

An Inverse Association of Weight and the Occurrence of Asymptomatic Gallbladder Stone Disease in Hypercholesterolemia Patients in Northwest China: A Case-Control Study.

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Abstract

Background Despite the fact that the majority of gallstones formed in the gallbladder are mainly composed of cholesterol, as they are formed from cholesterol-supersaturated bile, there is still no consensus regarding the contribution of blood serum lipids in the pathogenesis of gallbladder stone disease (GSD). Here, we aimed to investigate the relationship between hypercholesterolemia and the risk of new-onset asymptomatic GSD, and to determine the prevalence of factors associated with new-onset asymptomatic GSD in patients with hypercholesterolemia.

Methods In this case-control study, we enrolled 927 Chinese patients with new-onset asymptomatic gallstone disease and 845 healthy controls starting in August 2012. Patients were matched for age, gender, race, occupation, systolic blood pressure, diastolic blood pressure, and fasting blood glucose levels (FBG). Body mass index, nonalcoholic fatty liver disease (NAFLD) and serum lipids indexes were compared and the relationships between BMI, blood lipid and gallbladder stone hazards were examined by using logistic multivariate regression models.

Results The result showed a significant higher morbidity with GSD in hypercholesterolemia than non-hypercholesterolemia patients ($X^2=17.211$, $P<0.001$). Of hypercholesterolemia patients, LDL-c (OR=1.493, $P=0.029$) and NAFLD (OR=2.723, $P=0.022$) were significant risk factors for GSD, while male sex (OR=0.244, $P=0.033$), weight (OR=0.961, $P=0.022$), HDL-c (OR=0.305, $P<0.001$), and FBG (OR=0.687, $P=0.034$) significantly negatively correlated with GSD in univariate analysis. Multivariate logistic regression indicated weakly positive correlations with NAFLD (OR=3.284, $P=0.054$), and significant negative correlations with weight (OR=0.930, $P=0.018$), HDL-c (OR=0.144, $P<0.001$), and GSD.

Conclusion Hypercholesterolemia acts as an independent risk factor for new-onset asymptomatic GSD, while obesity and NAFLD are synergistic factors. Interestingly, we are the first to report that elevated weight was inversely associated with GSD in patients with hypercholesterolemia.

Introduction

Gallbladder stone disease (GSD) is a frequent problem in developed countries, representing a major health burden (1). In the United States, approximately 10%–20% of the national adult population currently carries gallstones, and the prevalence is rising. Nearly 750,000 cholecystectomies are performed annually. Cholelithiasis is strongly associated with gallbladder, pancreatic and colorectal cancer. 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. The direct and indirect costs of gallbladder surgery are estimated to be \$6.5 billion (2). With the westernization of the Chinese diet and environment, GSD is no longer rare among the Chinese population and has become a major health problem coincidentally (3). Asymptomatic gallstones have become prevalent in the general population, imposing heavy economic burdens because of diagnosis, treatment, and indirect health care costs (4). The prevalence of asymptomatic gallstones is 12.1% in China, with an increasing trend (5).

Although extensive research has tried to identify risk factors for GSD, several studies indicated that definitive findings remain inconclusive (6). Traditionally, studies have suggested that cholesterol gallstone disease depends on a complex interplay between genetic factors, lifestyle and diet, acting on specific pathogenic mechanisms (7). Until recently, it has been understood that cholesterol gallstone formation is mediated by genetic and environmental factors (8) and inflammation-mediated pathogenesis of cholesterol gallstones has not yet been considered seriously (9). Overweight, obesity, dyslipidemia, insulin resistance and altered cholesterol homeostasis have been linked to increased gallstone occurrence, and are therefore modifiable by primary prevention measures related to diet, lifestyle, and environmental factors (including rapid weight loss, bariatric surgery, somatostatin or analogue therapy, transient gallbladder stasis and hormone therapy) (10, 11).

To our knowledge, these studies have also shown that hyperlipidemia is associated with gallstones; nevertheless, the relationship between levels of serum lipids (blood cholesterol, triglyceride, low density lipoprotein, high density lipoprotein) and gallstones remain unclear. However, it is well known that cholesterol gallstones account for 80–95% of the gallstones found during cholecystectomy (12, 13), as they are formed from cholesterol-supersaturated bile (14). In accordance with this viewpoint, another recent study showed that high levels of cholesterol were associated with gallbladder disorders such as cholesterosis

and gallstone disease, suggesting a positive association between hyperlipidemia and gallstones in humans (15, 16). In addition, obesity is a risk factor for gallstone disease. Dietary factors that may prevent the development of gallstones include polyunsaturated fat, monounsaturated fat, fiber, and caffeine. Obesity may be associated with high levels of serum cholesterol (17).

In northwest China, many types of local foods are associated with specific ethnic groups. Recently, hyperlipidemia, obesity and GSD patients have been increasing yearly, coincident with the westernization of the Chinese diet and increased population mobility. In this study, we aimed to investigate the relationship between risk factors such as obesity and hypercholesterolemia with new-onset asymptomatic gallstone disease in a case-control study. We reviewed the clinical records of patients with gallbladder stone during a 6-year period so as to determine whether hyperlipidemia was related to new-onset asymptomatic gallstone disease in a northwestern population in China. The findings in this study would hopefully shed new light on the etiology of GSD in the context of the current lifestyle.

Methods

Subjects selection and data eligibility

In this retrospective analysis, we considered 927 Chinese patients, aged 30 to 82 years, who had undergone routine health check-ups annually in the healthcare center of the Affiliated Hospital of Medical School: Xi'an Jiaotong University, Xi'an, China, from August 2012 to July 2018. They were diagnosed with new-onset gallbladder stone by abdominal ultrasonography examination in 2018. Ninety-two patients were excluded from the analysis for the following reasons: 1) BMI <18.5 Kg/m²; 2) history of gastrointestinal surgery, hepatobiliary disease, weight loss, any cancer; 3) new diagnosis of nonalcoholic fatty liver disease (NAFLD) within two years; 4) BMI had not been maintained within the corresponding BMI category since 2012; i.e., BMI was elevated beyond the range of 24–27.99 Kg/m², defined as overweight; 5) the data were missing any of the following items: age, height, weight, systolic pressure (SBP), diastolic pressure (DBP), serum cholesterol (Chol), triglyceride (TG), low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), fasting blood glucose, or ultrasonographic examination for gallbladder; and 6) future of matching failure in any item following: age, gender, race, occupation, diet including drinking, SBP, DBP and fasting blood glucose. A total of 825 healthy controls, who had undergone health check-ups annually in same healthcare center since August 2012, were matched with subjects. This study was approved by the institutional review board and ethics committee of the Affiliated Hospital, Xi'an Jiaotong University and was conducted in accordance with the institutional ethics committee requirements. The need to obtain consent from the subjects was waived by the institutional review board. The corresponding author and all co-authors had access to all data from this study and reviewed and approved the manuscript.

Data questionnaires

Each subject was asked to complete a questionnaire to collect demographic data and clinical indicators. The questionnaire was designed by the authors and included the following items: telephone numbers, address, marital status, gravidity, oral contraceptive use, hypertension, history of diabetes mellitus, hyperlipidemia, gastrointestinal surgery, chronic liver disease, systemic diseases, family medical conditions, and other medications. Age was validated using the identity card presented to the nurse.

Determination of clinical parameters

In addition to completing the questionnaire, participants were asked to complete a screening panel including common cancer biomarkers, hypertension and transabdominal ultrasonography performed at the site. Blood samples were collected after a 10-h fast from an antecubital vein. These samples were used to assay serum TG, LDL-c, HDL-c, T-Chol, FBG analyses were done using the glucose oxidase method from DiaSys Diagnostic Systems GmbH (Germany). All measurements were done in a central laboratory in a blinded fashion, and according to the manufacturer's instructions. Blood pressure was measured three times by RBP 900 automatic blood pressure measuring instrument (Shenzhen Reycome Science and Technology Ltd. China), and the lowest figure would be available. Participants sat relaxed or had a rest for 30 min.

Determination of obesity factors

An HW-900Y ultrasonic wave height and weight scale (Jiangsu Hengfeng weighting, China) was used to measure the height and weight of all patients by a clinician during the medical examination. Weight was measured without shoes and in light clothing to the nearest 0.1 kg. Height was determined to the nearest 0.1 cm without shoes. WC was measured using a flexible, tension-sensitive, non-stretching tape measure placed directly on the skin. Participants stood relaxed, with arms folded comfortably across the chest so multiple WC measurements could more easily be made. Measures were made at the end of normal expiration with special attention paid to ensure the tape was positioned perpendicular to the long axis of the body and parallel to the floor. A series of four measurements were taken by a single, trained researcher from the right side at the following anatomical locations: *i*) superior border of the iliac crest, *ii*) midpoint between the iliac crest and the lowest rib, *iii*) umbilicus, and *iv*) minimal waist (18). Waist-to-hip ratio (WHR) was calculated as WC in centimeters divided by height in centimeters and multiply by a hundred (percentage, %). Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Patients were grouped by BMI according to expert consensus for medical nutrition therapy of overweight/obesity in China (19), where patients with $\text{BMI} < 23.9 \text{ kg}/\text{m}^2$ were considered in the normal range, $24\text{--}27.9 \text{ kg}/\text{m}^2$ were considered over-weight, and $>28 \text{ kg}/\text{m}^2$ were considered obese. High total cholesterol (hypercholesterolemia) was defined as a serum total cholesterol level of $\geq 6.22 \text{ mmol}/\text{L}$ ($240 \text{ mg}/\text{dL}$) or $\text{LDL-C} \geq 4.14 \text{ mmol}/\text{L}$ ($160 \text{ mg}/\text{dL}$) were diagnosed with hypercholesterolemia, based on blood lipoprotein profiles by the joint committee for developing Chinese guidelines on prevention and treatment of dyslipidemia in adults and The Adult Treatment Panel III (20-22).

Type-B ultrasonic examination for diagnosing GSD and NAFLD

A color Doppler ultrasonic instrument (Toshiba, SSA-510A, Japan) was used to perform to find gallbladder and hepatic diseases. The subjects were fasting and in the supine position. The liver, gallbladder, pancreas and spleen were examined in turn. If a hyperechoic mass with a clear acoustic shadow was seen in the gallbladder cavity, and the location of the mass changed with gravity, a gallstone was diagnosed. No intrahepatic or extrahepatic bile duct stones were found using B-mode ultrasonography.

Fatty liver was diagnosed if patients with the following items A+B and any of items C–F (23): A, No history of alcohol overconsumption ($<210 \text{ g}$ per week in men and $<140 \text{ g}$ per week in women during the past 12 months). No long-term history of taking steatogenic medications, i.e., amiodarone, methotrexate, tamoxifen or glucocorticoids. Exclusion of the diseases that can lead to fatty liver such as genotype 3 HCV infection, Wilson's disease, autoimmune hepatitis, total parenteral nutrition, hypo- β -lipoproteinemia, congenital lipodystrophy, and celiac disease; B, Echoes of diffuse enhancement were exhibited in the near-field of the hepatic region, and the decayed echo in the far-field; C, There were unclear echoes of intrahepatic duct; D, The liver was enlarged mildly to moderately and its edge angle was blunt; E, Color Doppler images suggested that the strikes of intrahepatic blood vessels were normal while the intrahepatic color blood flow signal were reduced or difficult to visualize; and; F, Unclear or incomplete echoes of the hepatic right lobe membrane and diaphragm were found.

Statistical analysis

Descriptive data of participant characteristics were expressed as means \pm standard deviations (SD) for continuous variables, and percentage (%) for categorical variables. Student's t-test and the Chi square test was applied to compare continuous variables and categorical variables, respectively. The relationships between BMI, WC, WHtR, NAFLD, blood lipid and gallbladder stone hazards were examined by using logistic univariate and multivariate regression models, and were stratified by hypercholesterolemia. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

1. Analysis of general characteristics and serum index between gallbladder stone and control groups

The characteristics and serum indexes in the gallbladder stone and control groups are summarized in Table 1. There were 835 of 927 patients with GSD and 835 control subjects of 3471 healthy participants aged 30 to 82 years. Each group included 322

(38.6%) female participants. There was significantly higher weight, BMI, WC, WHtR, serum T-Chol, TG, LDL-c levels and lower HDL-c levels in the GSD group than in the controls ($P<0.05$, respectively) (Table 1). There were 452 (54.1%) normal BMI, 319 (38.2%) overweight and 64 (7.7%) obese participants in the controls; in the GSD group, 331 (39.6%) had normal BMI, 386 (46.2%) were overweight and 118 (14.1%) were obese. There were 40 (5.4%) and 81 (10%) participants with hypercholesterolemia in the GSD and the control group, respectively. Statistical analysis showed significantly higher hypercholesterolemia in the GSD versus the control group ($P<0.001$). In addition, there were 178 (21.1%) and 232 (27.5%) participants with NAFLD in the GSD and control groups, respectively. Statistical analysis showed significantly more NAFLD in the GSD group than in the control group ($P=0.002$).

2. The differences of hazard rate of gallbladder stone between patients with hypercholesterolemia and controls stratified by overweight and obesity or NAFLD

The differences in hazard rate of gallbladder stone in hypercholesterolemia and controls by obesity and overweight are summarized in Fig. 1 and Table 2. Among those with overweight and obesity, there were 39 and 15 participants with hypercholesterolemia in the GSD group, respectively, and 18 and 6 in the control group, respectively. There were significant differences in gallbladder stone morbidity between the hypercholesterolemia and control group in terms of overweight and normal BMI ($\chi^2=4.813$ and 10.424 ; $P=0.028$, and 0.001 , respectively), while there was no significant difference in obesity ($\chi^2=0.466$, $P=0.495$).

As shown in Figure 2 and Table 3, regarding NAFLD and non-NAFLD, there were 32 and 52 participants with hypercholesterolemia in the GSD group, respectively, and 9 and 31 in the control group, respectively. There was a significant difference regarding gallbladder stone morbidity between hypercholesterolemia and control groups in terms of NAFLD and non-NAFLD ($\chi^2=8.902$ and 7.839 ; $P=0.003$ and 0.005 , respectively).

3. Relationships between the indexes with BMI, WHtR, blood lipid, NAFLD, hyperlipidemia and hazard of cholesterol gallstone.

Table 4 shows the risk factors for developing GSD based on univariate and multivariate logistic regression. Univariate logistic regression showed significantly positive correlations for weight, BMI, WC, WHtR, NAFLD, hypercholesterolemia, serum T-Chol, TG and LDL-c levels with hazard of GSD ($P<0.05$, all), while there were significantly negative correlations between serum HDL-c levels and risk of GSD ($P<0.001$). In addition, compared with patients with normal BMI, there was significantly more GSD in overweight and obese patients ($P<0.001$, both). Multivariate logistic regression including WC showed that there were significantly positive correlations between WC, NAFLD, hypercholesterolemia and risk of GSD ($P<0.05$, all), while there were significantly negative correlations between serum HDL-c, TG levels, BMI and risk of GSD ($P<0.05$, all). Multivariate logistic regression including WHtR showed that there was significantly positive correlations between WHtR, NAFLD, hypercholesterolemia, and risk of GSD ($P<0.05$, all), while there were significantly negative correlations between serum TG, HDL-c levels, BMI and risk of GSD ($P<0.05$, all).

To investigate the possible reasons that caused this result, we further analyzed data using univariate and multivariate logistic regression analysis (Table 5). The differences between GSD and control group were studied by stratifying with hypercholesterolemia. Univariate logistic regression showed significantly positive correlations between NAFLD, serum LDL-c levels, and risk of GSD ($P<0.05$ for all), high-level T-chol was a weak risk factor for GSD ($P=0.082$), while there were significantly negative correlations for male, weight, DBP, serum HDL-c, FBG levels and risk of GSD ($P<0.001$). Multivariate logistic regression showed that there were weak positive correlations between NAFLD and risk of GSD ($P=0.054$), and significantly negative correlations between serum HDL-c levels, weight, and hazard of GSD ($P<0.01$, both), with a weak negative correlation between serum LDL-c and hazard of GSD ($P=0.071$).

Discussion

GSD is a common disease that can progress to severe cholecystitis; it is a strong risk factor for gallbladder cancer (GBC). Recent European studies have shown that hypertriglyceridemia, hypercholesterolemia and low levels of high-density lipoprotein cholesterol (HDL) are common in patients with cholelithiasis (24, 25). To verify our initial hypothesis, we performed this

clinically-based, age-, sex-, diet-, nation-, blood pressure-, and FBG-matched case-controlled study of the risk factors for asymptomatic GSD, of the epidemiologic factors that are known risk factors for GSD. We found that elevated BMI, enlarged WC and WHtR, NAFLD, and HC are very likely important risk factors for hazard of new-onset asymptomatic GSD (24-27). Multivariate logistic regression further strengthened the notion that hypercholesterolemia may be an independent risk of new-onset asymptomatic gallstone diseases, and abdominal obesity and NAFLD might promote the occurrence of asymptomatic gallbladder stone disease.

First, we confirmed that there were no significantly positive correlations between GSD and WC, WHtR after further adjusted by hypercholesterolemia, though obesity has been recognized for its strong association with gallstone diseases. We found that obesity per se was not linked directly to cholelithiasis risk, and it was highly probable that both share several pathophysiologic and genomic pathways (28): On the one hand, hormone-sensitive lipase and adipose triglyceride lipase, discovered recently in adipose tissue, mediate the mobilization of stored triacylglycerol (29). Elevated triglyceride levels might decrease sensitivity to cholecystokinin (30), and might increase both biliary cholesterol saturation and increase bile viscosity by enhancing mucin production (31), thereby adding to the enhanced risk of gall stone disease. On the other hand, there is a vicious circle: Obesity might result in increasing levels of cholesterol secretion from liver, and bile supersaturation in biliary secretion of cholesterol. Meanwhile, there is a linear relationship between cholesterol production and body fat (32), and biliary cholesterol saturation, bile acid synthesis, turnover rates and bile acid pool sizes are increased in obesity (30, 33). In addition, it is clear that abdominal adiposity is associated with insulin resistance. Hepatic insulin resistance directly increases cholesterol secretion and reduces bile acid synthesis, leading to bile crystallization and stone formation. Hepatic insulin resistance has been identified as a key determinant of cholesterol gallstones formation by itself (34, 35).

Second, our study showed that the prevalence NAFLD was higher in GSD than in controls, suggesting a positive association between NAFLD and the risk of new-onset asymptomatic gallstone disease. A recent study reported that NAFLD was significantly associated with gallstone formation (36). It is worth noting that our multivariate regression showed that there was a weak positive correlation between GSD and NAFLD in hypercholesterolemia patients, and even based on the above, we tend to agree with the notion that NAFLD, possibly including hypertriglyceridemia, might be a secondary actor in overweight/obesity and hypercholesterolemia patients after eliminating blood pressure and diabetes (blood sugar, insulin resistance). These are the following supporting facts: first, NAFLD is typically characterized by atherogenic dyslipidemia featuring higher triglyceride levels with greater circulating very-low-density lipoprotein levels, lower levels of dense LDL-c and low levels of dysfunctional HDL-c (41). A recent report supported the notion that hypercholesterolemia is a major risk factor for the initiation and development of NAFLD (42), resulting from high-cholesterol diet, lipase deficiencies and liver inflammation (43, 44). Second, NAFLD, which affects approximately 12% to 40% of the general population, up to 95% of obese people, and nearly 70% of the overweight, is especially increased among middle-aged populations with obesity, type 2 diabetes, dyslipidemia, and other metabolic syndromes. NAFLD was observed in 96.5% ($p < 0.001$) of subjects with overweight, hypertriglyceridemia, and hypercholesterolemia (37). Third, NAFLD is strongly associated with obesity, which might trigger decreased expression of leptin receptor in liver tissue and insulin resistance (38). The latter two interactions promote the occurrence and development of fatty liver (39).

We found that hypercholesterolemia may be an independent risk for new-onset asymptomatic gallstone diseases, and recent studies give strong backing to this notion. First, our logistic regression showed that TG and TC were not significantly correlated with GSD in patients with hypercholesterolemia, suggesting that the increased cholesterol and triglycerides play an integrally synergistic role in the pathogenesis of GSD: High levels of secretion of cholesterol in bile and the subsequent supersaturation of bile contribute to the formation of bile mud, increased triglycerides reduce gallbladder movement, reduce the sensitivity to cholecystokinin (CCK), and thereby reduce the gallbladder movement (30, 40). A recent report strongly supported the notion that sphingolipid ceramide accumulation in hypercholesterolemia causes inflammatory responses of the gallbladder (41). Second, we found that serum LDL-c levels were significantly positively associated with the risk of new-onset asymptomatic GSD in participants with hypercholesterolemia. This is in agreement with findings of Ivanchenkova et al. (42), who found that serum LDL-c levels were increased in gallbladder cholesterosis and were a risk factor for gallbladder cholesterosis, resulting in the minor particles of LDL being more rapidly penetrated into the gallbladder tissue, where the gallbladder wall is intensively involved with macrophages, participating in the formation of foamy cells. Lauridsen et al. (43) found that accelerating elevated

LDL-c levels play a synergistic role with the continuous development and formation of gallstones in patients who have undergone cholecystectomy for symptomatic gallstones. Third, a study found that raised HDL-c levels were inversely associated with gallstone prevalence (44), implying that improvement HDL-c levels may be one of the mechanisms in the treatment and prevention of cholesterol gallstone disease (45). Probably, HDL-c, a precursor of bile acids, represents a major source of biliary cholesterol; however, elevated serum HDL increases primary bile acid formation which solubilizes cholesterol and reduces biliary cholesterol saturation (31), both which are important for reducing the lithogenicity of the bile (44). HDL might mediate the transport of excess cholesterol from lipid-laden macrophages within the vascular wall back to the liver for excretion into the bile, which represents the major route for irreversible removal of cholesterol from the body (46).

Interestingly, elevated weight was inversely associated with GSD in patients with hypercholesterolemia. We synthesize the relevant data with the following viewpoints: On the one hand, rapid weight loss leads to a change in cholesterol metabolism and consequently increases the concentration of cholesterol in the bile to a level at which not all cholesterol can be dissolved by bile salts. Undissolved cholesterol is prone to crystallize into stones, especially in the presence of calcium and mucin, a glycoprotein that stimulates cholesterol crystal aggregation (47). On the other hand, we consider lost weight to be a risk factor for GSD in patients with hypercholesterolemia, resulting from the participants including lean individuals, who may have diet models characterized by irrational vegetarian diets during weight loss. This results in not maintaining reasonably high intake of monounsaturated fats and fiber, olive oil and fish (ω -3 fatty acids), vegetable protein, fruit, coffee, or vitamin C (7, 48). A recent study showed that a supplementation with 5% chitosan oligosaccharide, a common food additive for weight loss, may cause liver damage via higher hepatic cholesterol accumulation and higher intestinal cholesterol uptake in high fat diet-fed rats (49). A carbohydrate-restricted, high-fat diet increased LDL-cholesterol concentrations because this effect of weight loss was related to the lack of suppression of both fasting and 24-h free fatty acids (50). However, weight loss or improper diet may cause imbalance of cholesterol homeostasis, and incomplete and slow gallbladder emptying may lead to cholestasis, increasing the risk of gallstone formation.

Strengths and limitations of this study. Strengths of this study include the large number of participants, a retrospective design, and complete follow-up for morbidities. The data came from participants who regularly undergo annual physical screening with long-term follow-up. We reviewed the case histories for more than five years, confirming that the patients had newly presented to the case group. The matched participants had the same occupations and came from similar environments. Our healthcare center, the largest institution in northwest China, is responsible for the health survey of multi-ethnic groups in the adjacent three provinces. The large scale as well as broad coverage of multi-ethnic people made the data in current study very informative and persuasive. Nevertheless, the present study has several limitations. First, this was not a multicenter and cohort study, and the statistics may be biased as a result. Second, the limited ethnic population may affect the generalizability of our findings. In particular, the association between BMI and gallbladder stone may differ among ethnic and regional groups with varying dietary structures and genetic diversity. Third, our study lacked data such as chemical composition analysis, cholesterol gallbladder stone-related risk factors, bile acid levels, and gastrointestinal dysfunction, because imbalance between bile salts and cholesterol in bile fluid cause bile fluid turn to become sludge, crystals and eventually gallstones.

Conclusions

We found that hypercholesterolemia may be an independent risk factor for new-onset asymptomatic gallstone disease. Abdominal obesity and NAFLD might promote the occurrence of asymptomatic gallbladder stone disease. The formation of gallbladder stones is enhanced with constant high concentrations of total cholesterol, which relates to the hypersecretion of cholesterol in the bile and the subsequent supersaturation of bile. This contributes to the formation of biliary sludge. In addition, hypertriglyceridemia consequently reduces gallbladder motility with decreased sensitivity to cholecystokinin. Notably we were the first to find that elevated weight was inversely associated with GSD in patients with hypercholesterolemia, suggesting that weight loss or improper diet may cause imbalance of cholesterol homeostasis. Incomplete and slow gallbladder emptying may lead to cholestasis, which increases the risk of gallstone formation. However, further study is needed to confirm this mechanism.

Abbreviations

GSD: gallbladder stone disease; 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; HC: hypercholesterolemia.

Declarations

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Availability of data and materials

The authors declare that the data supporting the findings of this study are available within the article.

Authors' contributions

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

Ethics approval and consent to participate

The study was reviewed and approved by the First Affiliated Hospital of Xi'an Jiaotong University. No.XJTU1AF2019LSK-017. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Informed consent:

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

Data sharing:

The technical appendix, statistical code and dataset are available from the corresponding author at bwsheng@126.com. No additional data are available.

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Tables

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

	Before matching				After matching			
	Control Group (N=3471)	GSD group (N=927)	χ^2/T value	P value	Control group (N=835)	GSD group (N=835)	χ^2/T value	P value
Female (%)	1713 (49.4%)	331 (35.7%)	55.537	<0.001	38.6%, 322	38.6%,322	0.000*	1.000
Age (Year)	59.32±13.7	59.14±12.3	-6.041*	<0.001	58.68±11.4	58.65±11.4	-0.060	0.952
Han (%)	2982 (85.9)	790(85.2)	0.284	0.594	760 (91.0)	765 (91.6)	0.189*	0.664
Occupation (%)			62.257*	<0.001			0.476*	0.976
Worker	218 (6.3)	62 (6.7)	0.202	0.653	62 (7.5)	60 (7.2)	0.027*	0.869
Professional technician	316 (9.1)	112 (12.1)	7.043	0.008	112 (13.5)	109 (13.1)	0.051*	0.821
Manager	193 (5.6)	81 (8.7)	11.693	0.001	81 (9.7)	79 (9.5)	0.028*	0.868
Retiree	2062 (59.4)	583 (62.9)	3.729	0.053	515 (61.9)	518 (62.0)	0.023*	0.880
Others	682 (19.6)	89 (9.6)	57.144	<0.001	62 (7.5)	69 (8.3)	0.406*	0.524
SBP(mmHg)	120.99±17.9	122.70±17.5	-2.586	0.01	122.05±17.2	122.22±16.2	0.209	0.834
DBP(mmHg)	76.76±10.6	77.49±10.77	-1.839	0.066	77.33±10.5	77.10±9.7	-0.465	0.642
FGB(mmol/L)	5.27±1.3	5.18±1.4	-0.677	0.499	5.38±1.5	5.34±1.2	-0.758	0.449
Height(cm)	165.27±8.6	166.95±8.2	-5.339	<0.001	166.38±7.2	166.71±8.1	0.870	0.384
Weight(Kg)	65.82±11.4	68.38±11.2	6.053	<0.001	66.77±10.7	68.44±10.9	3.170	0.002
BMI(Kg/m ²)	24.00±3.1	24.44±2.9	0.905	<0.001	24.04±2.8	24.54±2.8	3.580	<0.001
Normal BMI(%)	1726 (49.7%)	431 (46.6%)	2.774	0.096	452 (54.1%)	331 (39.6%)	35.332*	<0.001
Overweight(%)	1126 (32.4%)	392(42.4%)	31.477	<0.001	319 (38.2 %)	386 (46.2%)	11.033*	0.001
Obesity(%)	619 (17.8%)	101 (10.9%)	27.441	<0.001	64 (7.7 %)	118 (14.1 %)	18.226*	<0.001
WC(cm)	82.41±7.0	83.53±7.8	4.182	<0.001	82.83±6.7	87.75±7.9	13.759	<0.001
WHR(%)	49.97±4.7	49.82±4.0	-6.768	<0.001	49.84±4.1	52.73±5.0	12.827	<0.001
T-Chol(mmol/L)	4.88±0.9	4.90±1.0	0.610	0.542	4.65±0.8	4.87±0.9	5.329	<0.001
TG(mmol/L)	1.49±0.8	1.83±1.3	9.911	<0.001	1.51±0.8	1.83±1.2	6.120	<0.001
HDL-c(mmol/L)	2.53±1.0	1.28±0.3	-35.764	<0.001	2.25±0.9	1.28±0.3	-28.046	<0.001
LDL-c(mmol/L)	2.0±1.3	3.0±0.8	22.215	<0.001	2.00±1.0	2.99±0.8	21.502	<0.001
Drink (%)	506 (13.5)	124 (13.4)	0.009	0.925	105 (12.6)	107 (12.8)	0.022*	0.883
Eating habits (%)			117.822	<0.001			0.148	0.986
Vegan	127 (3.7)	78 (8.4)	32.396	<0.001	69 (8.3)	71 (8.5)	0.031	0.860

vegetarian	508 (14.6)	115 (12.4)	3.074	0.080	114 (13.7)	110 (13.2)	0.082	0.774
Meat & vegetarians	2730 (78.7)	544 (58.7)	142.746	<0.001	470 (56.3)	468 (56.0)	0.010	0.921
Carnivorous diet	376 (10.8)	190 (20.5)	55.295	<0.001	182 (21.8)	186 (22.3)	0.056	0.813
NAFLD	744(21.4)	227(24.5)	4.083	0.043	178(21.1)	232(27.5)	9.448	0.002
HC	327 (9.4)	106 (11.5)	3.343	0.068	40(4.8)	84(10.1)	17.211	<0.001

GSD: gallbladder stone disease; 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; HC: hypercholesterolemia.

Table 2. The difference of GSD between Hypercholesterolemia and non-hypercholesterolemia adjusted by overweight, obesity and normal BMI

	Overweight		Obesity		Normal BMI	
	GSD	Control	GSD	Control	GSD	Control
Model 1	39*	18	15&	6	30§	16
Model 2	347**	301	103&&	58	301§§	436

Note GSD: gallbladder stone disease Model 1 Hypercholesterolemia Model 2 Non-hypercholesterolemia

*vs **: $\chi^2=4.813$, P=0.028, OR=1.879, 95%CI: 1.053~3.355

& vs &&: $\chi^2=0.466$, P=0.495, OR=1.408, 95%CI: 0.518~3.826

• vs §§: $\chi^2=10.424$, P=0.001, OR=2.716, 95%CI: 1.455~5.070

Table 3. The difference of GSD between hypercholesterolemia and non adjusted by NAFLD and non-NAFLD

	NAFLD		non-NAFLD	
	GSD	Control	GSD	Control
Model 1	32*	9	52&	31
Model 2	203**	169	551&&	626

Note GSD: gallbladder stone disease group Model 1 Hypercholesterolemia Model 2 Non-hypercholesterolemia

*vs *: $\chi^2=8902$, P=0.003, OR=2.960, 95%CI: 1.374~6.375

& vs &&: $\chi^2=7.839$, P=0.005, OR=1.906 95%CI: 1.204~3.017

Table 4. Univariate and multivariate analysis of gallbladder stone and BMI, WHtR, blood lipid, NAFLD and HTC

Factors	Univariate			Multivariate1			Multivariate2		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Weight	1.013	1.004-1.022	0.004	*	*	*	*	*	*
BMI	1.045	1.010~1.081	0.011	0.243	0.202~0.291	<0.001	0.596	0.544~0.652	<0.001
Normal	1								
Overweight	1.652	1.346~2.029	<0.001	/	/	/	/	/	/
Obesity	2.518	1.800~3.522	<0.001	/	/	/	/	/	/
WC	1.080	1.065~1.095	<0.001	1.677	1.571~1.790	<0.001	/	/	/
WHtR	1.116	1.092~1.141	<0.001	/	/	/	1.340	1.273~1.409	<0.001
TG	1.382	1.237~1.543	<0.001	0.817	0.713~0.935	0.003	0.814	0.721~0.919	0.001
HDL-c	0.120	0.095~0.151	<0.001	0.140	0.103~0.191	<0.001	0.076	0.056~0.104	<0.001
LDL-c	2.625	2.330~2.957	<0.001	*	*	*	*	*	*
TC	1.273	1.140~1.420	<0.001	*	*	*	*	*	*
FBG	0.974	0.906-1.047	0.481	-	-	-	-	-	-
NAFLD	1.475	1.180~1.845	0.001	1.746	1.202~2.537	0.003	1.449	1.042~2.018	0.028
HC	2.195	1.502~3.208	<0.001	2.397	1.398~4.112	0.001	2.392	1.456~3.929	0.001
SBP	1.001	0.996~1.007	0.67	-	-	-	-	-	-
DBP	1.000	0.991~1.010	0.919	-	-	-	-	-	-
Drink	1.022	0.766~1.363	0.883	-	-	-	-	-	-

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

*eliminated for the definition of BMI or hyperlipidemia in multivariate regression

- eliminated for no statistical significance in univariate regression

Table 5. Univariate and multivariate analysis of gallbladder stone and BMI, WHtR, blood lipid, NAFLD stratified by HC

Factors	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
Gender (M)	0.244	0.097-0.612	0.003	0.412	0.112-1.518	0.183
Age	1.000	0.968-1.033	0.999	-	-	-
Weight	0.961	0.929-0.994	0.022	0.930	0.875-0.988	0.018
BMI	0.917	0.811~1.036	0.164	-	-	-
WC	1.010	0.961~1.062	0.686	-	-	-
WHtR	1.067	0.987~1.154	0.105	-	-	-
SBP	0.993	0.972-1.015	0.547	-	-	-
DBP	0.957	0.919-0.995	0.029	0.957	0.905-1.011	0.119
FBG	0.687	0.485-0.973	0.034	0.814	0.519-1.277	0.370
TC	1.526	0.948~2.457	0.082	1.722	0.818~3.627	0.153
TG	1.229	0.916~1.648	0.169	-	-	-
HDL-c	0.305	0.169~0.548	<0.001	0.144	0.055~0.376	<0.001
LDL-c	1.493	1.043~2.139	0.029	0.527	0.263~1.056	0.071
NAFLD	2.723	1.155~6.420	0.022	3.284	0.979~11.013	0.054
Drink	1.318	0.392~4.436	0.650	-	-	-

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; HC: hypercholesterolemia.

- eliminated for no statistical significance in univariate regression