Modular analyze system (Roche Modular DPP, Hitachi Ltd, Tokyo, Japan).

Diagnosis criteria

Gallstone disease was defined as the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadowing) during abdominal ultrasonography or as a history of cholecystectomy because of gallstone disease.

Obesity was defined as a body mass index (BMI) $\geqslant$ 25 kg/m^2 in both men and women according to the redefined World Health Organization criteria for the Asia Pacific Region[14]. High blood pressure was defined as a systolic blood pressure (SBP) $\geqslant$ 140 mmHg or a diastolic blood pressure (DBP) $\geqslant$ 90 mmHg or a history of hypertension. Subjects with an FPG $\geqslant$ 1260 mg/L and/or a history of diabetes were considered to have diabetes mellitus (DM). Hypertriglyceridemia was defined as a triglyceride concentration $\geqslant$ 1500 mg/L. Low HDL-C was defined as an HDL-C level < 350 mg/L in men or < 390 mg/L in women. Hypercholesterolemia was defined as a total cholesterol level $\geqslant$ 2200 mg/L. High LDL-C was defined as an LDL-C level $\geqslant$ 1550 mg/L.

Table 1 OR of individual risk factors and their association with gallstone disease

Risk factors	*n*	Gallstone (%)	OR	95% CI
Sex				
Men	181/1825	9.9	1.00	-
Women	203/1748	11.6	1.19	0.97-1.48
Age (yr)				
18-39	89/1622	5.5	1.00	-
40-64	226/1695	13.3	2.65	2.05-3.42
$\geqslant$ 65	69/256	27.0	6.36	4.48-9.01
BMI				
< 25.0 kg/m^2	281/2841	9.9	1.00	-
$\geqslant$ 25.0 kg/m^2	103/732	14.1	1.49	1.17-1.90
Hypertension				
No	269/2933	9.2	1.00	-
Yes	115/640	18.0	2.17	1.71-2.75
FPG				
< 1100 mg/L	341/3417	10.0	1.00	-
$\geqslant$ 1100 mg/L and < 1260 mg/L	14/60	23.3	2.75	1.49-5.05
$\geqslant$ 1260 mg/L	29/96	30.2	3.90	2.49-6.12
Triglyceride				
< 1500 mg/L	206/2445	8.4	1.00	-
$\geqslant$ 1500 mg/L	178/1128	15.8	2.04	1.64-2.52
HDL				
< 350 mg/L (men); < 390 mg/L (women)	26/133	19.5	1.00	-
$\geqslant$ 350 mg/L (men); $\geqslant$ 390 mg/L (women)	358/3440	10.4	0.48	0.31-0.74
Total cholesterol				
< 2200 mg/L	343/3323	10.3	1.00	-
$\geqslant$ 2200 mg/L	41/250	16.4	1.70	1.20-2.43
LDL				
< 1550 mg/L	360/3429	10.5	1.00	-
$\geqslant$ 1550 mg/L	24/144	16.7	1.71	1.09-2.68

Statistical analysis

Categorical data are presented as the number of cases and percentages. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). Odds ratios (ORs) were calculated with the variables coded in a multivariate form. Pearson's Chi-square or Fisher's exact tests were used for categorical variables. Multiple logistic regression analysis was performed to investigate the independent factors associated with gallstone disease. In all cases, tests of significance were 2-tailed, $P < 0.05$ indicated statistical significance.

RESULTS

A total of 3573 subjects undergoing an annual health examination from January to December 2007 were included: 1825 men and 1748 women. The prevalence of gallstone disease among the study subjects was 10.7% (384/3573): 9.9% in men and 11.6% in women. The results of univariate analysis of individual factors and their association with gallstone disease among the 3573 subjects are shown in Table 1. The factors significantly

Table 2 Multivariate logistic regression analysis for gallstone disease

Variables	OR	95% CI	*P*
Female sex	1.70	1.35-2.15	< 0.001
Age (yr)			
40 to 64	2.44	1.88-3.17	< 0.001
⩾ 65	5.83	4.02-8.44	< 0.001
FBG ⩾ 1260 mg/L	2.12	1.31-3.43	0.002
Triglycerides ⩾ 1500 mg/L	1.67	1.31-2.13	< 0.001

The dependent variable was the presence or absence of gallstone disease. The covariates included sex, age of 40-64 and ⩾ 65 years, BMI ⩾ 25.0 kg/m^2, high blood pressure (SBP ⩾ 40 mmHg or DBP ⩾ 90 mmHg or a history of hypertension), an FPG level between 1100 and 1260 mg/L and ⩾ 1260 mg/L, a triglyceride level ⩾ 1500 mg/L, an HDL level ⩾ 350 mg/L in men or ⩾ 390 mg/L in women, a total cholesterol level ⩾ 2200 mg/L, and an LDL level ⩾ 1550 mg/L.

associated with gallstone disease were an age of 40-64 years and an age ⩾ 65 years, a BMI ⩾ 25.0 kg/m^2, high blood pressure, an FPG level between 1100 and 1260 mg/L, an FPG level ⩾ 1260 mg/L, a triglyceride level ⩾ 1500 mg/L, a total cholesterol level ⩾ 2200 mg/L, and an LDL level ⩾ 1550 mg/L ($P < 0.05$). In contrast, a low HDL-C level was inversely associated with gallstone disease ($P < 0.05$). As shown in Table 1, the prevalence of gallstone disease for each metabolic disorder was 14.1% for obesity, 18.0% for hypertension, 30.2% for DM, 15.8% for hypertriglyceridemia, and 10.4% for a low HDL-C level.

In order to identify the risk factors, we further performed a multivariate logistic regression analysis (backward stepping); the results are shown in Table 2. Women aged 40-64 years and ⩾ 65 years, with an FPG level ⩾ 1260 mg/L, and a triglyceride level ⩾ 1500 mg/L were positively correlated with gallstone disease.

The incidence of metabolic disorders in the groups with and without gallstone disease is shown in Table 3. Obesity, hypertension, DM, hypertriglyceridemia, a low HDL-C level, and hypercholesterolemia were found in 26.8%, 29.9%, 7.6%, 46.4%, 6.8%, and 10.7% of subjects with gallstone disease, respectively. In the group without gallstone disease, the incidences of obesity, hypertension, DM, hypertriglyceridemia, a low HDL-C level, and hypercholesterolemia were 19.7%, 16.5%, 2.1%, 29.8%, 3.4%, and 6.6%, respectively. The incidences of all metabolic disorders were higher in the group with gallstone disease than in the group without gallstone disease ($P < 0.01$).

The results of univariate analysis of metabolic factors and their association with gallstone disease in different sexes are shown in Table 4. In men, the factors significantly associated with gallstone disease were high blood pressure, an FPG level between 1100 and 1260 mg/L, an FPG level ⩾ 1260 mg/L, and a triglyceride level ⩾ 1500 mg/L ($P < 0.05$). In women, the factors significantly associated with gallstone disease were a BMI ⩾ 25.0 kg/m^2, high blood pressure, an FPG level between 1100 and 1260 mg/L, an FPG level ⩾ 1260 mg/L, a triglyceride level ⩾ 1500 mg/L, a total cholesterol level ⩾ 2200 mg/L, and an LDL-C level ⩾ 1550 mg/L ($P < 0.05$). A low HDL-C level was inversely associated with gallstone disease only in women ($P < 0.05$).

To control the covariates simultaneously, multivariate logistic regression analysis (backward stepping) was performed (Table 5). The analysis revealed that an FPG level ⩾ 1260 mg/L was a significant independent predictor of gallstone disease in men ($P = 0.005$) and a BMI ⩾ 25.0 kg/m^2 and a triglyceride level ⩾ 1500 mg/L were predictors of gallstone disease in women ($P < 0.05$).

DISCUSSION

One of the important benefits of early screening for gallstone disease is that ultrasonography can detect asymptomatic cases, which results in early treatment and the prevention of serious outcomes such as acute gallstone pancreatitis and gallbladder cancer[15]. However, few reports on the prevalence and possible etiology of gallstone disease have been published in China. In the present study, gallstone disease appeared to be common in the test population, i.e. an estimated 10.7% of the test population in Chengdu, China, had gallstone disease. The reported prevalence of gallstone disease is approximately 3.6% in Japan and 4.3%-5.0% in Taiwan[16-18]. The apparently higher prevalence rate in our study may have been due to the Westernized lifestyle of our patients, who were of middle-to-high income class. Another possible reason for such differences has been related to the fact that this was a hospital-based study which was unlikely the population study that could represent the general population.

The present study, in accordance with reports from Western countries and other regions of Asia, showed that an older age is a significant risk factor for gallstone disease[16,18,19]. In contrast, gallstone disease is virtually absent in children and adolescents aged 8-19 years[20]. Long-term exposure to many risk factors, as is true for the elderly, may increase the risk of gallstone disease. At the same time, sedentary activity, which is greater in the elderly than in younger populations, may also increase the risk of gallstone disease[21,22]. Furthermore, gallstone disease is also an acquired disease influenced by chronic environmental factors plus an aging effect[23].

In concordance with the findings of previous studies, female sex was also a major risk factor for gallstone disease in the present study. The commonly perceived opinion that women are at greater risk of developing gallstone disease than men may largely be due to extraneous risk factors, such as pregnancy and sex hormones. The number of pregnancies is the main one related to the high rates of gallstone disease in women. Sex hormones are most likely to be responsible for the increased risk. Estrogen increases biliary cholesterol secretion causing cholesterol super saturation of bile. Thus, hormone replacement therapy in postmenopausal women has been described to be associated with an increased risk for gallstone disease[24,25]. Some studies have also shown a relation between oral contraceptive use and a high prevalence of gallstone disease[26,27].

Table 3 Prevalence of metabolic disorders in the subjects with and without gallstone disease *n* (%)

Metabolic disorders	Gallstone disease	No gallstone disease	χ^2	*P*
Obesity	103/384 (26.8)	629/3189 (19.7)	10.603	0.001
Hypertension	115/384 (29.9)	525/3189 (16.5)	42.387	< 0.001
Diabetes mellitus	29/384 (7.6)	67/3189 (2.1)	40.550	< 0.001
Hypertriglyceridemia	178/384 (46.4)	950/3189 (29.8)	43.529	< 0.001
Low HDL-C	26/384 (6.8)	107/3189 (3.4)	11.157	0.001
Hypercholesterolemia	41/384 (10.7)	209/3189 (6.6)	8.954	0.003

Table 4 Univariate analysis of metabolic risk factors for gallstone disease in gender

Risk factors	Men				Women			
	n	Gallstone disease (%)	OR	95% CI	*n*	Gallstone disease (%)	OR	95% CI
BMI								
< 25 kg/m^2	113/1235	9.1	1.00	-	168/1606	10.5	1.00	-
≥ 25 kg/m^2	68/590	11.5	1.29	0.94-1.78	35/142	24.6	2.80	1.85-4.24
Hypertension								
No	120/1391	8.6	1.00	-	149/1542	9.7	1.00	-
Yes	61/434	14.4	1.73	1.25-2.41	54/206	26.2	3.32	2.33-4.73
FPG								
< 1100 mg/L	152/1710	8.9	1.00	-	189/1707	11.1	1.00	-
≥ 1100 mg/L and < 1260 mg/L	11/47	23.4	3.13	1.56-6.28	3/13	23.1	2.41	0.66-8.83
≥ 1260 mg/L	18/68	26.5	3.69	2.10-6.49	11/28	39.3	5.20	2.40-11.26
Triglyceride								
< 1500 mg/L	79/1012	7.8	1.00	-	127/1433	8.9	1.00	-
≥ 1500 mg/L	102/813	12.5	1.69	1.24-2.31	76/315	24.1	3.27	2.38-4.49
HDL								
< 350 mg/L (men); < 390 mg/L (women)	167/1738	9.6	1.00	-	191/1702	11.2	1.00	-
≥ 350 mg/L (men); ≥ 390 mg/L (women)	14/87	16.1	1.80	0.99-3.27	12/46	26.1	2.79	1.42-5.48
Total cholesterol								
< 2200 mg/L	163/1682	9.7	1.00	-	180/1641	11.0	1.00	-
≥ 2200 mg/L	18/143	12.6	1.34	0.80-2.26	23/107	21.5	2.22	1.37-3.62

Table 5 Multivariate logistic regression analysis for gallstone disease in gender

Variables	Men		Women	
	OR	95% CI	OR	95% CI
BMI ≥ 25.0 kg/m^2	-		1.59	1.01-2.50 (P = 0.046)
FBG ≥ 1260 mg/L	2.30	1.28-4.12 (P = 0.005)	-	
Triglyceride ≥ 1500 mg/L	1.37	0.99-1.90 (P = 0.057)	2.17	1.54-3.07 (P < 0.001)

The dependent variable was the presence or absence of gallstone disease. The covariates included a BMI ≥ 25.0 kg/m^2, high blood pressure (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or a history of hypertension), an FPG level between 1100 and 1260 mg/L and ≥ 1260 mg/L, a triglyceride level ≥ 1500 mg/L, a low HDL level (men: ≥ 350 mg/L; women: ≥ 390 mg/L), and a total cholesterol level ≥ 2200 mg/L.

Previous population studies have reported inconsistent associations of DM with gallstone disease. A study in Rome showed that DM was associated with an increased risk of gallstone disease in men and women separately[28]. A study of Hispanic Americans found a positive association between DM and self-reported gallstone disease in women, but not in men[26]. A study in Italy failed to find any relation between DM and gallstone disease in men and women combined[29]. The present analyses showed a positive association between DM and gallstone disease in men, but not in women. The mechanism underlying the relation of DM with gallstone disease may be fasting hyperinsulinemia, which can overly activate the rate-limiting enzyme for cholesterol synthesis[30] and finally leads to cholesterol saturation in the bile. Reduced motility of the gallbladder in persons with diabetes is another possible explanation[31,32].

In our study, obesity only showed a positive association with gallstone disease in women. Previous studies have found disparate findings for BMI or relative weight in men with gallstone disease[29,33,34]. However, three population screening surveys using ultrasonography failed to find a positive association between BMI and gallstone disease in men in Italy, Denmark, and the United States[26,35,36], whereas all three showed a positive association in women. The discrepant findings for BMI in men with gallstone disease have not been fully explained. A possible reason for these findings may be that BMI is not a suitable standard of obesity in men. Waist-to-hip ratio may be a better measure of obesity. The mechanism responsible for the increased risk of gallstone disease in obese persons may be the increase in bile saturation that results from an increase in the biliary secretion of cholesterol, which likely depends on the higher synthesis rate of cholesterol in obese persons[23].

The present study showed that hypertriglyceridemia was a risk factor for gallstone disease only in women.

However, high total cholesterol, low HDL-C, and high LDL-C levels were negatively associated with the risk of gallstone disease in both men and women. The present finding is different from that of previous studies, which noted a positive relation between hypertriglyceridemia and gallstone disease[36]. However, a cross-sectional study in Denmark failed to find a significant association between gallstone disease and plasma lipid levels (including triglyceride, total cholesterol, HDL-C, and LDL-C)[37]. Further studies are needed to clarify whether elevated levels of plasma lipids are independent risk factors for gallstone disease.

A major limitation of the present study was the potential self-selection bias due to the hospital-based study design, which resulted in a sample that was not representative of the general population in western China. However, we believe that our findings are useful as background data for future studies of the epidemiology of gallstone disease in China. Second, our measurements were inadequate. Some factors that might play an important role in gallstone disease development, such as oral contraceptive use and waist-to-hip ratio, were not collected in detail. Third, measurement error and different pathogenicities may have occurred, because the measurements were only made at one time point. Therefore, future studies need to determine whether these factors affect the results of our study.

In conclusion, older age, and female sex are associated with the prevalence of gallstone disease in both men and women. Obesity and hypertriglyceridemia were positively associated with gallstone disease in women, but not in men, whereas DM (FPG $\geqslant$ 1260 mg/L) was positively associated with gallstone disease only in men.

COMMENTS

Background

Gallstone disease is one of the most prevalent gastrointestinal diseases with a substantial burden to health care systems. Because the pathogenesis of gallstone disease is still not well defined and strategies for prevention and efficient non-surgical therapies are missing, further studies are required. Many researchers have shown that gallstone disease is related to age, sex, and metabolic disorders, such as obesity, dyslipidemia (hypertriglyceridemia), and type 2 diabetes. However, the findings concerning metabolic disorders and gallstone disease are disparate in different regions and ethnicity.

Research frontiers

There are a cluster of metabolic syndromes which includes obesity, glucose intolerance, increased low-density-lipoprotein cholesterol, triacylglycerol, diminished high-density-lipoprotein cholesterol and hypertension. The number of gallstone patients is increasing with a high prevalence of metabolic syndrome.

Innovations and breakthroughs

This study confirmed that age and sex are positive risk factors for gallstone disease; but, the association between metabolic disorders and gallstone disease is different for men and women. Furthermore, the study complemented the background prevalence of gallstone disease in Chengdu, China.

Applications

The results of this paper can guide clinicians to target high-risk groups for related inspection and early treatment. Furthermore, preventive strategies can be identified and planned according to these results.

Terminology

Gallstone disease, formally known as cholelithiasis, occurs when gallstones formed in the bile duct, which are abnormal masses of a solid mixture of cholesterol crystals, mucin, and calcium bilirubinate proteins. It is asymptomatic in most patients. Sometimes it can cause dyspepsia and other gastrointestinal symptoms or biliary colic or Mirizzi syndrome.

Peer review

This paper provides information about the incidence and risk factors of gallstone disease in China. The results of this study can give information for further research to explore the pathogenesis of gallstone disease and the role of metabolic syndrome in the process of gallstone formation.

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