Inverse association between fasting blood glucose and occurrence of gallbladder cancer in type 2 diabetes mellitus patients: a case-control study

Bin-Wu Sheng (bwsheng@126.com)
Xi'an Jiaotong University School of Medicine https://orcid.org/0000-0001-5322-5180
Jianqin Zhang
Xi'an Jiaotong University School of Medicine
Min Chen
Xi'an Jiaotong University School of Medicine
Mao Ma
Xi'an Jiaotong University School of Medicine

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Abstract

Purpose

To explore the reason for the correlation between diabetes mellitus (DM) and gallbladder cancer (GBC) in an epidemiological setting.

Methods

We summarized the clinical and laboratory data of 2210 GBC patients within 3524 Chinese patients in our hospital from January 2009 to December 2020. Seventeen influencing factors for GBC, including gender, body mass index (BMI), fasting blood glucose (FBG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), retinol binding protein (RBP), lipid indexes, and others, were analyzed by unconditional logistic regression analysis in this case-control study.

Results

On univariate logistic regression, GBC likelihood was significantly and positively correlated with serum triglyceride, low-density lipoprotein cholesterol, FINS, and HOMA-IR; being female; BMI; DM; NAFLD; and GSD, and it was significantly negatively correlated with high-density lipoprotein cholesterol and FBG concentrations in serum and with hypertension. In multivariate analysis, FINS was significantly positively associated with GBC risk, while DM had an insignificant negative association, and FBG levels were also not important. HOMA-IR was a most remarkable independent factor of GBC risk in DM patients. FBG levels showed a significant negative relationship to GBC in DM individuals.

Conclusions

Our findings revealed that the efficient treatment of insulin-resistance is an important approach for decreasing GBC risk, as opposed to lowering blood sugar alone, especially in DM patients. Interestingly, FBG might have an inverse association with the development of GBC in type 2 DM patients. Exciting, we found initially that a dramatic drop in RBP might be helpful in predicting the occurrence of GBC.

Introduction

Evidence is being gathered confirming that type 2 diabetes mellitus (DM) results in a consistent increase in the risk of cancers, including those of the liver and colorectum; the pancreas, biliary tract, and esophagus in males; and breast and endometrium in females (1). Individuals with insulin resistance (IR) are at an increased risk of developing many medical problems, including obesity, type 2 DM, metabolic syndrome (MetS), and certain cancers (2, 3). Several prospective epidemiological studies showed that excessive weight along with low physical inactivity is a key determining factor in the development of IR with associated hyperglycemia and hyperinsulinemia, which further promote tumor development involving several biological pathways, e.g., chronic low-grade inflammation, glucose toxicity, advanced glycosylated end-product metabolism, and the adenosine monophosphate kinase pathway (4). Moreover, a population-based study suggested that MetS and IR have roles in the etiology of biliary tract cancers and biliary stones (5). However, recent epidemiological data support the postulation that obesity protects against some cancers, as it has association with a reduced likelihood of premenopausal breast cancer, a lower incidence rate and mortality of small cell lung and head/neck cancers (from the World Cancer Research Fund/American Institute for Cancer Research and the International Agency for Research on Cancer Working Group), as well as a better survival rate for those with metastatic colorectal and non-small cell lung cancers and renal cell carcinoma (6, 7). Our previous study additionally highlighted that elevated weight was inversely associated with gallbladder stone diseases (GBD) in patients with hypercholesterolemia, which implies there is an unknown link between GBD and gallbladder cancer (GBC) (8). Furthermore, the potential risk factors underlying the associations between the above factors, especially IR in relation to obesity, DM, MetS, and cancers, have not been fully clarified.

GBC, with its typically late manifestation and poor prognosis, is the most prevalent biliary tract tumor type. A new epidemiology inquiry by the Global Health Observatory revealed that morbidity from GBC varies between countries and differentiates with the frequency of potential risk factors, including excess weight/obesity, hyperlipidemia, lifestyle, and DM (9). A study conducted in recent years demonstrated a close relationship between obesity and GBC, in which obesity was found to disturb the metabolism of lipids and endogenous hormones, affect motility of the gallbladder, increase incidences of gallstones, and hence are fundamental contributors to GBC (10). The rates of IR, type 2 DM, hypertension, dyslipidemia, etc., increase in obese patients, and in type 2 DM-linked hyperinsulinemia, insulin receptors or insulin growth factor (IGF) might mediate target cells to directly or indirectly promote cancer through the mechanisms of proliferation, anti-apoptosis, angiogenesis, and lymphogenesis (7). Disrupted blood glucose control participates in the emergence of cancer, and the link between genomic damage and blood glucose control is clear and strong in type 2 DM patients (11) and may, for example, impair the function of gallbladder emptying (12). Thus, an important research aim is to prevent the occurrence of GBC and reduce its mortality by clarifying the epidemiological mechanisms of GBC that relate to IR, including hyperglycemia and hyperinsulinemia. In this case-control investigation, we aimed to dissect the role of common risk factors (e.g., IR) on the etiology of GBC by comparing clinical and laboratory data.

Material And Methods

Subject selection and data eligibility

We considered retrospective anthropometric and laboratory parameters (blood lipids, fasting blood glucose [FBG], fasting insulin [FINS], etc.) of 2210 study subjects enrolled from 3524 Chinese GBC patients aged 30 to 80 years in the first Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an, China, from Jan 2009 to Dec 2020, as shown in Figure 1. We compared them to 2210 matched subjects without cancer from more than 3808 individuals

who attended check-ups in same healthcare facility each year. All participants in the two groups were matched by age, ethnicity, occupation, and drinking habits. This study complied with the Institutional Ethics Committee requirements of the above-mentioned hospital (No: XJTU1AF2020LSK-160).

Data questionnaires and determination of clinical parameters

Participants had been interviewed with questions about ethnicity; ID number; occupation; history of medication, DM, hypertension, surgery, hepatobiliary disease, and any cancers, including family histories. Participant identities were confirmed using their identity cards and their height and weight recorded during the medical examination or in-hospital by a full-time nurse. All study points for each GBC patient were completed by the surgeons in charge during their stay in hospital and stored in our hospital information system. For the controls, a screening panel, including common tumor marks, transabdominal ultrasonography, and measurements pertaining to our study items, was completed, and the data were stored in our medical information management system.

Antecubital vein blood samples were drawn after a 10-h fast, and the serum was assayed for total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), FBG, retinol-binding protein (RBP), and FINS. GPO-PAP and COD-PAP methods were applied to TG and TC analyses, respectively. Homogenous methods were used in LDL-c and HDL-c analyses, and the glucose oxidase approach measured FBG. An immunoturbidimetry assay or radioimmunoassay was used to measure the concentration of blood RBP and FINS, respectively. All assays were blind and carried out in the same central laboratory by following the manufacturers' protocols. Blood pressure readings were recorded thrice after sitting while relaxed or resting for 30 min with an RBP 900 automatic blood pressure measuring instrument (Shenzhen Reycome Science and Technology Ltd., China), and the lowest figures were used in the analyses. By adopting an HW-900Y ultrasonic wave height and weight scale (Jiangsu Hengfeng Weighting, China), we measured the height and weight of all patients. $BMI = Weight(Kg) / Height^2 \left(m^2\right)$

Type-B ultrasonic-based diagnosis of GSD and NAFLD

A Color Doppler ultrasonic instrument (Toshiba, SSA-510A, Japan) was utilized to examine volunteers for gallbladder and hepatic diseases. After fasting and placement in the supine position, each patient's liver, gallbladder, pancreas, and spleen were examined in turn. Both gallstones and non-alcoholic fatty liver disease (NAFLD) were diagnosed as mentioned in our previous publication (8).

Determination of diabetes, hypertension, and insulin resistance

Diabetes diagnosis was completed by a professional endocrinologist according to the latest diagnostic criteria used in China. The newest diabetes patients were diagnosed based on the guidelines for type 2 DM prevention and treatment in China 2020 (13). Hypertension was diagnosed by a cardiovascular specialist who followed guidelines on the pharmacological treatment of hypertension in adults published by the World Health Organization. Those with Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg were diagnosed as having hypertension, as advised in the newest edition (14). The derivation of the homeostasis model assessment-insulin resistance (HOMA-IR) incorporated fasting glucose and insulin according to the formula:

$$HOMA - IR = [FBG(mmol/L) \times FIN(mU/L)]/22.5$$

,

HOMA-IR ≥ 2.69 was defined as IR according to epidemiological survey data (from 13045 Chinese population survey data collected by the China Diabetes Prevention & Control Cooperative Group) in China in 2014 (15).

Statistical analysis

All data underwent statistical analysis in SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA), and significance was considered from a P value < 0.05. Data are presented as mean ± standard deviation (SD), as they were continuous and tended towards a normal distribution and there were a sufficient number of participants. Continuous and categorical variables are presented as values and frequency (%), respectively. Variables from two groups were compared via a Pearson's chi-square test (categorical variables) or Student's t-test (continuous variables). The relationships between gender, BMI, RBP, FBG, FINS, blood lipids, NAFLD, hypertension, diabetes, and gallbladder cancer risks were determined via multivariate logistic regression models and stratified by the involvement of IR or not.

Results

1. General characteristics and serum indexes of the GBC and control groups

Differences in the general characteristics and serum indexes of GBC and control groups are outlined in Table 1: 2210 out of the 2265 GBC patients and 2210 subjects of the 3808 healthy controls aged 30 to 80 years, and 1421 (64.3%) and 1034 (46.8%) females in the GBC and control groups, respectively. There was a higher risk of GBC for females (HR = 2.048, 95%CI: 1.816-2.311). There were significantly higher BMI, FINS, TG, LDL-c, and HOMA-IR and lower SBP, DBP, HDL-c, and FBG levels in the GSD group compared with the controls, and there were significantly higher incidences of DM, NAFLD, GSD, and IR in GSD patients (P<0.05, Table 1).

2. Relationships between studied indexes and risk rate of GSC

Factors related to the of risk GBC development based on univariate and multivariate logistic regression are listed in Table 2. A significantly positive correlation between serum TG, LDL-c, FINS, HOMA-IR levels, female sex and BMI, DM, NAFLD, GSD, and GBC risk (P<0.05), and a significantly negative correlation between serum RBP, HDL-c, FBG levels, SBP, DBP, and HBP and GBC risk (P<0.001, all) were revealed by univariate logistic regression. On inclusion of HOMA-IR in multivariate logistic regression, we found no significant correlation between BMI, HBP, and risk of GSD (P>0.05, all), while these had a significantly negative association with GBC risk in DM and NAFLD patients (P<0.05, all). However, after including FINS and FBG in the multivariate analysis, FINS was positively associated with GBC risk (P<0.001), while the association with DM and FBG levels was insignificant (P>0.05).

To investigate the possible causes of the above results, we analyzed data using univariate and multivariate logistic regression analyses (as shown in Tables 3, 4, and 5). The difference between the GBC and control groups was studied by stratifying the patients by IR. Univariate logistic regression calculated no significantly positive correlation between BMI, GSD, NAFLD and GBC risk (P > 0.05, all), and similar results were seen for serum TG, LDL-c, HDL-c, RBP, FINS, FBG, HOMA-IR, DBP, SBP, HBP versus overall, while an inversion result was done for DM. Multivariate logistic regression, including HOMA-IR, indicated GBC risk had a positive correlation with serum TG, LDL-c, and HOMA-IR levels (P<0.01) and a significantly negative correlation with serum HDL-c, RBP levels, and DM (P<0.001, all). Significant positive relationships between GBC risk and serum TG, LDL-c, and FINS levels, and negative relationships between GBC risk and serum RBP, HDL-c were observed when we included FINS and FBG, while there was no significant correlation with female sex, FBG, or DM (Table 3).

In the non-IR patients, similar results were obtained for gender, BMI, GSD, NAFLD, HBP, DBP, SBP, serum TG, LDL-c, HDL-c, RBP, HOMA-IR, FINS, FBG versus overall data in univariate logistic regression, while the association between DM and GBC risk was inverted (OR = 0.03, 95%CI: 0.01-0.095) versus overall (OR= 1. 252, 95%CI: 1.037~1.512). In multivariate analysis, the inclusion of HOMA-IR showed the relationships between GBC risk and serum TG, LDL-c levels, HOMA-IR levels, GSD, and being female were significantly positive, but those for serum RBP, HDL-c levels, DM, and NAFLD were significantly negative (P < 0.05, respectively); when considering FBG and FINS, the outcomes were similar to the above results, and elevated FINS levels predicted a high GBC risk, while elevated FBG levels lowered the chance of GBC (P<0.05, respectively, Table 4).

Data for the DM patients were analyzed while considering HOMA-IR (in relation to IR) or FBG (Table 5). On univariate logistic regression, significantly positive correlations between serum TG, LDL-c, FINS levels, female sex, HOMA-IR, GSD, and risk of GBC (P<0.05, respectively) emerged, while the latter had a significantly negative correlation with serum RBP, HDL-c, FBG levels, SBP, DBP, and BMI (P<0.05, respectively). The inclusion of HOMA-IR in the multivariate logistic regression showed no significant correlation between serum HDL-c levels, BMI, GSD, SBP, DBP, or GBC risk (P>0.05, respectively), while the other indexes had similar relationships to GBC risk, as revealed by univariate logistic regression. There were significant positive correlations between female sex, serum TG and LDL-c, HOMA-IR and GBC risk, and significant negation between serum RBP and GBC risk by multivariate analysis considering HOMA-IR; when considering FBG and eliminating FINS levels in the analysis, there was a negative correlation between FBG and GBC (OR=0.843, P=0.014), and similar outcomes were revealed for Female, serum TG, LDL-c and RBP, while negative correlations were seen for SBP and serum HDL-c (P<0.05, all).

Discussion

In this clinical case-control study of patients matched for age, ethnicity, occupation, familial history of cancer, and drinking habits in northwestern China, we identified HOMA-IR levels to be a risk factor for GBC but GSD and female (16) patients, and type 2 DM had an increased risk of GBC as a recent study also discovered (17). Interestingly, we found controlling HOMA-IR or insulin levels, rather than FBG levels, can more effectively lower GBC risk relating to DM, and there was no significantly higher morbidity from GBC in IR patients with GSD or NAFLD, including females.

Our multivariate logistic regression considering HOMA-IR stratified by IR showed that DM and GBC risk had a significantly negative correlation, while after including FINS and FBG levels, the significant association between DM and GBC risk, as well as FBG levels, was absent. In contrast, the relationships between the risk of GBC and FINS, HOMA-IR were significantly positive. Moreover, HOMA-IR was the most remarkable independent risk factor for GBC in the non-IR and total patient groups. The results tended to further indicate that hyperinsulinemia or insulin resistance have key roles in increasing GBC risk, and poor blood glucose control might increase GBC risk, even in non-IR patients. On the one hand, the above results are supported by a recent study in which insulin was seen to reduce the levels of IGF-binding protein (IGFBP)-1 and IGFBP-2 in the circulation, resulting in a circulating IGF increase; and IGF and insulin might stimulate target cells to move toward malignant transformation (18). On the other hand, to our knowledge, the goal of diabetes treatment is to correct metabolic disorders, improve clinical symptoms (such as polyuria and increased eating and drinking), and delay the occurrence of diabetic complications by controlling blood sugar concentration. In China, the most common hypoglycemic drugs are insulin secretagogues and metformin. The former may induce hyperinsulinemia after long-term oral administration, especially in IR patients. The latter, metformin hydrochloride, a first-line hypoglycemic drug, induced porcelain gallbladder in C57Bl/6 mice while reducing the chance of gallstone formation (19) and may reduce blood glucose by promoting the uptake of glucose by peripheral tissues, inhibiting gluconeogenesis, delaying the absorption of glucose in the intestine, reducing hepatic glycogen output, and increasing the utilization of sugar by inducing the anaerobic fermentation of sugar in the small intestine, which leads to increased triglyceride liver synthesis. Triglyceride synthesis in cells is heavily reliant on the glycerol and fatty acids produced by glucose metabolism; glycerol is derived from the glycolysis-produced dihydroxyacetone phosphate, and fatty acids are synthesized by acetyl coenzyme A, a product of the oxidative decomposition of sugar (20). In short, a high-carbohydrate diet or sugar accumulation plays the role of a bridge (21), which supports the idea that inappropriately controlled blood glucose might promote GBC risk with hypertriglyceridemia or/and IR.

As our study showed, high TG levels are the most significant players related to GSC risk, especially in IR patients (OR=96.437). Hirasawa et al. analyzed the association between endometrial cancer and the risk of MetS in a case-control study and verified that hypertriglyceridemia was significantly frequent in endometrial cancer patients (22). Retrospective analysis by Wuermli et al. of anthropometric and laboratory parameters of 504 prostate patients and 565 age-matched patients with benign prostatic hyperplasia highlighted a relationship between hypertriglyceridemia and a greater risk of prostate cancer (23).

Although few reports have clarified the mechanisms of their correlation, we propose that hypertriglyceridemia is closely associated with IR, and chronic hyperinsulinemia in the IR state could stimulate very-low-density lipoprotein (VLDL)-triglyceride synthesis (20). Reportedly, the VLDL receptor is a participant in the pathogenesis of GBC by its mitogen-activated protein kinase-based regulation of the expression of fibroblast growth factor receptor signaling pathway components (24). Moreover, it is known that hypertriglyceridemia closely relates to NAFLD, which may progress into non-alcoholic steatohepatitis, triggering the development of hepatocellular carcinoma (21). The present study demonstrated that NAFLD might not be a predictive factor of GBC risk in IR or DM patients, possibly because it is linked to the disorder of glucose metabolism.

Other authors have variously suggested that the association between cancer advancement or risk and cholesterol-related parameters is either positive, negative, or neutral (25). A recent study of Bangladeshi women revealed total cholesterol and BMI to be independent predictors of breast cancer (26), while our results showed that BMI and TC might not be independent predictors of GBC after matching for age, ethnicity, occupation, drinking habits. Although an early case report demonstrated GBC cells of hypercholesterolemia patients can secrete a substance that stimulates LDL receptor activity as result of reducing serum cholesterol (27), few research efforts have clarified the cellular mechanisms. It is known that the synthesis of a molecule of cholesterol requires 18 molecules of acetyl CoA, 36 molecules of ATP, and 16 molecules of Nicotinamide adenine dinucleotide phosphate (NADPH); most of the acetyl CoA and ATP come from the aerobic oxidation of sugar in mitochondria, and the NADPH is obtained from the pentose phosphate pathway metabolism of sugar in the cytosol (28). However, this situation can be completed difficultly in tumor tissue because its patterns of glucose metabolism is anaerobic glycolysis. In turn, LDL-c was an independent risk factor for GBC in our results, including patients stratified by IR and non-IR, potentially because blood LDL is a product of VLDL breakdown, which is the main form of endogenous triglyceride transport (20). Similarly, anthropometric and laboratory parameters in non-IR patients revealed that abnormal lipid metabolism is closely related to GBC, which might result from a disorder of fatty acid binding protein regulation (29).

Most notably, our study revealed that indexes relating to glucose metabolism (including TG, FINS, LDL-c, RBP, and HOMA-IR levels) had significant correlations with GBC in DM patients. Our multivariate analysis further demonstrated that HOMA-IR was the most significant factor predicting GBC risk (OR=5.756), while FBG levels had a negative association with GBC (OR=0.869). These outcomes prompted us to think that hyperinsulinemia, a common phenomenon in DM, directly or indirectly regulates the activity of IGF-1, contributing to the proliferation and inhibition of apoptosis in GBC cells (31). Moreover, more and more research focuses on the roles of the insulin/IGF system and dyslipidemia in cancers of females (32). Therefore, the disorder of blood glucose, not just hyperglycemia, plays a key role in carcinogenesis. Furthermore, we consider interventions employing medical nutritional therapy to treat obesity, IR, and DM to be superior to other measures, including bariatric surgery, especially as this bypass procedure might be related to remnant gastric cancer from *Helicobacter pylori* infections in the residual stomach (33). Instead, it is important to treat diabetes by adjusting diet and increasing aerobic exercise to control body weight and prevent IR (34-36); drugs are the second most effective way to control diabetes, and anti-IR drugs should be the first choice, as these might have further benefits of tumor prevention.

Notably, serum RBP-4 was found to be mostly positively associated with type 2 DM and obesity (37). Huang et al. demonstrated that retinoic acid 6, RBP-4's only known specific membrane receptor, was expressed in β-cells and mediates the inhibitory effect of RBP-4 on insulin synthesis through the Janus kinase 2/STAT1/ISL-1 pathway (38), while our findings showed that serum RBP levels to have a significant negative association with GBC, including the IR patients, although the OR was low (0.922-0.964). To our knowledge, RBP-4 is the main retinol transporter in plasma, thus the serum RBP levels we studied might reflect true RBP-4 levels (39). Moreover, among the several secreted bioactive signaling molecules of adipose and liver tissue, RBP-4 has been associated with systemic insulin resistance, dyslipidemia, type 2 diabetes, and other metabolic diseases (40). A recent study revealed that RBP-4, which links obesity and cancer, is one of the pathogenic mechanisms of cancers, including prostate cancer, that is related to obesity (41), breast cancer (42), pancreatic cancer (43), and more. However, Sobotka et al. (44) found that low levels of RBP-4 at the time of renal cellar cancer diagnosis are associated with poorer prognosis after surgery, and Lorkova et al. (45) verified a decrease in RBP-4 levels in ovarian cancer patient sera by two independent methods. The observed RBP-4 decrease in our research results could advocate RBP-4 as a potential diagnostic or prognostic biomarker of tumors with high malignancy and poor prognosis, such as GBC.

Strengths and limitations

We reviewed more than 2000 GBC cases during the previous 12 years that were matched for occupation, environment, age, ethnicity, and drinking habits, adding strength to our study. However, the present study has several limitations. First, case control studies typically all have the limitations of recall bias (ability of patients to remember their exposure and habits), the uncertainties over the links between cause and effect, and sampling bias. Second, there is still no cohesive explanation for the negative correlations between HBP, SBP, DBP, and GBC in our study. Third, we chose to define IR using HOMA-IR in a large dataset from an epidemiological inquiry in China because the reference values for indirect indicators of IR diagnosis might be affected by the age, gender, and ethnicity of the study population and laboratory methods used for the determination of glucose and insulin concentrations (46). Final, there might have been errors in the family history of cancer due to the small family units in China and Chinese personality characteristics; therefore, we haven't completed an accurate data on family history of cancer and matching, as these statistics may be biased.

Conclusions

Taken together, our findings help to verify that IR, as well as female sex and GBD, are closely related to the predictive risk of GBC for four levels of patient stratification (total, IR, non-IR, and DM). We found that correct anti-insulin treatment is more important for decreasing GBC risk than lowering blood sugar, especially for DM patients. Interesting, there might be an inverse association between FBG and the occurrence of GBC in type 2 DM patients. It was initially found that a sharp drop in RBP might be a predictor of GBC, and the observed RBP-4 decrease is advocated as a potential diagnostic or prognostic biomarker of tumors with high malignancy and poor prognosis, including GBC. Although we have the above new findings, due to the relatively small

volume, regional and ethnic limitations, they need to be confirmed by a large number of prospective studies and multi center validation, as well as further research in animal experiments in future studies.

Abbreviations

GBC: gallbladder cancer; BMI: body mass index; TG: triglyceride; TC: total cholesterol; 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; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus; MetS: metabolic syndrome; IGF: insulin growth factor; NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; VLDL: very low-density lipoprotein; IGFBP: insulin growth factor binding proteins 1; NADPH: Nicotinamide adenine dinucleotide phosphate hydride.

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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=3808)	GC group (N=2265)	t or χ^2	P value	Control group (N=2210)	GS Group (N=2210)	t or χ^2	P value
Female (%)	1892 (49.6%)	1519 (67.1%)	173.53*	<0.001	1034 (46.8)	1421 (64.3)	137.224*	<0.001
Age (Years)	56.53±13.6	63.06±12.2	19.323	<0.001	61.4±11.2	61.4±10.9	0.031	0.976
Han (%)	3272 (85.9)	1930 (85.2)	0.588*	0.443	1938 (87.7)	1905 (86.2)	2.172*	0.141
Occupation (%)			8.041*	0.09			1.963*	0.743
Worker/peasant	1039 (27.3)	629 (27.9)	0.218*	0.694	608 (27.5)	609 (27.6)	0.001*	0.973
Professional technician	727 (19.1)	458 (20.2)	7.311*	0.007	464 (21.0)	453 (20.5)	0.166*	0.683
Manager	594 (15.6)	310 (13.7)	11.547*	0.001	305 (13.8)	307 (13.9)	0.008*	0.931
Retiree	1119 (29.4)	699 (30.9)	4.193*	0.041	700 (31.7)	686 (31.0)	0.206*	0.650
Others	329 (8.6)	169 (7.5)	47.683*	<0.001	133 (6.0)	155 (7.0)	1.799*	0.180
Drinking (%)	197 (5.0)	122 (4.9)	0.456*	0.499	72 (3.4)	92 (4.4)	2.544*	0.111
SBP (mmHg)	121.45±18.2	120.01±17.8	-3.021	0.003	124.28±17.9	120.24±17.7	-7.380	<0.001
DBP (mmHg)	77.32±10.9	76.29±10.2	-3.683	<0.001	77.44±10.5	76.45±10.2	-3.118	0.002
FINS (mU/L)	8.52±2.2	15.58±5.9	54.762	<0.001	7.86±2.2	15.52±5.9	56.929	<0.001
FBG (mmol/L)	5.27±1.3	5.41±1.7	3.276	0.001	5.69±1.4	5.42±1.7	-5.593	<0.001
HOMA-IR	1.94±0.6	3.84±2.3	38.042	<0.001	1.95±0.7	3.83±2.3	35.399	<0.001
RBP (mmol/L)	52.02±23.4	35.52±22.8	-26.970	<0.001	53.35±17.9	35.69±23.1	-27.682	<0.001
Height (cm)	165.19±8.6	162.73±7.5	-11.745	<0.001	164.55±8.2	162.66±7.4	-7.883	<0.001
Weight (kg)	65.78±11.5	64.91±16.8	-2.192	0.028	65.48±10.6	64.84±17.1	-1.462	0.144
BMI (kg/m^2)	24.01±3.1	24.46±5.8	3.382	0.001	24.12±3.0	24.45±6.0	2.318	0.021
TC (mmol/L)	4.89±0.9	4.99±1.1	3.683	<0.001	4.98±1.0	4.98±1.2	-0.04	0.968
TG (mmol/L)	1.52±2.6	2.72±1.4	23.937	<0.001	1.55±0.8	2.73±1.4	33.818	<0.001
HDL-c (mmol/L)	2.97±1.0	2.57±1.0	-14.950	<0.001	2.97±1.0	2.52±1.1	-14.138	<0.001
LDL-c (mmol/L)	1.97±1.3	3.61±1.6	41.643	<0.001	2.13±1.4	3.60±1.5	32.606	<0.001
HBP (%)	951(25.0)	479 (21.1)	11.670*	0.001	626 (28.3)	431 (19.5)	47.495*	<0.001
DM (%)	475 (12.5)	421 (18.6)	41.260*	<0.001	223 (10.1)	272 (12.3)	5.470*	0.019
NAFLD (%)	836 (21.9)	870 (38.4)	186.863*	<0.001	583 (26.4)	811 (36.7)	54.655*	<0.001
GSD (%)	308(8.1)	774 (34.1)	643.108*	<0.001	280 (12.7)	708 (32.0)	245.207*	<0.001
IR (%)	150 (3.9)	1547 (68.3)	3101.851*	<0.001	65 (2.9)	1033 (46.7)	1314.786*	<0.001

GBC: gallbladder cancer; BMI: body mass index; TG: triglyceride; TC: total cholesterol; 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; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus.

* means χ^2 for making a difference with student test

Table 2

Univariate and multivariate analyses of gallbladder cancer risk

Factors	Univariate				Multivariate (with HOMA-IR)				Multivariate (with FINS and FBG)			
	B	OR	95%CI	P	B	OR	95%CI	P	B	OR	95%CI	P
Gender (F)	0.764	2.146	1.894~2.431	<0.001	0.670	1.954	1.518~2.515	<0.001	0.486	1.626	1.240~2.132	<0.001
BMI	0.022	1.022	1.004~1.041	0.018	0.009	1.009	0.989~1.030	0.363	0.017	1.017	0.990~1.045	0.215
RBP	-0.051	0.951	0.947~0.955	<0.001	-0.049	0.952	0.945~0.959	<0.001	-0.044	0.957	0.950~0.964	<0.001
TG	1.989	7.308	6.421~8.318	<0.001	1.421	4.142	3.501~4.902	<0.001	1.458	4.298	3.604~5.125	<0.001
TC	-0.001	0.999	0.944~1.057	0.968	-	-	-	-	-	-	-	-
HDL-c	-0.418	0.659	0.620~0.7	<0.001	-0.495	0.610	0.542~0.686	<0.001	-0.509	0.601	0.529~0.683	<0.001
LDL-c	1.249	3.486	3.201~3.796	<0.001	0.861	2.366	2.098~2.668	<0.001	0.870	2.387	2.105~2.707	<0.001
HOMA-IR	1.613	5.020	4.505~5.595	<0.001	2.153	8.610	7.055~10.508	<0.001	*	*	*	*
DM	0.225	1.252	1.037~1.512	0.019	-3.847	0.021	0.01~0.045	<0.001	-0.866	0.420	0.169~1.043	0.062
NAFLD	0.492	1.635	1.436~1.862	<0.001	-0.63	0.532	0.373~0.761	0.001	-0.620	0.538	0.367~0.790	0.002
GSD	1.194	3.300	2.827~3.853	<0.001	0.714	2.043	1.525~2.736	<0.001	0.692	1.998	1.468~2.718	<0.001
DBP	-0.009	0.991	0.985~0.997	0.002	/	/	/	/	-	-	-	-
SBP	-0.013	0.987	0.984~0.991	<0.001	/	/	/	/	-	-	-	-
FINS	0.547	1.727	1.670~1.786	<0.001	-	-	-	-	0.631	1.880	1.774~1.992	<0.001
FBG	-0.115	0.891	0.855~0.929	<0.001	-	-	-	-	-0.051	0.950	0.818~1.105	0.507
HBP	-0.497	0.609	0.528~0.701	<0.001	-0.192	0.826	0.595~1.147	0.253	-0.203	0.816	0.571~1.168	0.268
Drinking	0.255	1.290	0.942~1.767	0.112								

BMI: body mass index; TG: triglyceride; TC: total cholesterol; 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; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus

*eliminated for the definition of HOMA-IR in multivariate regression

- eliminated for no statistical significance in univariate regression

/ eliminated for its association to HBP

Table 3

Univariate and multivariate analysis of gallbladder cancer risk in the patients with insulin resistance

	Univariate				Multivariate (with HOMA-IR)				Multivariate (with FINS and FBG)			
	β	OR	95%CI	P	β	OR	95%CI	P	β	OR	95%CI	P
Age	-0.006	0.994	0.971~1.017	0.598	-	-	-	-	-	-	-	-
Gender (F)	0.875	2.399	1.448~3.974	0.001	0.071	1.074	0.333~3.459	0.905	0.053	1.054	0.224~4.961	0.947
BMI	-0.037	0.964	0.900~1.032	0.291	-	-	-	-	-	-	-	-
RBP	-0.054	0.947	0.938~0.957	<0.001	-0.078	0.925	0.903~0.948	<0.001	-0.085	0.918	0.889~0.948	<0.001
TG	4.569	96.437	37.667~246.9	<0.001	3.287	26.76	6.714~106.66	<0.001	3.184	24.145	4.888~119.27	<0.001
TC	-0.060	0.942	0.790~1.122	0.500	-	-	-	-	-	-	-	-
HDL-c	-0.226	0.797	0.637~0.998	0.048	-0.707	0.493	0.275~0.884	0.018	-0.871	0.418	0.193~0.906	0.027
LDL-c	2.882	17.852	10.10~31.554	<0.001	1.869	6.479	2.734~15.351	<0.001	1.996	7.362	2.457~22.058	<0.001
HOMA-IR	0.238	1.269	1.050~1.535	0.014	0.852	2.343	1.386~3.961	0.001	*	*	*	*
DM	-2.248	0.106	0.058~0.191	<0.001	-2.956	0.052	0.013~0.213	<0.001	-1.800	0.165	0.024~1.126	0.066
NAFLD	-0.136	0.873	0.523~1.457	0.603	-	-	-	-	-	-	-	-
GSD	0.142	1.153	0.670~1.983	0.607	-	-	-	-	-	-	-	-
DBP	-0.030	0.971	0.948~0.994	0.013	/	/	/	/	-	-	-	-
SBP	-0.035	0.966	0.953~0.979	<0.001	/	/	/	/	-	-	-	-
FINS	0.719	2.053	1.773~2.376	<0.001	*	*	*	*	0.547	1.727	1.310~2.278	<0.001
FBG	-0.341	0.711	0.656~0.771	<0.001	*	*	*	*	0.118	1.126	0.697~1.818	0.628
HBP	-0.909	0.403	0.241~0.674	0.001	-0.281	0.755	0.212~2.688	0.665	-0.450	0.637	0.119~3.409	0.599
Drinking	-0.538	0.584	0.257~1.328	0.199								

BMI: body mass index; TG: triglyceride; TC: total cholesterol; 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; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus.

*eliminated for the definition of HOMA-IR in multivariate regression

- eliminated for no statistical significance in univariate regression

/ eliminated for its association to HBP

Table 4

Univariate and multivariate analysis of gallbladder cancer risk in the patients with non-insulin resistance

	Univariate				Multivariate (with HOMA-IR)				Multivariate (with FINS and FBG)			
	β	OR	95%CI	P	β	OR	95%CI	P	β	OR	95%CI	P
Age	-0.001	0.999	0.992~1.006	0.746	-	-	-	-	-	-	-	-
Gender (F)	0.763	2.145	1.838~2.502	<0.001	0.631	1.880	1.440~2.454	0.001	0.490	1.633	1.234~2.161	0.001
BMI	0.026	1.027	1.004~1.050	0.022	0.012	1.012	0.990~1.035	0.283	0.018	1.019	0.990~1.048	0.211
RBP	-0.062	0.940	0.934~0.945	<0.001	-0.046	0.955	0.947~0.962	<0.001	-0.039	0.962	0.954~0.970	<0.001
TG	1.687	5.402	4.734~6.164	<0.001	1.364	3.911	3.298~4.637	<0.001	1.522	4.579	3.799~5.519	<0.001
TC	-0.042	0.959	0.891~1.033	0.271	-	-	-	-	-	-	-	-
HDL-c	-0.460	0.631	0.585~0.681	<0.001	-0.490	0.613	0.541~0.694	<0.001	-0.507	0.602	0.528~0.688	<0.001
LDL-c	1.046	2.845	2.601~3.112	<0.001	0.841	2.318	2.050~2.620	<0.001	0.830	2.294	2.020~2.606	<0.001
HOMA-IR	1.934	6.914	5.865~8.151	<0.001	2.466	11.773	8.878~15.613	<0.001	*	*	*	*
DM	-3.499	0.030	0.010~0.095	<0.001	-5.195	0.006	0.001~0.036	<0.001	-2.413	0.09	0.014~0.562	0.01
NAFLD	0.578	1.782	1.525~2.083	<0.001	-0.507	0.602	0.412~0.880	0.009	-0.765	0.465	0.311~0.697	<0.001
GSD	1.229	3.418	2.851~4.099	<0.001	0.735	2.085	1.534~2.834	<0.001	0.809	2.246	1.635~3.084	<0.001
DBP	-0.010	0.990	0.983~0.997	<0.001	/	/	/	/	-	-	-	-
SBP	-0.012	0.988	0.984~0.992	<0.001	/	/	/	/	-	-	-	-
FINS	0.530	1.699	1.6334~1.766	<0.001	*	*	*	*	0.583	1.792	1.672~1.921	<0.001
FBG	-1.217	0.296	0.259~0.338	<0.001	*	*	*	*	-0.396	0.673	0.537~0.845	0.001
HBP	-0.591	0.554	0.462~0.663	<0.001	-0.287	0.751	0.526~1.071	0.113	-0.009	0.914	0.631~1.326	0.636
Drinking	-0.365	0.694	0.432~1.115	0.131	-	-	-	-	-	-	-	-

BMI: body mass index; TG: triglyceride; TC: total cholesterol; 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; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus

*eliminated for the definition of HOMA-IR in multivariate regression

- eliminated for no statistical significance in univariate regression

/ eliminated for its association to HBP

Table 5

Univariate and multivariate analysis of gallbladder cancer risk in the patients with DM

	Univariate				Multivariate (with HOMA-IR)				Multivariate (with FINS and FBG))			
	β	OR	95%CI	P	β	OR	95%CI	P	β	OR	95%CI	P
Age	-0.015	0.985	0.968~1.003	0.102	-	-	-	-	-	-	-	-
Gender(F)	1.377	3.965	2.724~5.769	<0.001	2.056	7.816	1.768~34.547	0.007	1.489	4.434	2.08~9.454	<0.001
BMI	-0.055	0.946	0.898~0.997	0.039	-0.156	0.856	0.673~1.088	0.203	-0.138	0.871	0.778~0.976	0.017
RBP	-0.073	0.930	0.918~0.942	<0.001	-0.115	0.891	0.857~0.926	<0.001	-0.075	0.928	0.911~0.945	<0.001
TG	1.564	4.778	3.485~6.551	<0.001	1.084	2.957	1.908~4.582	<0.001	0.946	2.575	1.923~3.448	<0.001
TC	0.046	1.047	0.925~1.185	0.468	-	-	-	-	-	-	-	-
HDL-c	-0.449	0.638	0.534~0.763	<0.001	-0.484	0.616	0.282~1.345	0.224	-0.642	0.526	0.361~0.767	0.001
LDL-c	1.459	4.303	3.234~5.725	<0.001	1.389	4.010	1.865~8.626	<0.001	1.489	4.433	2.780~7.707	<0.001
HOMA-IR	1.400	4.057	3.191~5.157	<0.001	1.673	5.329	3.188~8.908	<0.001	*	*	*	*
NAFLD	-0.001	0.999	0.698~1.428	0.994	-	-	-	-	-	-	-	-
GSD	1.009	2.742	1.781~4.222	<0.001	-0.422	0.656	0.101~4.276	0.659	0.664	1.943	0.790~4.779	0.148
DBP	-0.020	0.980	0.964~0.997	0.023	-0.015	0.985	0.912~1.064	0.698	0.007	1.007	0.964~1.052	0.758
SBP	-0.037	0.964	0.953~0.975	<0.001	-0.029	0.971	0.919~1.026	0.279	-0.039	0.962	0.936~0.989	0.006
FINS	0.663	1.940	1.668~2.256	<0.001	*	*	*	*	^	^	^	^
FBG	-0.219	0.804	0.746~0.866	<0.001	*	*	*	*	-0.173	0.842	0.733~0.966	0.014
HBP	-0.270	0.763	0.534~1.091	0.138	-	-	-	-	-	-	-	-
Drinking	0.407	1.502	0.951~2.371	0.081	-	-	-	-	-	-	-	-

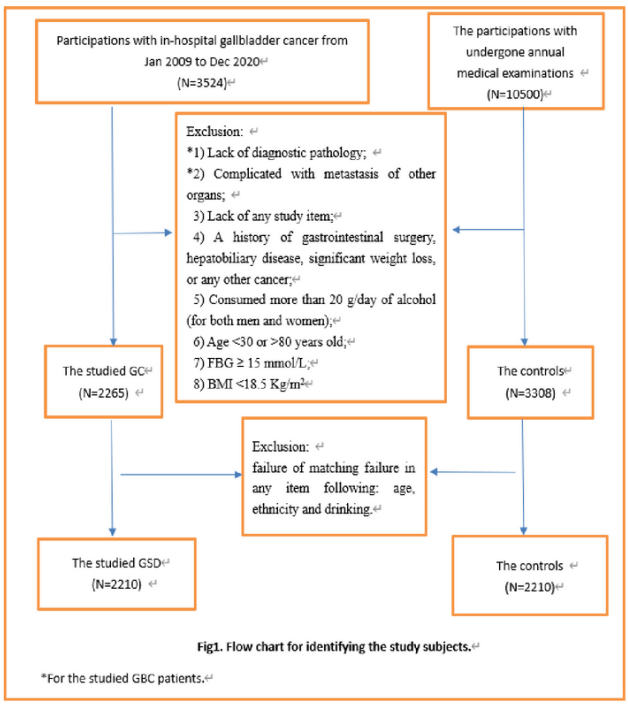
BMI: body mass index; TG: triglyceride; TC: total cholesterol; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; FINS: fasting blood insulin; RBP: Retinol binding protein; HOMA-IR: Homeostasis Model Assessment of IR; IR: insulin resistance; HBP: high blood pressure; DM: Diabetes mellitus.

* eliminated for the definition of HOMA-IR in multivariate regression

- eliminated for no statistical significance in univariate regression

^ eliminated for a clear result on FBG in multivariate regression

Figures



Step 1: it shows that 3524 Chinese GBC patients at the time of preliminary diagnosis before surgery in our hospital from Jan 2009 to Dec 2020, 10500 healthy controls with undergone annual medical examinations in the same healthcare center for more than five years;

Step 2: It shows that 2265 patients with GSD and 3308 healthy controls were included by the above criteria;

Step 3: There were 2210 GBC patients and healthy controls aged from 30 to 80 years, respectively after matching age, ethnicity and drinking.

Figure 1

Please See image above for figure legend.