RESEARCH ARTICLE

A Study of Alcohol Consumption and Obesity as Main Risk Factor for Symptomatic Gallbladder Stone: a Case-Control Study

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Abstract

Background: Gallbladder stone (GBS) is a common gastrointestinal disease that can progress to severe cholecystitis and is a strong risk factor for gallbladder cancer (GBC). The present study was conducted to evaluate region-specific causes of GBS which was proved as major risk factor for GBC in Jeju Island, Korea. **Methods:** Age and sex match case-control study was performed among 171 pairs of case and controls. The cases were patients who were diagnosed with GBS, had definite clinical symptoms, and underwent a cholecystectomy in Cheju Halla General Hospital, Jeju, Korea during 2010-2014. The control group included 1:1 age and sex-matched participants without GBS at the Health Promotion Center in the same institute during the same period. We compared the histories of previous chronic diseases (hypertension, diabetes, hyperlipidaemia, vascular occlusive diseases, or parity), alcohol consumption (standard drinks/week [SDW]), smoking habits, body mass index (BMI), and presence of concomitant polypoid lesions of the gallbladder. **Results:** A dose-dependent positive relationship existed between BMI and the risk of GBS: BMI 23–27.4 kg/m^2, OR=2.5, , p=0.24; 27.5–29.9 kg/m^2, OR=8.9, p=0.002; ≥30 kg/m^2, OR=7.2, p=0.004. A negative correlation existed between alcohol consumption and the risk of GBS: Standard drinks per week (SDW), OR=0.24, p=0.002; 15–29.9 SDW, OR=0.26, p=0.022; ≥30 SDW, OR=0.2, 95% p=0.005. **Conclusion:** The present results suggest that a higher BMI and less alcohol consumption are associated with a risk of symptomatic GBS.

Keywords: Alcohol consumption- BMI- case-control study- gallbladder stone- risk factor

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Introduction

Gallbladder stone (GBS) is a common benign gastrointestinal disease worldwide, with wide range of prevalences (4 - 62 % in adults, depends on sex, geography and ethnicity (Stinton LM et al., 2012). This benign disease is the most common reason for cholecystectomiy in rcent decades, and the direct and indirect costs of the disease has been estimated at more than $6,2 bilion in USA (Everhart JE et al., 2009; Shaffer EA et al., 2005). Apart from the medical burden, GBS is one of the important risk factor for gallbladder cancer (GBC) (Stinton LM et al., 2012). In former epidemiologic study for GBC risk factors, we obtained that GBC has postive relationship with GBS and negative with alcohol consumption, so we established the hypothesis that alcohol consumption might have identical effect on both diseases, GBC and GBS in same study population. (Cha BH, 2016). In these backgrounds, the present study was designed to determine the region-specific risk factors for GBS.

Materials and Methods

We performed a case-control study in a single institute. The protocol was approved by the Ethical Community of Institutional Review Boards of Cheju Halla General Hospital, South Korea and was registered at http://www.clinicaltrials.gov (Identifier No NCT02808546). Informed consent was obtained from all individual participants included in the study.

Between 2010 and 2014, patients with newly diagnosed GBS who underwent a cholecystectomy due to symptomatic GBS and acute calculous cholecystitis in the Digestive Disease Center of Cheju Halla General Hospital (Jeju, South Korea) were enrolled as cases. The control group included randomly selected participants (matched 1 to 1 for age and sex to the cases) who visited the health promotion centre in the same institute during the same period.

The diagnostic criteria for symptomatic GBS included typical clinical symptoms (e.g., abdominal pain [right

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quadrant or epigastric pain] with or without radiating pain) and positive imaging studies for gallstones or cholecystitis (ultrasound, computed tomography, or magnetic resonance imaging) and were confirmed using postoperative pathological results. All of the results were reviewed by an expert panel composed of a clinician, surgeon, radiologist, and pathologist.

Cases without confirmed GBS disease, despite strong suspicion of gallstone on imaging before surgery; with asymptomatic GBS who requested surgery to prevent serious disease; or with gallbladder cholesterol polyps, adenoma, or adenomyomatosis without stones in the pathologic results were excluded. Patients diagnosed with GBS based on abdominal ultrasound were excluded from the control group.

The following demographic and clinical characteristics were collected from medical records or, when data were missing, the patient or relatives using a structured questionnaire administered by well-trained research staff: age, sex, past histories of chronic diseases (hypertension, diabetes, hyperlipidaemia, vascular occlusive diseases [VODs], or parity), alcohol consumption, cigarette smoking, anthropometric measurements including body mass index (BMI), and presence of concomitant polypoid lesions of the gallbladder (PLGs). A medical history of hypertension, diabetes, or hyperlipidaemia was defined as medical treatment for the condition documented in the medical record at the time of survey. VODs included a history of a coronary artery disease event or intervention and a history of stroke. To standardize the amount of alcohol consumed, reported alcohol consumption was converted into standard drinks, which are defined as 14 g alcohol in various types of beverages according to the National Institutes on Alcohol Abuse and Alcoholism (NIAAA, https://www.niaaa.nih.gov/). Participants were divided into two categories, namely non-drinker (none or <3 standard drinks per week [SDW]) and drinker (≥3 SDW). BMI was categorized into two groups (<23 and ≥23 kg/m2) based on the Asia Pacific overweight criteria from the World Health Organization Expert Consultation (WHO Expert Consultation, 2004). A PLG was defined as an echogenic immobile protrusion from the gallbladder wall into the lumen on ultrasonography.

For the statistical analyses, we converted continuous or ordinal variables into dichotomous variables, for which the frequencies and percentages of each pair are presented. We used the McNemar test to compare the statistical differences in the proportion of each dichotomized variable between the matched groups (McNEMAR Q, 1947).

To estimate the potential risk factors associated with GBS, all of the statistically significant variables in the univariate analyses were assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs) in multivariate conditional logistic regression models. To assess the dose-dependent correlation between alcohol consumption and BMI for the risk of GBS, we divided the cases into 4 groups according to their SDW (SDW ;I <3, SDW; II 3–14.9, SDW; III 15–29.9 and SDW; IV ≥30) or BMI (I, <23 kg/m^2; II, 23–27.4 kg/m^2; III, 27.5–29.9 kg/m^2; IV, ≥30 kg/m^2). Then, we compared the OR in each subclass using multivariable conditional logistic regression models. Despite a lack of statistical significance in the univariate analysis, known important confounding factors in former literature were also included in the multivariable analyses. For two-sided tests, a p value < 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.0.2 (The R Foundations of Statistical Computing, Seoul, South Korea).

Results

Of the 230 eligible cases, 55 were excluded due to an ambiguous pathologic diagnosis, asymptomatic GBS, or diagnosis of another gallbladder disease without GBS (PLGs, adenomas, adenomyomatosis). Of the 7,263 healthy controls, 156 were excluded because they had a positive ultrasound result of GBS or sludge. Finally, 171 of the 175 patients with GBS and 171 matched controls from the 6,932 healthy controls were analysed.

In the univariate analyses, histories of hypertension, diabetes, hyperlipidaemia, VOD, parity, and PLGs were not significantly different between the groups (Table 1). BMI classification and amount of alcohol consumption showed statistical significant differences between case group and contols.

In the multivariate conditional logistic regression models, BMI was associated with a risk of GBS: BMI 23–27.4 kg/m^2, OR = 2.5, 95% CI = 1.3–4.9, p = 0.24; 27.5–29.9 kg/m^2, OR = 8.9, 95% CI = 1.3–4.9, p = 0.002; ≥30 kg/m^2, OR = 7.2, 95% CI = 1.9–27.4, p = 0.004. There was a dose-dependent negative correlation between the amount of alcohol consumption and GBS: 3–14.9 SDW, OR = 0.24, 95% CI = 0.1–0.6, p = 0.002; 15–29.9 SDW, OR = 0.26, 95% CI = 0.1–0.8, p = 0.022; ≥30 SDW, OR = 0.2, 95% CI = 0.06–0.61, p = 0.005 (Table 2).

Discussion

To verify our initial hypothesis, we performed this clinical based, age- and sex-matched case-controlled study of the risk factors for symptomatic GBS, of the epidemiologic factors that are known risk factors for GBS diseases. And we obtained same results about the relationship between alcohol consumption and GBC development, but different trend regarding BMI with previous study (Cha BH, 2016).

Regarding the negative relationship between alcohol consumption and symptomatic GBS in the present study, long-standing arguments of the effect of alcohol on the gallbladder exist. Some researchers insisted that heavy drinking is a strong risk factor (Lee Y-C et al., 2014; Chen YC et al., 2014)) for GBS, while other researchers suggest that alcohol has a preventive role (Kato I et al., 1992; Kono S et al., 2002; Halldestam I et al., 2009; Banim PJR et al, 2011). Other studies found no relationship (Cui Y et al., 2012; Panpimanmas S et al., 2009; Shukla VK et al., 2008; Pandey M et al., 2003). There are several pathophysiological studies that support the evidence that alcohol can increase high density lipoprotein cholesterol levels and cholecystokinin release; both of these responses

Table 1. Distribution of Clinical Risk Factors for Symptomatic Gallbladder Stone in Age-Sex Matched, Case-Control Pairs (Total N=342, 171 Matched Pairs)

Variables	Controls	Cases		Total pairs	p-value[1]
		No	Yes		
		N (%)	N (%)	N (%)	
Hypertension	No	96 (67.1)	32 (22.4)	128 (89.5)	0.1696
	Yes	14 (9.8)	1 (0.7)	15 (10.5)	
DM	No	130 (83.3)	11 (7.1)	141 (90.4)	0.6892
	Yes	14 (9.0)	1 (0.6)	15 (9.6)	
Hyperlipidemia	No	138 (88.5)	6 (3.8)	144 (92.3)	0.332
	Yes	11 (7.1)	1 (0.6)	12 (7.7)	
VOD	No	144 (92.3)	8 (5.1)	152 (97.4)	0.228
	Yes	3 (1.9)	1 (0.6)	4 (2.6)	
Alcohol	≥3 SDW	63 (42.6)	14 (9.5)	77 (52.0)	< 0.001
	< 3 SDW	59 (39.9)	12 (8.1)	71 (48.0)	
Multiparity[2]	No	19 (54.3)	4 (11.4)	23 (65.7)	0.751
	Yes	6 (17.1)	6 (17.1)	12 (34.3)	
Obesity[3]	No	65 (68.2)	65 (38.2)	130 (76.5)	< 0.001
	Yes	21 (12.4)	19 (11.2)	40 (23.5)	
PLG	No	163 (95.3)	2 (1.2)	165 (96.5)	0.2888
	Yes	6 (3.5)	0 (0.0)	6 (3.5)	

[1]p-value was estimated by McNemar test; [2]Multiparity was defined as 3 or more times in their life; [3]Obesity was defined as body mass index 25 or more; DM, diabetes melitus; VOD, vascular occlusive disease; SDW, standard drink per week; PLG, polypoid lesions of gallbladder

Table 2. the Matched Odds Ratios (Mor) of Multiple Predicted Values Correlating with Symptomatic GB Stone in Matched Cases for Age and Sex Using Conditional Logistic Regression Model

Variables		OR	95% CI	p value
DM	Yes	0.73	0.25 - 2.10	0.562
HTN	Yes	2.25	1.07 - 4.76	0.033*
Hyperlipidemia	Yes	1.3	0.38 - 4.39	0.668
VOD	Yes	2.52	0.32 - 19.37	0.374
Alcohol consumption	I (< 3 SDW[1])	1		
	II (3 – 14.9 SDW)	0.24	0.10 - 0.59	0.002**
	III (15 – 29.9 SDW)	0.26	0.08 - 0.83	0.022*
	IV (≥ 30 SDW)	0.19	0.06 - 0.61	0.005**
BMI (kg/m^2)	I (< 23)	1		
	II (23 – 27.4)	1.47	0.77 - 2.79	0.243
	III (27.5 – 29.9)	8.97	2.17 - 47.13	0.002**
	IV (≥ 30)	7.19	1.88 - 27.44	0.004**
PLG	Yes	0.25	0.02 - 2.91	0.269

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1; [1]Standard drink per week (SDW) defined as alcohol content in 1 drink = 14g per week; GB, gallbladder; OR, odd ratio; DM, diabetes melitus; HTN, hypertension; VOD, vascular occlusive disease; BMI, body mass index; PLG, polypoid lesions of gallbladde

are important mechanisms for preventing gallstone formation, by stimulating gallbladder contraction and flow of bile juice to the duodenum (Brien SE et al., 2011; Saluja AK et al., 2003; Little TJ et al., 2005). To confirm the specific effect of alcohol consumption on GBS formation, a systematic review and meta-analysis of published case-control and cohort studies should be conducted.

We could achieved the GBS risks was increased proportionally as BMI category was increased and this results is compatible to previous published articles (Chen CY et al., 1998; Cui Y et al., 2012; Grodstein F et al., 1994; Ishizuk H et al., 2003; Katsika D et al., 2007; Kurilovich SA et al., 2000). This results is different with former epidemiologic study which failed to prove the relation between obesity and GBC risk. We inferred the reason of discrepancy caused by the measurement error regarding BMI checked at the time of first diagnosis in the advanced cases (Cha BH, 2016).

In the present study, we included all of the chronic diseases related with metabolic syndrome, such as hypertension, diabetes, hyperlipidaemia, and VOD,

to investigate the risk of GBS. Although previous studies demonstrated that hypertension (Yu K et al., 2016), diabetes (Chen CY et al., 1998), and a history of hyperlipidaemia (Banim PJR et al., 2011) were risk factors for GBS, there were no strong relationships between these diseases and symptomatic GBS disease in the present study, except a history of hypertension. Because we obtained the past history of medical conditions only from medical records and interviews, the medical information might not reflect a correct stage among the various spectrums of chronic diseases. Therefore, we concluded that more relevant measurements of disease severity, chronicity, compliance, or control are needed to confirm the exact causal relationships between these chronic diseases and gallstone development risks. There have been several reports about other risk factors for GBS including helicobacter infection (Panday M, 2007) and parity (Andreotti G et al., 2010) but we could not assess those contributions due to lack of proper medical records. Because the present study was retrospectively conducted in a single institute, caution should be used when drawing conclusions from the results. This study has limitations: firstly, it was conducted among small number of cases, in a single institute, retrospectively. Secondly, we enrolled the cases who was confirmed target disease after surgery, which means many symptomatic patient those who refused surgical treatment for mild symptoms or could not undergo the operation due to co-morbidities, who were not included in the present analyses. There might be a issue that all enrolled cases could not present all symptomatic GBS population. Therefore we need to be cautious to draw all conclusions based on the present study results. In these reasons, Well designed cohort study and meta-analysis are warranted to clarify these subjects.

In conclusion, a higher BMI and less alcohol consumption increase the risk of symptomatic GBS disease, based on the present age- and sex-matched, case-control study.

Conflict of Interest

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