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A study on the correlation between gallbladder polyps and metabolic syndrome combined with fatty liver disease: An analysis of physical examination data

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Abstract
Background: Metabolic syndrome (MetS) was found to be most strongly associated with the risk of gallbladder polyps (GBP). Recent studies have shown that obesity and impaired glucose tolerance are associated with GBP, which is currently believed to be a risk factor for gallbladder cancer. Thus, it seems likely that the prevalence of GBP is increasing. However, little research has been conducted on the relation between GBP and MetS combined with fatty liver disease (FLD).
Objective: The purpose of this study was to evaluate the association between GBP and metabolic syndrome combined FLD.
Methods: A cross-sectional design was used. Data were collected through an adult health screening program by a hospital in Changhua County, Taiwan, between 2010 and 2014. After GBP and FLD were confirmed through abdominal ultrasound scanning, the results were verified by a gastroenterologist. The MetS was defined according to the criteria set by the 2007 Health Promotion Administration, Ministry of Health and Welfare. This study evaluated the GBP prevalence and risk factors based on data obtained from physical examinations and blood tests.
Results: The prevalence of MetS, GBP, and FLD was 18.8%, 12.9%, and 49.1%, respectively. The results indicated that there was no correlation between GBP and MetS combined with FLD. However, significant differences were observed in the influence on GBP of MetS combined with different degrees of FLD severity. MetS combined with mild FLD appeared to have the greatest effect on GBP, while MetS combined with severe FLD was found to have protective effects against GBP. The risk of GBP in male patients was higher than that in female patients (odds ratio [OR], 2.098; 95% confidence interval [CI], 1.717 to 2.563), and the risk of GBP in patients aged 40 or older was higher than that in patients under 40 (OR, 1.202; 95% CI, 1.019 to 1.417). Patients who had MetS combined with severe FLD showed a lower risk of GBP than patients who did not have MetS or FLD (OR, 0.395; 95% CI, 0.192 to 0.813).
Conclusions: MetS combined with different degrees of FLD affects GBP. The effect of FLD on GBP is greater than that of MetS. Male gender and aged 40 or older are risk factors for GBP. MetS combined with severe FLD is a protective factor against GBP.

Keywords: gallbladder polyps, metabolic syndrome, gallbladder cancer, fatty liver disease

1. Introduction

Recent studies have indicated that obesity and impaired glucose tolerance are associated with gallbladder polyps (GBP) and are currently considered to be risk factors for gallbladder cancer [1-7]. Furthermore, the prevalence of GBP seems to be increasing. Although gallbladder cancer survival rates are increasing with the advancement of radiodiagnostic equipment and medical technologies, cancer can easily metastasize in the early stages before there are symptoms, and it is often diagnosed only at later stages when it is too late for surgical treatment. Thus, the prognosis for gallbladder cancer is typically poor. GBP is the main risk factor for gallbladder cancer. Many studies have unsuccessfully attempted to distinguish between benign and malignant GBP and to determine GBP risk factors.

One study on healthy adults indicated that men who tested positive for hepatitis B surface antigen had an increased risk of GBP. Metabolic syndrome (MetS) is associated with a higher risk of GBP [8].

Many recent studies have shown that the prevalence of GBP in men is higher than that in women [2, 6, 9]. Therefore, male gender is considered to be a risk factor for GBP. The risk factors for GBP include male gender, hepatitis B virus infection, and cholecystitis [10].

MetS is a disease characterized by abdominal obesity, high levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), hyperglycemia, and hypertension. The number of patients with obesity, as well as MetS, has increased worldwide [11]. Hyperlipidemia is associated with cholelithiasis, which, in turn, is highly correlated with GBP. Thus, blood lipids and hyperlipidemia may be associated with GBP.

Past studies have indicated that GBP is associated with hyperlipidemia, diabetes, and obesity [12]. However, no studies have confirmed the association between these risk factors and GBP. It is also indicated that MetS cannot result in development of GBP; this contradicts with the findings reported in earlier studies [10]. According to one study

involving Korean patients, the risk factors for GBP include MetS, male gender, insulin resistance, and abdominal obesity; thus, MetS was highly associated with GBP in Korean patients [12]. Prior studies have suggested that GBP is associated with obesity [6], glucose intolerance, and increased BMI [1, 7]. Few studies have investigated the association between GBP and MetS combined with fatty liver disease (FLD). Therefore, this study used ultrasonography (USG) to analyze the prevalence of GBP in adult patients in central Taiwan and to examine its relation to MetS combined with FLD.

2. Methods

Study design

This study was designed as a cross-sectional study.

Participant Selection and Data Collection

Data was collected from adults who underwent physical examinations at a medical institution in Changhua County, Taiwan, between 2010 and 2014. This study evaluated the risk factors related to MetS, FLD, and GBP. The effective sample included 18,654 participants.

Definitions

In this study, MetS was defined according to the criteria set by the Health Promotion Administration, Ministry of Health and Welfare, in 2007. Accordingly, three of the following five criteria were grounds for definition: (1) elevated blood pressure: blood pressure of at least 130/85 mmHg or use of antihypertensive medications, (2) hypertriglyceridemia: serum triglycerides of at least 150 mg/dL, (3) reduced HDL-C: HDL-C < 40 mg/dL in men and < 50 mg/dL in women, (4) hyperglycemia: raised fasting plasma glucose (FPG) of 100 mg/dL or more or use of drug treatment of elevated glucose, and (5) central obesity: waist circumference ≧90 cm in men and ≧80 cm in women.

GBP and FLD: the cases examined in this study involved patients diagnosed with GBP and FLD based on abdominal ultrasounds conducted by gastroenterologists and recorded in physical examination files.

Hepatitis B: patients were diagnosed based on blood biochemical examination conducted by gastroenterologists.

Ethical considerations

The data in this study was secondary data obtained from a database containing numerical records of adults 'physical examinations. In consideration of the ethical principles of data acquisition and analysis, personally identifiable information (i.e. information related to personal names and identities) was removed from the data. The data used in this study was collected and analyzed after receiving Institutional Review Board (IRB) approval.

Statistical analysis

The statistical methods applied to prove the hypotheses in this study included descriptive statistics (frequency distribution, proportion, mean values, standard deviations) and inferential statistics (Chi-Square test, $\chi 2$; logistic regression analysis). Data management and statistical analyses were performed with SPSS 18.0 for Windows, and all of the statistical tests were 2-tailed with a level of 0.05.

3. Results

As shown in Table 1, the average age was 38.5±10.4 years, with 11,458 participants (61.4%) aged under 40. The majority of participants (13,279; 71.2%) were male. The blood biochemical examination results indicated a 10.2% prevalence of dysglycemia (1,898 participants), a 24.4% prevalence of triglyceride abnormalities (4,549 participants), a 12.1% prevalence of HDL-C abnormalities (2,261 participants), a 18.8% prevalence of MetS (3,510 participants), and a 14.2% prevalence of positive hepatitis B surface antigen (1,221 participants). The abdominal ultrasounds revealed GBP in 12.9% of patients (2,415) and FLD in 49.1% of patients (9,162).

Based on the demographic data provided in Table 2, the proportion of men with GBP was greater than that of women with GBP (15.2% vs. 7.4%). The proportion of patients with GBP aged 40 and older was higher than that of patients with GBP under 40 (13.7% vs. 12.5%), reaching a statistically significant difference ($p<0.05$). With regard to MetS and compositional factors, apart from a high prevalence of GBP among patients with hypertension, other variables did not show statistically significant differences. However, the prevalence of GBP was higher among patients who tested positive for hepatitis B surface antigen (HBsAg[+]) than those who tested negative (15.1% vs. 12.4%).

Tables 3 and 4 show the analysis of MetS combined with FLD, the degrees of FLD severity (mild, moderate, and severe), and GBP, demonstrating that a large percentage of patients who did not have MetS, but did have FLD, suffered from GBP. No significant difference was observed between patients who had both MetS and FLD and those who had neither MetS nor FLD, indicating that FLD had a greater impact on GBP. Furthermore, patients with MetS and mild FLD had a higher risk of GBP.

This study used logistic regression analysis to examine the potential factors influencing GBP. As shown in Table 5, the risk of GBP in male patients was 2.098-fold higher than that in female patients (95% CI, 1.717 to 2.563). Patients aged 40 and older had a higher risk of GBP (OR, 1.202; 95% CI, 1.019 to 1.417). After adjusting for other influencing factors, HBsAg(+) was not included in the regression model as it did not reach a statistically significant difference. MetS combined with severe FLD was found to be a protective factor (OR, 0.395; 95% CI, 0.192 to 0.813).

Table 1: 2010-2014 descriptive statistics: demographic data and physical and blood biochemical examination results (n=18,654)

Variable	Number of people	%	Mean±SD	Variable	Number of people	%	Mean±SD
Gender				**Fasting plasma glucose**			89.2±19.7
Male	13,279	71.2		Normal	16,756	89.8	
Female	5,375	21.8		Abnormal (≧100mg/dL)	1,898	10.2	
Age			38.5±10.4	Triglycerides			124.2±111.2
<40 years old	11,458	61.4		Normal	14,105	75.6	
≧40 years old	7,196	38.6		Abnormal (≧150mg/dL)	4,549	24.4	
Height (cm)			167.8±8.1	High-density lipoprotein cholesterol			56.4±18.3
Weight (Kg)			68.9±13.7	Normal	16,393	87.9	
Waist circumference			81.7±10.6	Abnormal (male, <40 mg/dL; female, <50 mg/dL)	2,261	12.1	
Normal	13,615	73.0		Metabolic syndrome			
Abnormal (male, ≧90; female,≧80)	5,039	27.0		No (<3 abnormalities)	15,144	81.2	
Systolic blood pressure (mmHg)			125.9±16.2	Yes (≧3 abnormalities)	3,510	18.8	
Diastolic blood pressure (mmHg)			80.5±11.0	Polyps			
Blood pressure				No	16,239	87.1	
Normal	12,861	68.9		Yes	2,415	12.9	
Abnormal (≧130/85mmHg)	5,793	31.1					
Hepatitis B				Fatty liver disease			
Negative	7,371	85.8		No	9,492	50.9	
Positive	1,221	14.2		Yes	9,162	49.1	

Table 2: Differential analysis of 2010-2014 demographic data, metabolic syndrome and its compositional factors, and gallbladder polyps (n=18,654)

Variable	No GBP (n=16,239)		GBP (n=2,415)		*p* value
	Number of people	%	Number of people	%	
Gender					<.001
Male	11,261	84.8	2,018	15.2	
Female	4,978	92.6	397	7.4	
Age					.019
<40 years old	10,027	87.5	1,431	12.5	
≧40 years old	6,212	86.3	984	13.7	
Waist circumference					.577
Normal	11,841	87.0	1,774	13.0	
Abnormal (male, ≧90; female, ≧80)	4,398	87.3	641	12.7	
Blood pressure					.034
Normal	11,241	87.4	1,620	12.6	
Abnormal (≧130/85mmHg)	4,998	86.3	795	13.7	
Fasting plasma glucose					.788
Normal	14,583	87.0	2,176	13.0	
Abnormal (≧100mg/dL)	1656	87.2	242	12.8	
Triglycerides					.962
Normal	12,278	87.0	1,827	13.0	
Abnormal (≧150mg/dL)	3961	87.1	588	12.9	
High-density lipoprotein cholesterol					.340
Normal	14,285	87.1	2,108	12.9	
Abnormal (male, ＜40 female, ＜50mg/dL)	1,954	86.4	307	13.6	
Metabolic syndrome					.639
No (<3 abnormalities)	13,175	87.0	1,989	13.0	
Yes (≧3 abnormalities)	3,064	87.3	446	12.7	
Hepatitis B					.010
Negative	6,456	87.6	915	12.4	
Positive	1,037	84.9	184	15.1	

Note: Two-tailed chi-square analysis, significance level α=0.05.

Table 3: Differential analysis of 2010-2014 metabolic syndrome combined with fatty liver disease and gallbladder polyps (n=18,257)

Variable	No polyps (n=15,898)		Polyps (n=2,359)		*p* value
	Number of people	%	Number of people	%	
Metabolic syndrome combined with fatty liver disease					<.001
No metabolic syndrome; no fatty liver disease	8,012	88.1	1083	11.9	
No metabolic syndrome; with fatty liver disease	5,163	85.4	886	14.6	
Metabolic syndrome and fatty liver disease	2,723	87.5	390	12.5	

Table 4: Differential analysis of 2010-2014 metabolic syndrome combined with fatty liver disease and gallbladder polyps (n=12,208)

Variable	No polyps (n=10,735)		Polyps (n=1,473)		*p* value
	Number of people	%	Number of people	%	
Metabolic syndrome combined with fatty liver disease					.359
No metabolic syndrome; no have fatty liver disease	8,012	88.1	1,083	11.9	
Metabolic syndrome and fatty liver disease	2,723	87.5	390	12.5	
Metabolic syndrome combined with fatty liver disease					.005
No metabolic syndrome; no fatty liver disease	8,012	88.1	1,083	11.9	
Metabolic syndrome combined with mild fatty liver disease	1,129	85.8	187	14.2	
Metabolic syndrome combined with moderate fatty liver disease	1,328	87.9	183	12.1	
Metabolic syndrome combined with severe fatty liver disease	266	93.0	20	7.0	

Table 5: Regression analysis of gallbladder polyp risk factors (n=8,592)

Variables	β	wald	OR(95%CI)	*p* value
Gender	0.741	52.544	2.098 (1.717-2.563)	<.001
Age	0.184	4.747	1.202(1.019-1.417)	.029
MetS and severe FLD	-0.928	6.368	0.395 (0.192-0.813)	.012

Note 1: Stepwise regression analysis was used. The following variables were included in the regression model: gender (male/female), age (≧40vs. <40), reference group (0: no MetS and no FLD) vs. (1: MetS and mild FLD) vs. (2: MetS and moderate FLD) vs. (3: MetS and severe FLD), hepatitis B (positive vs. negative)
Note 2: Dependent variable; 1 polyps, 0 no polyps.

4. Discussion

The prevalence of GBP varies from country to country [13] and can differ between urban and agricultural areas [14]. The prevalence of GBP in Korea is 3% [1]. Recent studies have confirmed that the percentage of the population with GBP in China (6.9%) is smaller than that in Taiwan (9.5%) [13], but larger than those in Denmark (4.3%) [9], Japan (5.6%) [6, 15], and Germany (6.1%) [16]. In this study, patients with GBP were diagnosed using abdominal ultrasounds, and the prevalence of GBP among the participants was 12.9% (2,415 participants), higher than the values reported in earlier studies. A possible reason for such findings is that the participants in this study were patients who underwent physical examinations in a hospital and might have had prior health issues.

The percentage of male patients with GBP was found to be higher than that of female patients with GBP (15.2% vs. 7.4%). Past studies have indicated that men have a higher risk of GBP at any age than women (apart from men older than 70) [2, 6, 7, 10, 12, 17]; however, a few studies have reported conflicting results [18, 19]. Some studies have maintained that there is no relation between gender and prevalence [9, 20]. This indicates inconsistencies with regard to the correlation between gender and GBP.

GBP is only diagnosed as malignant in 3-8% cases [21]. However, gallbladder cancer is a fatal disease with a 5-year survival rate of less than 5%, and its early diagnosis and treatment can greatly increase survival rates [22]. GBP is the main risk factor for gallbladder cancer. Many studies have unsuccessfully attempted to distinguish between benign and malignant GBP and to determine GBP risk factors. The clinical implications of ultrasound diagnosis include the diagnosis of GBP malignancy. However, GBP are benign in most cases, and 46-70% are cholesterol polyps [21, 23, 24]. Cholesterol polyps typically have a small diameter (2-10 mm) and cannot become malignant [19, 23].

There is currently little information regarding the prevalence of GBP in Taiwan, and the definitions of the related risk factors are not comprehensive. Past studies have indicated that GBP is associated with hyperlipidemia, diabetes, and obesity [12]. However, no studies have confirmed the association between these risk factors and GBP, nor have they indicated that MetS cannot lead to the development of GBP. The results of this study did not show any association between MetS and its compositional factors and GBP, which is similar to the results of past research [10].

Although previous research has indicated that hyperlipidemia, diabetes, and obesity are risk factors for GBP [19], this association was not confirmed by the results of this study. Moreover, it is suggested that MetS is not a risk factor for GBP, which is similar to results of past studies [10], and local inflammation, such as hepatitis B virus (HBV), and cholecystitis likely have a greater effect than MetS. Further research and analysis was conducted for HBV and HBC infections.

The results revealed that HBV is a risk factor for GBP [25], which is not surprising, as similar results have been obtained in many studies on areas related to HBV epidemic [13, 26, 27]. Little is known with regard to the role of HBV in GBP formation. One study suggested that the potential reasons include inflammatory reactions and changes in gall composition [27]. Recent case-control studies published in China indicated that HBV infection is a risk factor that can induce GBP and that GBP factors include age, gender, BMI, HBV, and diabetes. However, the prevalence of gallstones and GBP in China has rarely been reported, and the definitions of the risk factors are not comprehensive [7, 14, 28, 29].

There is a lack of surveys on the current prevalence of MetS combined with FLD. This study indicated a 7.9% prevalence of MetS combined with mild FLD (1,546 participants), a 5.3% prevalence of MetS combined with moderate FLD (1,044 participants), a 0.5% prevalence of MetS combined with severe FLD (90 participants), a 1.2% prevalence of MetS combined with mild to moderate FLD (229 participants), and a 0.4% prevalence of MetS combined with moderate to severe FLD (84 participants). These findings can serve as a reference for future related studies. Further attempts were made to analyze the relation between GBP and combinations of MetS and FLD of different degrees. A chi-square analysis showed

that FLD had a greater effect on GBP than did MetS. A comparison analysis was conducted for FLD (none, mild, moderate, severe), the presence/absence of MetS, and GBP. Results indicated that the rate of GBP was high in patients who had MetS combined with mild FLD, and low in patients who had MetS combined with severe FLD. Patients who had MetS combined with moderate to severe FLD were grouped together, and the comparison results indicated that the rate of GBP was higher in patients who had MetS combined with mild FLD. Logistic regression analysis was conducted in order to examine the association between GBP and MetS combined with FLD. The results indicated that patients who had MetS combined with severe FLD had a lower risk of GBP. The factors influencing GBP included male gender and ages equal to 40 or older. Due to the differences between this study and previous studies in terms of design and predictors, the results are difficult to compare. Nevertheless, the findings of this study can serve as a reference for comparison in future related studies.

5. Limitations

This study had certain limitations. Data was obtained from physical examination data, and certain examination items could not be retrieved, such as cholecystitis and TGW, as well as information about patients ’diet, lifestyle, and physical activity. This could have influenced the conclusions. Cholesterol polyps, adenomatous polyps, and inflammatory polyps were considered to be GBP regardless of their size and shape. This could have influenced the results in this study. However, unless it is confirmed by postoperative histopathology, GBP is difficult to diagnose, which is why all polyps are classified into one category.

Future studies can classify polyps based on their size, quantity, and physical examination results. The participants in this study were patients from a single hospital and, thus, the results cannot be generalized to the overall population. Nevertheless, due to the large sample-size used, the results of this study can serve as a reference for related research.

6. References

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