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Research Article

THE ASSOCIATION BETWEEN METABOLIC SYNDROME COMBINED WITH FATTY LIVER DISEASE AND GALLSTONE DISEASE—DATA ANALYSIS OF HEALTH EXAMINATIONS

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ABSTRACT

Background : In Taiwan, the prevalence rate of gallstone disease (GD) is estimated to be 5%-10% among adults. Several reports have suggested that females and old age individuals have a higher prevalence rate of GD. In addition, hyperglycemia, dyslipidemia and obesity, which are common features of metabolic syndrome, are risk factors for GD.Few studies have examined the relationship between metabolic syndrome combined with fatty liver disease and gallstone disease. **Purpose:** This study aimed to investigate the relationship between metabolic syndrome combined with fatty liver disease and gallstone disease. **Methods:** This study applied cross-sectional data analysis. Participants received physical examination at a local hospital in Kaohsiung, Taiwan, from 2011 to 2014. Fatty liver disease and gallstone disease were diagnosed by a gastroenterologist with abdominal ultrasonography. The metabolic syndrome was defined according to the standards set by Health Promotion Administration, Ministry of Health and Welfare, in 2007. Physical examination and blood test results were employed to evaluate the prevalence rate and risk factors of gallstone disease.**Results:** The results indicated that prevalence rate of GD was 5%. GD had a significantly higher prevalence among participants aged 40 years and older than those under 40 years old. GD prevalence rate was higher among participants with abnormalities associated with metabolic syndrome and its components than healthy participants. GD prevalence rate was significantly higher among participants with mild or moderate fatty liver combined with metabolic syndrome than those without the metabolic syndrome or with a different degree of fatty liver disease. Participants aged 40 years and older had a 2.88-fold higher risk of getting GD than those who were under 40 years old. The risk of GD increased 1.70-fold in participants with mild fatty liver disease combined with metabolic syndrome and 1.32-fold in participants with moderate fatty liver disease combined with metabolic syndrome. **Conclusion:** Prevalence and risk of GD is significantly higher in participants with metabolic syndrome. Awareness of GD prevalence rate and risk factors can facilitate effective GD prevention.

INTRODUCTION

Gallstone disease (GD) is a chronic disease. It consumes socioeconomic and medical resources. GD not only reduces one's life quality [1] but is also considered to be a risk factor of gallbladder cancer[2]. Therefore, recognizing GD risk factors is very important and can control the disease and reduce economic burden.

GD is a very common and expensive disease in many countries [3]. In developed countries, its prevalence rateis 10-15% and continues to increase[3,4]. Epidemiologic research showed that about 70-80% of patients diagnosed with GD have no symptoms, while 20% of patients develop symptoms or complications within 5 to 20 years after

diagnosis [4,5]. A recent large-scale epidemiologicstudy showed that cholecystectomy is performed in 41.3% of GD patients without any symptoms [6]. In the United States, abdominal and liver diseases caused by GD are the main reasons for patients to get hospitalized [7] and direct service expenditures on GD reachUS$5.8 billion, which is more than expenditures ongastroesophagealreflux disease [8].

In Taiwan, 5-10% of adultsare estimated to have GD. Many studies indicate a higher prevalence rate of GD in women and older adults. In addition, hyperglycemia, hyperlipidemia, and obesity are common symptoms of metabolic syndrome and risk factors of GD[9,10]. Many studies have shown the relation between GD and metabolic syndrome [11-13]. GD is one of the most common diseases in the world with the prevalence rate of 5-30%, which varies from area to area [9,14]. Many causes of GD have been reported, including female gender, older age, obesity, family history of GD, race, the use of oral contraceptives, number of pregnancies, amenorrhea [14,15-18], hepatitis C[19], and chronic kidney disease (CKD) [20].

It is considered that obesity is related to liver and gallbladder diseases, including GD[3,11,14], pancreatitis, and hepatic steatosis[21]. These diseases reflect abnormal cholesterol and triglyceride metabolism problems. Obesity-related GDis likely to cause gallbladder cancer due to higher BMI and obesity [22]. Metabolic syndrome and its components increase risk of GD4-fold in both female and male patients[23].

In western countries, high prevalence of non-alcoholic fatty liver disease (NAFLD) and GD is related to metabolic syndrome [23-25]. Moreover, NAFLD is often associated with a variety of risk factors such as obesity, diabetes, dyslipidemia,and insulin resistance [26,27]. Previous studies showeda higher prevalence rate of GD in people with NAFLD [28-31]; moreover, GD is probably an independent risk factor of NAFLD[32]. Research indicates that 25-30% of GD cases are diagnosed in patients with liver cirrhosis, which is a 2-fold risk as compared with the general population[4].

Currently, there are few studies in Taiwan that examined the relation between metabolic syndrome combined with fatty liver disease and gallstone. Recognition of GD prevalence and risk factors may help to improve strategies for GD prevention and treatment. Therefore, this study aimed to analyze the risk of GD in patients withmetabolic syndrome combined with fatty liver disease.

METHODS

Study design

This study adopted a cross-sectional study design.

Participants and data collection

This study collected data from participantswho underwent physical examination at a local hospital in Kaohsiung from 2011 to 2014 to evaluate the relationship between metabolic syndrome, fatty liver disease, and GD. The physical examination data wasobtained from the database in the participating hospital. This study collected and analyzed data after receiving an approval from Institutional Review Board (IRB). The total amount of participants was 19554.

Research participants were required to fast for 10 hours before the blood test. Blood biochemical test includedmetabolic syndrome components, which are triglyceride, high-density lipoprotein cholesterol (HDL-C), and plasma glucose.

Physical examination

(1) Waist circumference(WC)：WC was measured, on bare skin, to the nearest 0.1cm midway between the lower rib margin and the iliac crest at the end of gentle expiration.

(2) Blood pressure(BP)：Well-trained nurses measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) two times in the left arm of seated participants according to a standardized protocol. A third BP measurement was made if the first two BP readings differed by more than 10 mm Hg. The average of the two closest readings was calculated to determine the reported BP for each participant.

Definition of terms

GD and fatty liver disease:GD and fatty liver disease were diagnosed by a gastroenterologist withabdominal ultrasonography and registered in the physical examination database.

Metabolic syndrome: Metabolic syndrome status was defined accordingto the criteria set by the Health PromotionAdministration, Ministry of Health and Welfare in2007. Any three of the following five criteria weregrounds for identifying metabolic syndrome:(1) abdominal obesity: waist circumference (WC)_90 cm in men and _80 cm in women; (2) raisedtriglycerides (TG): _150 mg/dL; (3) reduced HDL-C:HDL-C <40 mg/dL in men and <50 mg/dL in women;(4) hypertension: blood pressure of at least130/85mmHg or taking antihypertensive medication;and (5) raised fasting plasma glucose (FPG) _100mg/dL and/or taking anti-glycemic medication.

DATA ANALYSIS

The statistical package SPSS 17.0 for Windows was used to perform descriptive and inferential statistical analysis. Discriptivestatistical analysisperformed counts, percentage, mean, and standard deviation calculations of data, while inferential statistical analysis performed comparison tests such as the chi-square test and univariable logistic regression of data. Results with $p< 0.05$ were considered statistically significant.

RESULTS

This study collected and analyzed 2011-2014 physical examination data from a total of 19554 participants. Table 1 shows that 55.4% (10824) of participants were male,63.6% (12431) were 40 years and older, 20.4% (3986) had abnormal WC, 29.8% (5825) had abnormal BP, 21.8% (4255) had abnormal glucose level, 25.4% (4958) had abnormal triglyceride levels, 28.8% (5626) had abnormal HDL-C, 18.0% (3528) had metabolic syndrome and 5.0% (971) had GD.

Table 2 shows that apart from gender, all variables had a significant difference on GD; for example,GD prevalence rate was significantly higher in participants aged 40 years and older than those under 40 years old ($p<.001$).

GD prevalence was significantly higher in participantswith abnormalities metabolic syndrome and its components ($p<.05$).Table 3 presents analysis results of the relationship between metabolic syndrome combined with fatty liver disease and GD. The findings showed that GD prevalence was higher in participants with mild and moderate fatty liver disease combined with metabolic

syndrome than those without metabolic syndrome or with a different degree of fatty liver disease. Severe fatty liver disease combined with metabolic syndrome had no statistically significant difference on GD prevalence. Logistic regression analysis was applied in order to examine whether metabolic syndrome and different degrees of fatty liver diseaseare risk factors of GD. The results indicated thatparticipants aged 40 years and older had a 2.88-fold higher risk of getting GD than those who were under 40 years old. The risk of GD increased 1.70-fold in participants with mild fatty liver disease combined with metabolic syndrome and 1.32-fold in patients with moderate fatty liver disease combined with metabolic syndrome.Gender and severe fatty liver disease combined with metabolic syndrome had no statistically significantdifference on GD risk.

DISCUSSION

This study collected and analyzed 2011-2014 physical examination data from a total of 19554 participants. The prevalence rate of GD in participants was 5.0% (917). In Taiwan, 5-10% of adultsare estimated to have GD.GD is one of the most common diseases in the world with the prevalence rate of 5-30%, which varies from area to area[9,14]. GD is common in many countries. In developed countries, GD prevalence rate is 10-15% and continues to increase[3,4]. Research indicates that 25-30% of GD cases are diagnosed in patients with liver cirrhosis, which is a 2-fold risk as compared with the general population [4]18.0% (3528) ofparticipants in this study had metabolic syndrome. Sheu et al. reported 24.2% prevalence rate of metabolic syndrome in Taiwan[33].The cross-sectional studyof Laiet al. discovered that the prevalence rate of metabolic syndrome is44.1%[34]. Due to the difference in definition standards and age groups examined by different studies, reported prevalence rates of metabolic syndrome tend to be inconsistent. With regard to metabolic syndrome components, 20.4% (3986) of the participants in this study had abnormal WC, which is much higher than 3.0% reported by Chuang et al. [35]. 29.8% (5825) of participants had abnormal BP, 21.8% (4255) had abnormal glucose level and 25.4% (4958) had abnormal triglyceride levels. 28.8% (5626) of the participants had abnormal HDL-C levels, which is lower than 29.7% reported by Hwang et al. in 2002. Moreover, in Hwang et al.'s study, fasting glucose, triglyceride, and HDL-C levels were 18.5%, 27.5%, and23.4%, respectively [36], which is considerably lower than glucose and HDL-C found in the participants in this study. The differences are probably due to the difference in cities' living environments and ethnic groups.

Another study by Wassink et al. at a medical center in the Netherlands found that the percentage of patients with abnormal BP, fasting glucose, triglyceride, and HDL-Clevels were 79%, 38%, 44%, and 42%, respectively [37], which are all higher than in Taiwan. Since the samples were collected from a medical center, it is assumed that the findings were related to health problems in the participants.

Currently, there are few studies related to the prevalence of fatty liver disease combined with metabolic syndrome. In this study, participants with mild fatty liver disease combined with metabolic syndrome accounted for 7.9% (1546) of the total sample. 5.3% (1044) of the participants had moderate fatty liver disease combined with metabolic syndrome and 0.5% (90) had severe fatty liver disease combined with metabolic syndrome. Thesefindings can be compared with results of future studies.

In this study, all variables apart from gender were found to have a significant difference on GD; for example, GD prevalence rate was significantly higher in participants aged 40 years and older than those under 40 years old ($p<.001$).GD prevalence was significantly higher in the participants with abnormal WC, BP, HDL-C, triglyceride andglucose levels, and metabolic syndrome ($p<.05$).Previous studies showedthe relation between GD andhyperlipidemia (high cholesterol, high triglycerides, low HDL-C, and high low-density lipoprotein cholesterol)[38-41]. Age, gender, ethnic group, obesity, and diabetes were found to be risk factors of GD [12-14,40,42]. Some studies also found that patients with liver diseases, particularly, cirrhosis,have a higher riskofGD[43,44]. Metabolic risk factors such as abnormal lipid, obesity, and glucose levelswere all reported to increase the risk of GD [9,19,45]. These findings are similar to those in this study.

Obesity isa global health issue which causes metabolic syndrome and is a risk factor of cardiovascular diseases. Obesity is considered to be related to liver and gallbladder diseases, including GD[3,11,14], pancreatitis, and hepatic steatosis[21]. These diseases reflect abnormal cholesterol and triglyceride metabolism problems. GD is a very common and expensive disease in many countries [3]. Its prevalence rate in adults is 10-15% and continues to increase [3,8,46]. Obesity-related GD is likely to cause gallbladder cancer due to higher BMI and obesity [22]. Metabolic syndrome and its components increase risk of GD 4-fold in both female and male patients[23]. Epidemiologic research showed that about 70-80% of patients diagnosed with GD have no symptoms, while 20% of patients develop symptoms or complications within 5 to 20 years after diagnosis[5,47].

In western countries, high prevalence of NAFLD and GD is related to metabolic syndrome[23,25,48]. Moreover, NAFLD is often associated with a variety of risk factors such as obesity, diabetes, dyslipidemia, and insulin resistance [26,27]. Previous studies showed a higher prevalence rate of GD in people with NAFLD [28-31]; moreover, GD is probably an independent risk factor of NAFLD[32].

Despite the lack of clear definition and detailed analysis ofNAFLD in this study and few studies exploring the relationship between fatty liver disease of different degrees combined with metabolic syndrome and GD, regression analysis indicated that people with fatty liver disease combined with metabolic syndrome had a higher risk of getting GD. The risk of GD increased 1.70-fold in participants with mild fatty liver disease combined with metabolic syndrome and 1.32-fold in patients with moderate fatty liver disease combined with metabolic syndrome. Severe fatty liver degree combined with metabolic syndromehad no statistically significant difference on GD risk, which may be due to the low percentage of such participants in this study. Therefore, it is necessary to conduct follow-up studies examining larger samples to more fully understand pathological changes associated with GD.

Limitations

This study has limitations. First, it was designed as a cross-sectional study; thus, only the "snapshot" of association between metabolic syndrome combined fatty liver and GD could be evaluated. Data took the form of

prevalence rate only. The analysis was purely correlational, and, therefore, no causal inferences can be made. Second, our study did not collect sufficient information on health and dietary habits from the participants. It is possible that residual confounding by these factors may also affect the metabolic syndrome combined fatty liver -GD link.

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Table 1. Descriptive statistics of participants' physical examination data (n=19554)

Variable	n	%	Mean ± SD
Gender			
Male	10824	55.4	
Female	8730	44.6	
Age			44.8±11.1
Under 40 years old	7123	36.4	
Over 40 years old	12431	63.6	
Waist circumference			78.4±10.9
Normal	15568	79.6	
Abnormal	3986	20.4	
Systolic pressure			119.9±16.8
Diastolic pressure			74.8±11.4
Blood pressure			
Normal	13729	70.2	
Abnormal (≧130/85mmHg)	5825	29.8	
Glucose			95.8±20.9
Normal	15299	78.2	
Abnormal (≧100mg/dL)	4255	21.8	
Triglyceride			125.8±97.5
Normal	14596	74.6	
Abnormal (≧150mg/dL)	4958	25.4	
HDL-C			50.6±12.3
Normal	13928	71.2	
Abnormal (male < 40, female < 50mg/dL)	5626	28.8	
Metabolic syndrome			
Normal	16026	82.0	
Abnormal	3528	18.0	
Gallstone			
Normal	18583	95.0	
Abnormal	971	5.0	

Table 2. Correlation of demographic characteristics, metabolic syndrome and its components, and gallstone disease (n=19554)

Variables	without gallstone disease(n=18583)		with gallstone disease (n=971)		p value
	n	%	n	%	
Gender					.160
Male	8312	95.2	418	4.8	
Female	10271	94.9	553	5.1	
Age					<.001
Under 40 years old	6956	97.7	167	2.3	
Over 40 years old	11627	93.5	804	6.5	
Waist circumference					<.001
Normal	14897	95.7	671	4.3	
Abnormal	3686	92.5	300	7.5	
Blood pressure					<.001
Normal	13174	96.0	555	4.0	
Abnormal (≧130/85mg/dL)	5409	92.9	416	7.1	
HDL					<.001
Normal	13312	95.6	616	4.4	
Abnormal (male < 40, female < 50mg/dL)	5271	93.7	355	6.3	
Triglyceride					.006
Normal	13905	95.3	691	4.7	
Abnormal (≧150mg/dL)	4678	94.4	280	5.6	
Glucose					<.001
Normal	14653	95.8	646	4.2	
Abnormal (≧100mg/dL)	3930	92.4	325	7.6	
Metabolic syndrome					<.001
Normal	15351	95.8	675	4.2	
Abnormal	3232	91.6	296	8.4	

Note: Chi-square two-tailed test was adopted. The significance level was α=.05.

Table 3. Correlation between metabolic syndrome combined with fatty liver disease and gallstone disease

Variables	without gallstone disease		with gallstone disease		p value
	n	%	n	%	
Mild fatty liver disease combined with metabolic syndrome					<.001
Normal (neither)	11356	96.2	451	3.8	
Abnormal (both)	1387	89.7	159	10.3	
Moderate fatty liver disease combined with metabolic syndrome					<.001
Normal(neither)	14476	96.0	609	4.0	
Abnormal (both)	973	93.2	71	6.8	
Severe fatty liver disease combined with metabolic syndrome					.471
Normal(neither)	15320	95.8	675	4.2	
Abnormal (both)	87	96.7	3	3.3	

Note:
1. Chi-square two-tailed test was adopted. The significance level was α=.05.
2. Sample sizes varied for different levels of fatty liver disease combined with metabolic syndrome

Table 4.Uni-variable regression analysis of risk factors for gallstone disease (n=19554)

Variables	β	wald	OR (95%CI)	*p* value
Gender	0.07	1.05	1.07 (0.94-1.22)	.305
Age	1.06	149.98	2.88 (2.43-3.41)	<.001
Mild fatty liver disease combined with metabolic syndrome	0.53	120.62	1.70 (1.55-1.87)	<.001
Moderate fatty liver disease combined with metabolic syndrome	0.28	18.03	1.32 (1.16-1.50)	<.001
Severe fatty liver disease combined with metabolic syndrome	-0.12	0.17	0.89 (0.50-1.58)	.677

Note:

1. Dependent variables: participants with gallstone disease versus participants without gallstone disease.
2. Independent variables: gender (male versus female), age (age ≥40 years versus <40 years), mild fatty liver disease combined with metabolic syndrome (both versus neither), moderate fatty liver disease combined with metabolic syndrome (both versus neither) and severe fatty liver disease combined with metabolic syndrome (both versus neither).

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