BMI is an Independent Risk Factor for New-onset Asymptomatic Gallbladder Stone Disease in Overweight Population: A Case-control Study in Northwest China

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Research article

Keywords: Obesity, overweight, asymptomatic gallstone disease, epidemiology

Posted Date: September 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-72359/v1

Abstract

Background: This case-control study aimed to assess associations of overweight/obesity with gallbladder stone disease (GSD).

Methods: We enrolled 345 new-onset asymptomatic GSD and 690 healthy controls who had undergone annual health check-ups at the Affiliated Hospital of Xi'an Jiaotong University, in 2012-2017. Height, weight, blood pressure, serum lipid indexes and fasting blood glucose were assessed, and associations were determined by logistic multivariate regression analysis.

Results: In overweight subjects, WC, BMI, WHtR, LDL-c and FBG showed significant positive correlations with GSD in univariate analysis, while HDL-c had a significant negative correlation (all P<0.05); in multivariate analysis, BMI (OR=37.738, P<0.001), WHtR (OR=1.128, P=0.042), LDL-c (OR=1.551, P=0.014) and FBG (OR=1.463, P=0.017) were significant risk factors, while HDL-c (OR=0.193, P<0.001) was a protective factor for GSD. In obese individuals, WC, BMI, WHtR, TG, LDL-c, and NAFLD showed significant positive correlations with GSD in univariate analysis, while HDL-c had a significant negative correlation (all P<0.05); BMI (OR=0.384, P=0.001) and HDL-c (OR=0.034, P<0.001) were protective factors, while WHtR (OR=2.863, P<0.001) and NAFLD (OR=4.730, P=0.037) were significant risk factors.

Conclusion: BMI is an independent risk factor for new-onset asymptomatic GSD in overweight population. Meanwhile, obesity is associated with asymptomatic GSD formation with concurrent hyperlipidemia and NAFLD.

Introduction

Gallbladder stone disease (GSD) is a major health problem in westernized Asian countries, with a high economic impact [1]. In the United States, approximately 10%~20% of the national adult populations currently carry gallstones, whose prevalence is rising; nearly 750,000 cholecystectomies are performed annually [2]. Cholelithiasis is strongly associated with gallbladder, pancreatic and colorectal cancers [3]. The National Institutes of Health estimates that almost 3,000 deaths (0.12% of all deaths) per year are attributed to complications of cholelithiasis and gallbladder disease, with direct and indirect costs of gallbladder surgery estimated at $6.5 billion [4]. GSD is no longer rare among Chinese individuals, and has become a major health problem coincident with the westernization of the Chinese diet and environment [5]. Asymptomatic gallstones have become prevalent in the general population, imposing a heavy economic burden on the society because of diagnostic, treatment and indirect health care costs [6]. In China, approximately 2.3%~6.5% of the national adult population currently carry gallstones; this prevalence is rising, and females are more affected than males, with a male-to-female ratio of 1:1.07–1.69 [7].

During the development of GSD, solid conglomerates of cholesterol monohydrate crystals, mucin gel, calcium bilirubinate and proteins accumulate and grow in the gallbladder [8]. Studies have suggested that GSD involves a complex interplay between genetic factors, lifestyle and diet, which act on specific pathogenic mechanisms [9]. Epidemiological data have confirmed that genetic factors account for only approximately 25% of the overall risk of gallstones, while metabolic and environmental factors are at least partially modifiable in stone-free risk groups [10]. Studies have shown that overweight, obesity, dyslipidemia, insulin resistance and altered cholesterol homeostasis are associated with increased gallstone occurrence, and therefore modifiable by primary prevention measures related to diet, lifestyle, and environmental factors such as rapid weight loss, bariatric surgery, somatostatin or analogue therapy, transient gallbladder stasis and hormone therapy [9, 10]. Meanwhile, the increasing prevalence of asymptomatic gallstones is currently at 12.1% in China [11].

Obesity, an increasing health issue and a well-established major risk factor for gallstone formation attracts growing attention [12–14]. While data remain unclear, this is partly explained by increased cholesterol turnover, which is linearly correlated to total body fat. Increased cholesterol is excreted in the bile, increasing the likelihood of cholesterol precipitation into gallstones because of higher cholesterol amounts relative to bile acids and phospholipids [15]. The incidence of overweight in China has increased significantly in recent years. However, studies assessing GSD in the context of overweight are scarce, and whether obesity and/or overweight are associated with the risk of asymptomatic gallstones in the newly affluent population remains undefined. Therefore, this case-control study aimed to assess the clinical data of patients newly diagnosed with gallbladder stones during a 5-year period in northwest China, determining whether obesity and/or overweight are associated with new-onset asymptomatic GSD by matching age, gender, serum total cholesterol, and blood pressure. These findings provide novel insights into the risk factors for GSD in the rising affluent population of China.

Methods

Patient selection and data eligibility

In this case-control study, patients who had undergone routine health check-ups annually in the healthcare center of the Affiliated Hospital of Medical School of Xi'an Jiaotong University from August 2012 to July 2017, and diagnosed with new-onset asymptomatic GSD by abdominal ultrasonography examination in 2017 were included. Diagnosis was completed by senior associate chief physicians with more than 10 years of experience in ultrasound diagnosis.

Inclusion criteria were: 1) age ≥ 18 years; 2) BMI ≥ 18.5 kg/m^2; 3) diagnosis of new-onset gallbladder stones by abdominal ultrasonography in 2017 [16–18]; 4) no previous diagnosis of gallbladder stone in annual check-ups before 2017 (2012–2016); 5) no clinical symptoms of gallbladder stone ; 6) no history of acute cholecystitis; 7) no history of hypertension or diabetes; 8) BMI maintained within the same category (overweight [BMI = 23-24.9 kg/m^2] or obesity [BMI ≥ 25 kg/m^2] [19]) from 2012 to 2017. Exclusion criteria were: 1) a history of gastrointestinal surgery, hepatobiliary disease, significant weight loss, or any cancer; 2) new diagnosis of nonalcoholic fatty liver disease (NAFLD) within two years; 3) lack of any of the data such as age, height, weight, waist circumference (WC), systolic pressure (SBP), diastolic pressure (DBP), serum total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), fasting blood glucose (FBG), and ultrasonographic examination for gallbladder.

Meanwhile, healthy controls, who had undergone health check-ups annually in the same healthcare center from August 2012 to July 2017, were matched for age, gender, ethnicity, profession, SBP, DBP and total cholesterol.

This study was performed in accordance with the Institutional Ethics Committee requirements of the Affiliated Hospital of Medical School of Xi'an Jiaotong University (No: XJTU1AF2019LSK-017). Informed consent was obtained from the patients before enrolment.

Questionnaire

Each participant filled a questionnaire containing items such as ethnicity, ID number, profession, and a history of medication, diabetes mellitus, gastrointestinal surgery, hepatobiliary disease, weight loss or any cancer. A nurse validated the patient age based on the identity card, and a full-time clinician measured the patient height and weight during the medical examination.

Determination Of Clinical Parameters

Common tumor markers, hypertension and transabdominal ultrasonograms were assessed. Blood samples were collected after a 10-h fast from the antecubital vein. Serum TG, LDL-c, HDL-c, TC, and FBG amounts were assayed. TG and TC measurements were performed by the GPO-PAP and COD-PAP methods, respectively, while LDL-c and HDL-c were quantitated by the homogenous method. The glucose oxidase method was carried out to analyze FBG levels. All measurements were performed by the same central laboratory in a blind fashion according to the manufacturers' instructions. Blood pressure was measured three times after sitting or rest for 30 min by an RBP 900 automatic blood pressure measuring instrument (Shenzhen Reycome Science and Technology Ltd. China).

Type-b Ultrasonic Examination For Diagnosing Gsd And Nafld

A Color Doppler ultrasonic instrument (Toshiba, SSA-510A, Japan) was used to detect gallbladder and hepatic diseases after fasting, with the patient in the supine position. The liver, gallbladder, pancreas and spleen were examined in turn. GSD was diagnosed as previously reported [16–18]. NAFLD was diagnosed based on previous reports [20, 21].

Determination Of Obesity Factors

An HW-900Y ultrasonic wave height and weight scale (Jiangsu Hengfeng weighting, China) was used to measure patient height and weight. BMI was determined as weight (kg) by squared height (m^2). Patients were grouped by BMI according to the WHO criteria for Asian populations: BMI < 23 kg/m^2, normal range; 23-24.9 kg/m^2, overweight; ≥25 kg/m^2, obesity [19]. WC was measured four times using a flexible, tension sensitive, non-stretching measuring tape placed directly on the skin, at the end of normal expiration by a trained researcher as described previously [22].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentage (%). Student's t-test and the Chi square test were performed to compare continuous and categorical variables, respectively. Associations of BMI and blood lipid levels with GSD were examined by logistic multivariate regression analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics and serum indexes in the GSD and control groups

The general characteristics and serum indexes in the GSD and control groups are summarized in Table 1. There were 345 patients with GSD and 690 healthy controls aged 30 to 82 years, with 140 (40.6%) and 291 (42.2%) female participants in the GSD and control groups, respectively. FBG, weight, WHtR, BMI, WC, TG, LDL-c and HDL-c significantly differed between the GSD and control groups (all $P < 0.05$) (Table 1). 273 (39.6%), 171 (24.8%) and 246 (35.6%) patients with normal weight, overweight and obesity in the control group, respectively, versus 73 (21.2%), 107 (31.0%) and 165 (47.8%) in the GSD group, respectively, indicating statistically significant differences ($P < 0.05$). There were 123 (17.8%) and 115 (33.3%) participants with NFALD in the control and GSD groups, respectively ($P < 0.001$).

Table 1
Demographic and clinical data of the patients before and after matching

	Before matching			After matching		
	Control group (N = 3471)	GS group (N = 645)	P value	Control group (N = 690)	GS Group (N = 345)	P value
Female (%)	1713 (49.4%)	291 (45.1%)	0.048	291 (42.2%)	140 (40.6%)	0.624
Age (Years)	56.32 ± 13.7	59.66 ± 12.2	< 0.001	59.65 ± 12.0	60.92 ± 11.5	0.107
Han (%)	2982 (85.9%)	580 (89.9%)	0.005	601 (87.1%)	303 (87.8%)	0.740
Occupation (%)			< 0.001			0.996
Worker	218 (6.3%)	42 (6.5%)	0.825	60 (8.7%)	29 (8.4%)	0.875
Professional technician	316 (9.1%)	78 (12.1%)	0.021	147 (21.3%)	75 (21.7%)	0.872
Manager	193 (5.6%)	56 (8.7%)	0.004	110 (15.9%)	54 (15.7%)	0.904
Retiree	2062 (59.4%)	407 (63.1%)	0.078	344 (49.9%)	174 (50.4%)	0.860
Others	682 (19.6%)	62 (9.6%)	< 0.001	29 (4.2%)	13 (3.8%)	0.737
SBP (mmHg)	120.99 ± 17.9	127.58 ± 19.5	< 0.001	126.91 ± 18.1	128.53 ± 18.0	0.173
DBP (mmHg)	76.67 ± 10.6	83.02 ± 12.1	< 0.001	82.31 ± 10.8	83.08 ± 11.6	0.292
FBG (mmol/L)	5.27 ± 1.3	5.18 ± 1.4	0.135	5.04 ± 1.0	5.21 ± 1.1	0.017
Height (cm)	165.26 ± 8.6	165.24 ± 8.5	0.946	165.24 ± 8.4	164.64 ± 8.3	0.277
Weight (kg)	65.82 ± 11.4	67.29 ± 11.5	0.003	65.99 ± 11.0	69.32 ± 11.1	< 0.001
BMI (kg/m^2)	24.00 ± 3.1	24.55 ± 3.0	< 0.001	24.07 ± 2.9	25.40 ± 3.0	0.001
Normal (%)	1472 (42.4%)	217 (33.6%)	< 0.001	273 (39.6%)	73 (21.2%)	< 0.001
Overweight (%)	750 (21.6%)	144 (22.3%)	0.685	171 (24.8%)	107 (31.0%)	0.034
Obesity (%)	1249 (36.0%)	284 (44.0%)	< 0.001	246 (35.6%)	165 (47.8%)	< 0.001
WC (cm)	82.41 ± 7.0	89.25 ± 8.0	< 0.001	76.92 ± 6.3	85.68 ± 8.8	< 0.001
WHtR (%)	49.96 ± 4.7	54.17 ± 5.1	< 0.001	46.63 ± 4.1	52.14 ± 5.7	< 0.001
TC (mmol/L)	4.88 ± 0.9	4.91 ± 1.1	0.505	4.80 ± 0.9	4.76 ± 1.0	0.512
TG (mmol/L)	1.49 ± 0.8	1.57 ± 0.9	0.027	1.37 ± 0.6	1.78 ± 1.2	< 0.001
HDL-c (mmol/L)	2.53 ± 1.0	2.19 ± 1.1	< 0.001	2.81 ± 0.9	1.35 ± 0.6	< 0.001
LDL-c (mmol/L)	1.99 ± 1.3	2.24 ± 1.3	< 0.001	1.74 ± 1.3	2.80 ± 0.9	< 0.001
Drink (%)	506 (146%)	87 (13.5%)	0.466	95 (13.8%)	77 (12.1%)	0.374
Eating habits (%)			< 0.001			0.995
Vegan	127 (3.7%)	56 (8.7%)	< 0.001	55 (8.0%)	28 (8.1%)	0.936
Vegetarian	508 (14.6%)	78 (12.1%)	0.084	116 (16.8%)	59 (17.1%)	0.907
Meat & vegetarians	2730 (78.7%)	382 (59.2%)	< 0.001	390 (56.5%)	192 (55.7%)	0.790
Carnivorous diet	376 (10.1%)	129 (20.0%)	< 0.001	129 (18.7%)	66 (19.1%)	0.866

GS: gallbladder stone; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference; WHtR: Waist height ratio; TC: total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease.

	Before matching			After matching		
NAFLD (%)	744 (21.4%)	190 (29.5%)	< 0.001	123 (17.8%)	115 (33.3%)	< 0.001

GS: gallbladder stone; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference; WHtR: Waist height ratio; TC: total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease.

Associations Of Various Parameters With Gsd

BMI, WHtR, TG, HDL-c, LDL-c, NAFLD and FBG were significantly associated with GSD in univariate analysis. Multivariate analysis showed that enlarged WHtR (OR = 1.276, 95%CI: 1.191–1.366; P < 0.001) and high-level LDL-c (OR = 1.549, 95%CI: 1.289–1.863; P < 0.001) were significant risk factors for GSD in this study population, while high-level HDL-c (OR = 0.141, 95%CI: 0.102–0.195; P < 0.001) was significant protective factors for GSD (Table 2).

Table 2
Univariate and multivariate analyses of gallbladder stone

Factors	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
BMI	1.164	1.112–1.217	0.001	0.772	0.687–0.867	< 0.001
Normal	1					
Overweight	2.340	1.643–3.333	< 0.001			
Obesity	5.576	4.029–7.716	< 0.001			
WHtR	1.251	1.212–1.291	< 0.001	1.271	1.187–1.361	< 0.001
TG	2.023	1.636–2.501	< 0.001	0.846	0.690–1.039	0.110
HDL-c	0.077	0.056–0.105	< 0.001	0.140	0.101–0.193	< 0.001
LDL-c	2.571	2.215–2.983	< 0.001	1.543	1.284–1.855	< 0.001
NAFLD	2.305	1.713–3.101	< 0.001	1.649	0.995–2.734	0.053
SBP	1.005	0.998–1.012	0.173			
DBP	1.006	0.995–1.018	0.292			
FBG	1.154	1.024–1.301	0.019	1.117	0.936–1.332	0.220
Drink	1.157	0839-1.597	0.374			

BMI: body mass index; WHtR: Waist height ratio; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose.

Demographic and clinical differences between the control and GSD subgroups in overweight and obese participants

There were 171 and 107 overweight participants in the control and GSD groups, respectively. Meanwhile, there were 246 and 165 obese individuals in the control and GSD groups, respectively. In both overweight and obese patients, NAFLD, BMI, WC, WHtR, HDL-c and LDL-c showed significant differences between the control and GSD groups (all P < 0.05). In obese patients, TG showed significant difference between the control and GSD groups (P < 0.001). The detailed data are shown in Table 3.

Table 3
Demographic and clinical data in overweight and obese patients

	Overweight			Obesity		
	Control group (N = 171)	GS Group (N = 107)	P value	Control group (N = 246)	GS Group (N = 165)	P value
Female (%)	72 (42.1%)	45 (42.1%)	0.994	63 (25.6%)	54 (32.7%)	0.118
Age (Years)	59.37 ± 11.4	61.38 ± 11.8	0.276	59.99 ± 12.8	60.63 ± 11.2	0.602
Han (%)	148 (86.5%)	95 (88.8%)	0.584	214 (87.0%)	145 (87.9%)	0.790
Occupation (%)			0.744			0.986
Worker	10 (5.8%)	7 (6.5%)	0.815	22 (8.9%)	13 (7.9%)	0.704
Professional technician	17 (9.9%)	12 (11.2%)	0.736	54 (22.0%)	36 (21.8%)	0.974
Manager	23 (13.5%)	17 (15.9%)	0.575	45 (18.3%)	28 (17.0%)	0.730
Retiree	94 (55.0%)	60 (56.1%)	0.538	112 (45.5%)	79 (41.4%)	0.640
Others	27 (15.8%)	11 (10.3%)	0.186	13 (5.3%)	9 (5.5%)	0.940
SBP (mmHg)	12372 ± 16.0	123.77 ± 15.3	0.981	132.95 ± 17.7	134.23 ± 17.9	0.474
DBP (mmHg)	80.30 ± 9.5	80.50 ± 10.0	0.873	85.44 ± 11.1	86.90 ± 12.1	0.211
FGB (mmol/L)	5.08 ± 1.0	5.42 ± 1.5	0.024	5.22 ± 1.2	5.22 ± 1.0	0.996
Height (cm)	165.03 ± 8.9	164.26 ± 8.7	0.480	166.50 ± 8.4	165.16 ± 7.8	0.103
Weight (kg)	77.35 ± 5.0	8154 ± 3.9	< 0.001	75.80 ± 9.3	756.51 ± 9.3	0.454
BMI (kg/m^2)	23.79 ± 0.5	24.30 ± 0.3	< 0.001	27.27 ± 1.9	27.89 ± 1.9	0.001
WC (cm)	77.35 ± 5.0	81.54 ± 3.9	< 0.001	82.46 ± 5.0	93.51 ± 4.5	< 0.001
WHtR (%)	46.96 ± 3.2	49.76 ± 3.2	< 0.001	49.65 ± 3.9	56.72 ± 3.5	< 0.001
TC (mmol/L)	4.85 ± 1.0	4.90 ± 1.1	0.655	4.73 ± 1.0	4.61 ± 1.0	0.242
TG (mmol/L)	1.46 ± 0.9	1.70 ± 1.1	0.052	1.19 ± 0.3	2.00 ± 1.4	< 0.001
HDL-c (mmol/L)	2.50 ± 1.1	1.41 ± 0.7	< 0.001	2.94 ± 0.9	1.21 ± 0.4	< 0.001
LDL-c (mmol/L)	2.08 ± 1.1	2.75 ± 1.0	< 0.001	1.97 ± 1.7	2.83 ± 0.9	< 0.001
Drink (%)	21 (12.3%)	14 (13.1%)	0.845	34 (13.8%)	26 (15.8%)	0.587
Eating habits (%)			0.939			0.975
Vegan	9 (5.3%)	7 (6.5%)	0.856	13 (5.3%)	9 (5.5%)	0.940
vegetarian	18 (10.5%)	13 (12.1%)	0.677	25 (10.2%)	15 (9.1%)	0.718
Meat & vegetarians	99 (57.9%)	62 (57.9%)	0.994	165 (67.1%)	110 (66.7%)	0.932
Carnivorous diet	45 (26.3%)	25 (23.4%)	0.580	43 (17.5%)	31 (18.8%)	0.736
NAFLD (%)	25 (14.6%)	23 (21.5%)	0.006	51 (34.9%)	83 (50.3%)	< 0.001

GS: gallbladder stone; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference; WHtR: Waist height ratio; TC: total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease.

Associations of various indexes with new-onset asymptomatic GSD in obese and overweight participants

Table 4 shows the risk factors for developing GSD based on univariate and multivariate logistic regression. In overweight patients, WC, BMI, WHtR, LDL-c and FBG showed significant positive correlations with GSD in univariate analysis, while HDL-c had a significant negative correlation (all P < 0.05). In multivariate analysis, elevated BMI (OR = 34.755, 95%CI: 12.244–98.656; P < 0.001), enlarged WHtR (OR = 1.128, 95%CI: 1.005–1.265; P = 0.04), high-level LDL-c (OR = 1.558, 95%CI: 1.104–2.198; P = 0.012) and FBG (OR = 1.433, 95%CI: 1.056–1.944; P = 0.021) were significant risk factors for GSD, while high-level HDL-c (OR = 0.192, 95%CI: 0.107–0.346; P < 0.001) was a protective factor (Table 4).

Table 4
Univariate and multivariate analysis of gallbladder stones in overweight and obese patients

Factors	Overweight						Obesity					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Weight	1.019	0.985–1.054	0.277				1.008	0.987–1.030	0.453			
WC	1.211	1.142–1.285	< 0.001				1.604	1.467–1.755	< 0.001			
BMI	11.429	5.989–21.81	< 0.001	34.755	12.244–98.656	< 0.001	1.185	1.066–1.317	0.002	0.412	0.243–0.698	0.001
WHtR	1.278	1.179–1.385	< 0.001	1.128	1.005–1.265	0.04	1.625	1.482–1.782	< 0.001	2.605	1.818–3.733	< 0.001
TG	1.275	0.985–1.650	0.065	0.767	0.546–1.080	0.125	10.901	6.078–19.552	< 0.001	4.444	0.946–20.871	0.059
HDL-c	0.224	0.148–0.338	< 0.001	0.192	0.107–0.346	< 0.001	0.020	0.009–0.045	< 0.001	0.043	0.016–0.119	< 0.001
LDL-c	1.756	1.381–2.232	< 0.001	1.558	1.104–2.198	0.012	2.001	1.614–2.482	< 0.001	1.353	1.067–1.716	0.013
TC	1.055	0834-1.336	0.645				0.886	0.723–1.085	0.242			
NAFLD	1.599	0.854–2.992	0.142				3.870	2.508–5.972	< 0.001	5.079	1.246–20.702	0.023
SBP	1.000	0.985–1.016	0.981				1.004	0.993–1.015	0.474			
DBP	1.002	0.977–1.027	0.872				1.011	0.994–1.028	0.211			
FBG	1.254	1.023–1.537	0.029	1.433	1.056–1.944	0.021	1.000	0.832-1.200	0.996			
Drink	1.075	0.521–2.218	0.845				1.150	0.661–1.999	0.622			

WC: waist circumference; BMI: body mass index; WHtR: Waist height ratio; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; TC: total cholesterol; NAFLD: nonalcoholic fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose.

In obese individuals, WC, BMI, WHtR, TG, LDL-c, and NAFLD showed significant positive correlations with GSD in univariate analysis, while HDL-c had a significant negative correlation (all P < 0.05). In multivariate analysis, elevated BMI (OR = 0.412, 95%CI: 0.243–0.698; P = 0.001) and high-level HDL-c (OR = 0.043, 95%CI: 0.016–0.119; P < 0.001) were protective factors, while enlarged WHtR (OR = 2.605, 95%CI: 1.818–3.733; P < 0.001), NAFLD (OR = 5.079, 95%CI: 1.246–20.702; P = 0.023) and high-level LDL-c levels (OR = 1.353, 95%CI: 1.067–1.716; P = 0.013) were significant risk factors for GSD (Table 4).

Discussion

We demonstrated that overweight is an independent risk factor for new-onset asymptomatic GSD, while obesity is associated with asymptomatic GSD formation with concurrent hyperlipidemia and NAFLD but does not promote GSD in non-NAFLD cases.

In this case-control study, control cases were matched for blood pressure, serum cholesterol, age and gender, and positive associations of overweight and obesity with asymptomatic GSD were obtained, as recently described [14, 23, 24]. In the present study, we confirmed that obese individuals had a higher rate of GSD compared with controls. Indeed, obesity is well known for its strong association with gallstone diseases [25, 26]. As shown above by multivariate logistic regression analysis, WHtR and NAFLD were significant risk factors for GSD in obese individuals. These findings suggested that obesity per se might not be directly associated with cholelithiasis risk, and it is highly probable that both ailments share several pathophysiologic and genomic pathways [27], as well as multiple comorbid conditions close associated with obesity, including diabetes and hyperlipidemia, although the interactions among these pathologies remain unclear [28]. A study investigating the association of gallbladder dysmotility with hypertriglyceridemia (HTG) showed that the former is frequently associated with obesity as well [29], suggesting that HTG might decrease sensitivity to cholecystokinin (CCK) rather than reducing CCK release, possibly adding to the enhanced risk of gall stone disease in HTG patients [30].

The mechanisms of cholelithiasis formation in obesity might include loss of gallbladder contractility, increased cholesterol secretion from the liver, and bile supersaturation by enhanced biliary secretion of cholesterol [6]; this is predominantly in women, particularly those with insulin-resistance [31]. Hypersecretion of cholesterol in the bile and subsequent bile supersaturation contribute to biliary sludge formation, consequently reducing gallbladder motility [32]. In addition, obesity increases bile cholesterol saturation possibly by raising serum triglycerides and lowering high-density lipoprotein (HDL) [33]. Elevated triglycerides increase both biliary cholesterol saturation and bile viscosity by enhancing mucin production [34]. High serum HDL increases primary bile acid formation, which solubilizes cholesterol and reduces biliary cholesterol saturation [34], corroborating the present results. Therefore, this and previous reports suggest that high total cholesterol levels, associated with obesity, might trigger cholesterol hypersecretion in the bile and subsequent bile supersaturation, thereby contributing to biliary sludge formation. Furthermore, hypertriglyceridemia reduces gallbladder motility, with decreased sensitivity to CCK [30, 32].

Abdominal circumference is a risk factor for gallbladder disease, independent of BMI [35, 36], while waist circumference is independently correlated with serum retinol binding protein 4 (RBP4) that might play an important role in gallstone formation in Type 2 diabetes mellitus [37]. In the present study, FBG in the GS group was higher than that in the control group among overweight patients, and multivariate analysis showed that FBG was an independent risk factor for GSD. Presumably, FBG gradually increases and even leads to diabetes in overweight patients with abdominal obesity, thus increasing the risk of GSD. Meanwhile, increased *de-novo* lipogenesis is a major driver of hepatic steatosis in the insulin resistance state owing to excessive activation of the lipogenic branch of the insulin signaling pathway in hepatocytes [38, 39]. NAFLD is an acquired metabolic disease of the liver, occurring in two phases: (1) triglycerides accumulate in the liver and (2) necrobiotic inflammatory reactions, fibrosis and cirrhosis take place [40]. Meanwhile, obese individuals are likely to have increased gallbladder volume accompanied by slow gallbladder evacuation and mucosal abnormalities, which are associated with gallstone formation [41]. There appears to be a vicious circle involving obesity, high intake of total carbohydrate/saturated fat calories, and asymptomatic cholelithiasis in the general population, in association with cholesterol stone formation. In agreement, the present study showed a significant positive association between serum TC and gallbladder stones in obese patients.

The recent study with 10 year-follow-up revealed that the rates of patients with diabetes, high cholesterol and gallstones increase with the degree of overweight; moreover, a dose-response relationship between BMI and the risk of developing chronic diseases is evident even among adults in the upper half of the healthy weight range (i.e., BMI of 22.0-24.9) [42]. A recent study suggested that reducing obesity may prevent gallstones, as 38% of incident cases of gallstones had BMI exceeding 25, defined as overweight in the Western population [34]. A case-control study found that BMI, triglycerides, low HDL-cholesterol, increased glycaemia and diabetes mellitus are significantly associated with gallstone disease in univariate logistic regression analysis, but only BMI retained significance in multiple logistic regression analysis [43]. A large prospective study of obese women reported a strong linear association of BMI with cholelithiasis incidence [44]. A recent study also showed a statistically significant positive correlation between BMI and the prevalence of asymptomatic cholelithiasis after stratification by normal, overweight, and obese groups according to the BMI, which was also shown to be a risk factor for asymptomatic cholelithiasis in both genders [6]. However, this study revealed a significant negative correlation between BMI and risk of GSD, which had significant positive correlations with WC,

and WHtR. Therefore, we speculate that chronic overweight or elevated BMI, particularly obesity progression, is accompanied with abdominal adiposity, hyperinsulinemia, insulin resistance, hyperleptinemia, hyperlipidemia and gallbladder dysmotility [25, 28]. The latter factors are induced by chronic overweight, promoting GSD through their respective mechanisms, while the inverse correlation between BMI and GSD may result from the above stronger confounding factors, which could interfere with the effect of BMI on GSD formation. In addition, overweight might not only impair biliary lipid composition, diminishing cholesterol saturation index to increase the incidence of cholesterol gallstones [45], but also reduce leptin to decrease gallbladder contractility [28]. Therefore, the formation of gallbladder stones is enhanced by the imbalance between the amounts of total cholesterol, bile acids and lecithin, in combination with the abovementioned factors in chronic overweight before obesity [46], corroborating the present results. The adipose tissue in overweight individuals contains macrophages and secretes inflammatory cytokines. Chronic inflammation caused by inflammatory products and oxidative stress may contribute to biliary tissue damage and high bile saturation with cholesterol among individuals with abnormal weight, leading to cholesterol gallstone formation [47]. Indeed, inflammation might produce mucin, accounting for enhanced cell proliferation and mucus secretion in the gallbladder, which may increase susceptibility to gallstone formation [48, 49].

Strengths And Limitations Of This Study

A sufficient number of participants, a case-control design, and complete follow-up for mortality are the strengths of this study. The data derive from participants who underwent regular annual physical screening with long-term follow-up. We reviewed cases for more than five years, ensuring that the patients were well-documented in the experimental group, and matched participants were assessed as controls. Of note, thousands of individuals undergo health examinations from all over Northwest of China in this region's largest Health center yearly. Nevertheless, the present study had several limitations. First, this was not a multicenter trial. The homogenous ethnic study population and the same eating habits may affect its generalizability. Secondly, participants were diagnosed by B-mode ultrasonography and laboratory parameters; therefore, misdiagnosis and missed diagnosis could not be ruled out. Thirdly, stone-related risk factors were not evaluated, including short-term overconsumption, high-energy and protein diet, and gastrointestinal dysfunction. Finally, we assessed newly-diagnosed asymptomatic patients with GSD, who might have had cholesterol gallstones, but lacked data of bile acid level and incidence of gastrointestinal dysfunction.

Conclusion

Overall, BMI is an independent risk factor for new-onset asymptomatic gallbladder stone in overweight patients after matching serum total cholesterol. Obesity, a well-known risk factor for asymptomatic cholelithiasis in the general population, is associated with cholesterol stone formation. Adults with abdominal obesity and hyperlipidemia may be at high risk of GSD, while elevated fasting blood glucose may increase the risk of GSD in this overweight population.

Nevertheless, these findings should be confirmed in future prospective studies investigating the individual and combined effects of serum lipids on gallstones, as well as other risk factors for the development of gallstones.

Declarations

Author Contributions

Jianqin Zhang and Binwu Sheng were responsible for analyzing the data, organizing the manuscript and literature review in the introduction and discussion; Mao Ma and Qingbin Zhao were responsible for interpreting the results. Binwu Sheng was responsible for drafting the introduction and conclusions, in addition to finalizing the writing.

Ethics approval:

The study was reviewed and approved by the First Affiliated Hospital of Xi’an Jiaotong University. The need for individual consent was waived by the committee because of the retrospective nature of the study (NO.XJTU1AF2019LSK-017).

Informed consent:

The need to obtain informed consent from the subjects was waived by the First Affiliated Hospital of Xi’an Jiaotong University.

Acknowledgment:

The authors thank all subjects for participating in this study. This work has been supported by funding by the “Natural Science Foundation of Shaanxi Province of China” (S2020-JC-YB-0959). The funding source had no role in the study design, collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication.

Conflicts of interest

The authors declare no conflict of interest

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