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Original Research Article

Research on interrelation between metabolic syndrome and its components and hepatitis B, hepatitis C, and fatty liver disease

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Abstract: The prevalence of metabolic syndrome increased from year to year has led to a bigger chance for interaction between metabolic syndrome and viral hepatitis. Thus, a hepatitis B carrier or a person infected with chronic hepatitis C who has metabolic syndrome may face a higher risk of liver cirrhosis and liver cancer. However, the mechanism behind this interaction remains unclear. The study aimed to investigate the interrelation between metabolic syndrome and its components, and hepatitis B, hepatitis C, and fatty liver disease. A cross-sectional study design was used. Data were collected through health examinations at a regional hospital in Kaohsiung City from 2011 to 2015 years. Subjects who had serological exam with positive hepatitis B, hepatitis C, fatty liver visible by abdominal ultrasound were considered as cases. The MetS was defined according to the criteria set by 2007 Health Promotion Administration, Ministry of Health and Welfare. The abnormality rate for metabolic syndrome was 17.4%, while the abnormality rates for the components of metabolic syndrome, i.e. (abnormal waist circumference, elevated blood pressure, hyperglycemia, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol (HDL-C)), were 20.1%, 28.8%, 21.4%, 25.1%, and 28.0%, respectively; the abnormality rate for hepatitis B was 15.4%; the abnormality rate for hepatitis C was 2.0%; 59.1% had fatty liver disease. After conducting a logistic regression analysis to investigate the factors influencing the occurrence of hepatitis B, it was found that male participants faced a higher risk (OR=1.47); participants aged 40 or older faced a higher risk (OR=1.27); participants with reduced HDL-C levels faced a higher risk (OR=1.14); and hypertriglyceridemia was a protective factor (OR=0.67). An analysis of the factors influencing the occurrence of hepatitis C indicated that participants aged 40 or older faced a higher risk (OR=2.13); and reduced HDL-C level was a protective factor (OR=0.67). Analysis of the risk for having moderate to severe fatty liver and normal to mild fatty liver has shown that male has higher risk than female OR=2.23; abnormal in waist circumferences, reduced HDL-C , hypertriglyceridemia, elevated blood pressure, hyperglycemia are all risk factors; the OR values are respectively 6.01, 1.61, 2.16, 1.47, 1.91. With respect to hepatitis B, participants with reduced HDL-C levels faced a higher risk, while a hypertriglyceridemia was a protective factor. With respect to hepatitis C, reduced HDL-C were protective factors. Participants whose metabolic syndrome components exhibited abnormal levels were more likely to develop moderate to severe fatty liver disease.
Keywords: Metabolic syndrome, chronic hepatitis B, chronic hepatitis C, fatty liver disease.

INTRODUCTION

Metabolic syndrome (MetS) refers to the concurrent occurrence of risk factors such as hypertension, diabetes, hyperlipidemia, and central obesity [1]. The clustering of these risk factors can increase the incidence and mortality rates of both diabetes and cardiovascular disease [2-4].

In Taiwan, liver cancer is one of the top two cancers among men and women, and chronic liver disease is a primary reason for the development of liver

cancer. Based on statistical data from the US, these important health issues have become the 12th leading cause of death in recent years [5,6].which is a clear indication of their influence on health. Evidence from many studies have shown that chronic liver disease patients who also have MetS, particularly those with type 2 diabetes, were more likely to experiencing a worsening of their condition with respect to the disease [7-12]. Studies have also revealed that the total mortality and liver-related mortality rates of chronic liver disease patients were linked to the components of MetS [13].

Chronic hepatitis B is a global health issue, and those with this disease face an increased risk of developing liver cirrhosis and hepatocellular carcinoma. Studies have shown that MetS patients who also have hepatitis B faced a higher risk of developing liver fibrosis, liver cirrhosis, and hepatocellular carcinoma [14]. A study found that female chronic hepatitis B patients had a higher risk of getting MetS. Previously, it was found there was a more than 100-fold increased risk in hepatitis B virus or hepatitis C virus carriers with both obesity and diabetes, indicating the synergistic effects of metabolic factors and hepatitis. [15]. The prevalence of the concurrent occurrence of MetS and chronic hepatitis B in the general population was about 0.99–1.74% [16, 17]. However, this would change across regions depending on the spread of chronic hepatitis B and MetS in each region. Chronic hepatitis B patients with MetS faced an increased risk of developing liver fibrosis and cirrhosis, and subsequently, hepatocellular carcinoma [18-21].

At present, few studies have investigated the correlation between chronic hepatitis B, chronic hepatitis C, and fatty liver disease, and MetS. A particular study focused on a region in southern Taiwan where the prevalence of hepatitis C was high, and looked at the incidence of MetS components of hepatitis C patients and a healthy control group. Compared to the healthy control group, and with respect to MetS components, hepatitis C patients had a higher prevalence of larger waist circumferences and hypertension [22]. In order to contribute to local empirical data, the study sought to investigate the interrelation between MetS and its components and hepatitis B, hepatitis C, and fatty liver. By doing so, it is hoped that the preliminary findings in this study can serve as a reference for health maintenance programs and a foundation for follow-up studies.

METHODS:

Study design

This cross-sectional study focused on people who underwent physical examinations at a regional hospital in Kaohsiung City between 2011 and 2015, and analyzed their physical examination and blood test data. The blood test items included triglyceride, high-density lipoprotein cholesterol (HDL-C), and plasma glucose.

Participants

(1)Inclusion criteria: The research subjects were people who underwent health examinations (or comprehensive screenings) between 2011 and 2015. Data from a total of 27,907 participants were analyzed in this study.

(2)Exclusion criteria: Data taken from people under the age of 20, blood test data that were incomplete, and data from repeating screenings.

Definition of Terms

(1) Metabolic syndrome 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 (TG) of at least 150 mg/dL, (3) reduced high-density lipoprotein cholesterol (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.

(2) Chronic hepatitis B and C:
Carriers of chronic hepatitis B and C, as diagnosed by gastrointestinal specialists via blood testing.

(3) Fatty liver disease:
Fatty liver disease as confirmed via abdominal ultrasound.

Ethical Considerations

The data collection and analysis in this study began after the research plan was reviewed by the Institutional Review Board (IRB).

Statistical Analysis

The present study analyzed data using SPSS 18.0 (SPSS for Windows release 18.0), with a

significance level of α= .05. The statistical methods included descriptive statistics (frequency distributions, proportion, mean values, standard deviations) and inferential statistics (Chi-Square test, $\chi 2$; logistic regression analysis).

RESULTS:

Table 1 Descriptive statistics of subject population characteristics, metabolic syndrome and its components, fatty liver examinations (n=27,907)

Variables	Number	%	Mean ± standard deviation	Variables	Number	%	Mean ± standard deviation
Gender				**Hypertriglyceridemia**			125.0±93.9
Male	15406	55.2		Normal	20907	74.9	
Female	12501	44.8		Abnormal (≧150mg/dL)	7000	25.1	
Age			44.4±11.1	**Reduced HDL-C**			50.9±12.4
< 40	10702	38.3		Normal	20086	72	
40 or older	17205	61.7		Abnormal (male < 40; female < 50mg/dL)	7821	28	
Age				**Metabolic syndrome**			
20-39	10702	38.3		Not present (< 3 abnormal items)	23043	82.6	
40-59	14474	51.9		Present (≧3 abnormal items)	4864	17.4	
60	2731	9.8		**Hepatitis B**			
Waist circumference			78.2±11.0	Normal(-)	16443	86.9	
Normal	22306	79.9		Abnormal(+)	2482	15.4	
Abnormal	5601	20.1		**Hepatitis C**			
Systolic blood pressure (mmHg)			119.6±16.6	Normal(-)	13776	98	
Diastolic blood pressure (mmHg)			73.8±11.9	Abnormal(+)	276	2	
Elevated blood pressure				**Fatty liver**			
Normal	19870	71.2		Normal	8300	40.9	
Abnormal (≧130/85mmHg)	8037	28.8		Mild fatty liver	7786	38.4	
Hyperglycemia			95.8±21.0	Moderate fatty liver	2956	14.6	
Normal	21922	78.6		Severe fatty liver	175	0.9	
Abnormal (≧100mg/dL)	5985	21.4		Mild to moderate fatty liver	807	4.0	
				Moderate to severe fatty liver	265	1.3	

Table 2 Analysis of subject population characteristics, metabolic syndrome and its components, and hepatitis B (n=18,925)[#]

Variables	Hepatitis B(-)(n=16443)		Hepatitis B(+)(n=2482)		*P*[*]
	Number	%	Number	%	
Gender					<.001
Male	8962	85.3	1547	14.7	
Female	7481	88.9	935	11.1	
Age					<.001
20-39	6973	88.4	915	11.6	
40-59	7826	84.7	1412	15.3	
60	1644	91.4	155	8.6	
Waist circumference					0.402
Normal	13137	87.0	1965	13.0	
Abnormal	3306	86.5	517	13.5	
Elevated blood pressure (mmHg)					<.001
Normal	11904	87.3	1737	12.7	
Abnormal (≧130/85mg/dL)	4539	85.9	745	14.1	
Reduced HDL-C					0.655
Normal	11949	87.0	1793	13.0	
Abnormal (male＜40; female＜50mg/dL)	4494	86.7	689	13.3	
Hypertriglyceridemia					<.001
Normal	12356	86.3	1963	13.7	
Abnormal (≧150mg/dL)	4087	88.7	519	11.3	
Hyperglycemia					0.979
Normal	12981	86.9	1960	13.1	
Abnormal (≧100mg/dL)	3462	86.9	522	13.1	
Metabolic syndrome					0.038
Not present (＜3 abnormal items)	13631	86.7	2009	13.3	
Present (≧3 abnormal items)	2812	88.0	383	12.0	

[*] Chi-square statistical analysis and two-tailed test were carried out, significant level α=.05.

[#] Due to the different analytical objectives, the sample sizes varied depending on the completeness of the analyzed variable data.

Table 3 Analysis of subject population characteristics, metabolic syndrome and its components, and hepatitis C (n=14,052)[#]

Variables	Hepatitis C(-) (n=13,776)		Hepatitis C(+) (n=276)		*P*[*]
	Number	%	Number	%	
Gender					0.210
Male	7412	98.2	138	1.8	
Female	6364	97.9	138	2.1	
Age					<.001
20-39	5030	98.9	58	1.1	
40-59	7212	97.8	165	2.2	
60	1534	96.7	53	3.3	
Waist circumference					0.049
Normal	10857	98.2	204	1.8	
Abnormal	2919	97.6	72	2.4	
Elevated blood pressure (mmHg)					0.046
Normal	9744	98.2	180	1.8	

Abnormal (≧130/85mg/dL)	4032	97.7	96	2.3	
Reduced HDL-C					0.001
Normal	9884	98.3	172	1.7	
Abnormal (male＜40; female＜50mg/dL)	3892	97.4	104	2.6	
Hypertriglyceridemia					0.921
Normal	10318	98.0	206	2.0	
Abnormal (≧150mg/dL)	3458	98.0	70	2.0	
Hyperglycemia					0.096
Normal	10619	98.1	201	1.9	
Abnormal (≧100mg/dL)	3157	97.7	75	2.3	
Metabolic syndrome					0.013
Not present (＜3 abnormal items)	11284	98.2	210	1.8	
Present (≧3 abnormal items)	2492	97.4	66	2.6	

* Chi-square statistical analysis and two-tailed test were carried out, significant level α=.05.
# Due to the different analytical objectives, the sample sizes varied depending on the completeness of the analyzed variable data.

Table 4 Analysis of subject population characteristics, metabolic syndrome and its components, and fatty liver disease (n=20,289) #

Variables	**Fatty liver (Normal/mild) (n=16,086)**		**Fatty liver (Moderate/severe) (n=4,203)**		***P*** *
	Number	**%**	**Number**	**%**	
Gender					<.001
Male	8660	72.9	3215	27.1	
Female	7426	88.3	988	11.7	
Age					<.001
20-39	6736	83.3	1352	16.7	
40-59	7945	76.7	2419	23.3	
60	1405	76.5	432	23.5	
Waist circumference					<.001
Normal	13559	89.0	1673	11.0	
Abnormal	2527	50.0	2530	50.0	
Elevated blood pressure (mmHg)					<.001
Normal	11881	84.7	2144	15.3	
Abnormal (≧130/85mg/dL)	4205	67.1	2059	32.9	
Reduced HDL-C					<.001
Normal	11734	84.3	2184	15.7	
Abnormal (male＜40; female＜50mg/dL)	4352	68.3	2019	31.7	
Hypertriglyceridemia					<.001
Normal	12298	86.9	1862	13.1	
Abnormal (≧150mg/dL)	3788	61.8	2341	38.2	
Hyperglycemia					<.001
Normal	13034	84.7	2358	15.3	
Abnormal (≧100mg/dL)	3052	62.3	1845	37.7	
Metabolic syndrome					<.001
Not present (＜3 abnormal items)	13846	87.2	2024	12.8	
Present (≧3 abnormal items)	2240	50.7	2179	49.3	

* Chi-square statistical analysis and two-tailed test were carried out, significant level α=.05.
# Due to the different analytical objectives, the sample sizes varied depending on the completeness of the analyzed variable data.

Table 5. Impact analysis of hepatitis B, hepatitis C and moderate/severe fatty liver disease (n=20,289) [#]

Items[@]	β	wald	OR(95%CI)	*p*[*]
Hepatitis B (without hepatitis B)				
Gender	0.39	71.64	1.473(1.35-1.61)	<.001
Age	0.24	27.94	1.27 (1.16-1.39)	<.001
Reduced HDL-C	0.13	6.67	1.14 (0.79-0.97)	.01
Hypertriglyceridemia	-0.40	50.72	0.67(0.60-0.75)	<.001
Hepatitis C (without hepatitis C)				
Age	0.75	25.65	2.13 (1.59-2.85)	<.001
Reduced HDL-C	0.40	10.12	0.67 (0.52-0.86)	.01
Moderate/severe fatty liver (normal/mild fatty liver)				
Gender	0.80	294.67	2.23(2.03-2.44)	<.001
Waist circumference	1.79	1893.5	6.01(5.54-6.51)	<.001
Reduced HDL-C	0.48	122.23	1.61(1.48-1.75)	<.001
Hypertriglyceridemia	0.77	323.59	2.16(1.99-2.35)	<.001
Elevated blood pressure	0.38	83.57	1.47(1.35-1.59)	<.001
Hyperglycemia	0.65	230.22	1.91(1.76-2.08)	<.001

[*] Stepwise regression analysis was used.
[@]The following variables were included in the regression model: Gender (female), age (<40 years old), Waist circumference (normal), reduced HDL-C (normal), Hypertriglyceridemia (normal), Elevated blood pressure (normal), and Hyperglycemia (normal). ( ) is indicated as the reference group.
[#] Due to the different analytical objectives, the sample sizes varied depending on the completeness of the analyzed variable data.

27,907 research subjects were included in this study. Table 1 shows that a 55.2% majority of the subjects were male; a 61.7% majority of the subjects were aged 40 or older; the abnormality rate for metabolic syndrome was 17.4%; the abnormality rates for the MetS components, i.e. abnormal waist circumference, elevated blood pressure, hyperglycemia, hypertriglyceridemia, and reduced HDL-C, were 20.1%, 28.8%, 21.4%, 25.1%, 28.0%, and 37.0%, respectively; the abnormality rate for hepatitis B was 15.4%; the abnormality rate for hepatitis C was 2.0%; 59.1% had fatty liver disease.

The incidence of hepatitis B was found to be higher in male patients, higher in patients aged 40-59, and higher in patients who had higher elevated blood pressure. As for triglyceride and MetS, the group with normal exhibited hepatitis B abnormality rates that were. All of these differences were statistically significant (Table 2). Table 3 compared the differences among hepatitis C patients and it was found that patients aged 55 or older had a higher abnormality rate for hepatitis C; patients with abnormal waist circumference and elevated blood pressure measurements exhibited a higher abnormality rate for hepatitis C. All of these differences were, statistically speaking, marginally significant. Patients with reduced HDL-C and MetS exhibited a, significantly higher abnormality rate for hepatitis C. Table 4 shows that patients with abnormal MetS and its components exhibited a higher prevalence of moderate to severe fatty liver disease.

As seen in Table 5, after conducting a logistic regression analysis to investigate the factors influencing the occurrence of hepatitis B, it was found that male participants faced a higher risk (OR=1.47); participants aged 40 or older faced a higher risk (OR=1.27); participants with reduced HDL-C levels faced a higher risk (OR=1.14); and a hypertriglyceridemia was a protective factor (OR=0.67). An analysis of the factors influencing the occurrence of hepatitis C indicated that participants aged 40 or older faced a higher risk (OR=2.13); and a reduced HDL-C level was a protective factor (OR=0.67). With regard to the risk of developing moderate to severe fatty liver disease, as opposed to normal to mild fatty liver disease, the results showed that male participants faced a higher risk (OR=2.23); at abnormal waist circumferences, reduced HDL-C, hypertriglyceridemia, elevated blood pressure, and hyperglycemia were risk factors with the statistically significant OR values of 6.01, 1.61, 2.16, 1.47, and 1.91, respectively.

DISCUSSION

With respect to MetS, it has been shown that patients with obesity and diabetes were more likely to develop fatty liver and hepatocellular carcinoma [14].

Thus, the metabolic liver disease caused by MetS has become an important cause of chronic liver disease. Additionally, chronic hepatitis B, chronic hepatitis C, and fatty liver are the primary causes of chronic hepatitis, liver cirrhosis, liver failure, and hepatocellular carcinoma in Taiwan. The incidence of hepatitis B was found to be higher in male patients, higher in patients aged 40-59, and higher in patients who had elevated blood pressure. As for triglyceride and MetS, the group with normal levels exhibited hepatitis B abnormality rates that were. In a population-based cross-sectional study involving 53,528 participants, it was shown that participants who tested positive for hepatitis B surface antigens faced a lower risk of developing MetS compared to those who tested negative for hepatitis B surface antigens. The study also revealed a negative correlation between hypertriglyceridemia, hypertension, and positive test results for hepatitis B surface antigens [23].which is in line with the results from this study. After conducting a logistic regression analysis to investigate the factors influencing the occurrence of hepatitis B, it was found that male participants faced a higher risk (OR=1.47); participants aged 40 or older faced a higher risk (OR=1.27); participants with reduced HDL-C levels faced a higher risk (OR=1.14); and a hypertriglyceridemia was the protective factor (OR=0.67). A previous study showed that participants who tested positive for hepatitis B surface antigens faced a lower risk of developing MetS compared to those who tested negative for hepatitis B surface antigens. Furthermore, negative correlation between hypertriglyceridemia, hypertension, and positive test results for hepatitis B surface antigens was revealed [24],which is consistent with the results from this study.

A comparison of the differences among hepatitis C patients found that patients aged 40 or older had a higher abnormality rate for hepatitis C; patients with abnormal waist circumference and elevated blood pressure measurements exhibited a higher abnormality rate for hepatitis C. All of these differences were, statistically speaking, marginally significant. Patients with reduced HDL-C and with MetS exhibited a significantly higher abnormality rate for hepatitis C. Some metabolic distributions have indicated direct and indirect links with hepatitis C infections. Many studies have shown that hepatitis C infections was linked to fat metabolism [25-27], i.e. abnormal fat levels were commonly found among chronic hepatitis C patients. 30% to 70% of chronic hepatitis C patients also had fatty liver diseases [28, 29], and there were many reasons that led to the occurrence of fatty liver, including diabetes, hyperlipidemia, and obesity [30-32]. Studies have indicated that a high body mass index, the presence of type 2 diabetes, a higher age, and drinking, will raise the severity of fatty degeneration among hepatitis C patients, and exacerbate liver fibrosis in hepatitis C and obese patients [33]. A logistic regression analysis of the factors influencing the occurrence of hepatitis C indicated that: participants aged 40 or older faced a higher risk (OR=2.13); and reduced HDL-C was a protective factor (OR=0.67). Chan et al. also found that hepatitis C patients exhibited a lower concentration of serum high-density lipoproteins [23]. The above findings are consistent with the results from this study.

The data of the research subjects were taken from a health checkup database, and fatty liver cases mostly involved non-alcoholic fatty liver disease (NAFLD). However, given the present lack of studies comparing fatty liver levels, this study therefore looked at the link between MetS and its components and various levels of fatty liver disease. The results indicated that abnormal waist circumference, reduced HDL-C, hypertriglyceridemia, elevated blood pressure, and hyperglycemia were risk factors with the statistically significant OR values of 6.01, 1.61, 2.16, 1.47, and 1.91, respectively. The study found that patients with MetS and its components faced a higher risk of moderate to severe fatty liver disease. Relevant studies have indicated that the prevalence of NAFLD (including developed and developing countries in Asia and the West) has been rising [34-36]. Compared to healthy people, obese individuals with MetS or visceral obesity were more likely to develop NAFLD [37-39]. Previous studies have shown that MetS and its components were risk factors that could independently predict the risk of NAFLD [40]. The development of NAFLD was closely linked to MetS. This was reflected in the fact that about 90% of NAFLD patients suffered from more than one MetS component, and about 33% of NAFLD patients suffered from three or more MetS components [41].

A series of cross-sectional studies showed that MetS and its components were linked to the increase in NAFLD risk among Taiwanese adults [42], Japanese men and women [43], residents of south Indian cities [44], American adolescents [45] and Mexican patients [46]. Furthermore, in a prospective study that involved ethnic Japanese participants and utilized the physical examination system, MetS was confirmed as a strong predictor of NAFLD [47]. Both obesity and dyslipidemia were also confirmed as major precursors for MetS. MetS is a cluster that is related to insulin resistance (IR), and it may lead to the clustering of abnormal liver lipid metabolism and hepatic inflammation, and subsequently, NAFLD [48-

50].Hyperglycemia and hypertension were also seen as major precursors of MetS, and they have been known to damage the endothelium and exhibit IR characteristics, which may lead to NAFLD [51]. The findings from the above studies were similar to the ones from this study.

Limitations

The study still had some limitations that are worth noting. First, data was derived only from one hospital; as such, due to sample deviation, the results may not be generalizable to all hospitals in Taiwan. However, as a large sample was used, the results may be used by related studies as a reference. Second, only examination data was analyzed and not all potential influencing factors of chronic hepatitis B, chronic hepatitis C and FLD were included. Therefore, inferences must be made carefully.

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