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• CLINICAL RESEARCH •

Metabolic syndrome is directly associated with gamma glutamyl transpeptidase elevation in Japanese women

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Abstract

AIM: This study aimed to determine whether metabolic syndrome is directly or indirectly, through fatty liver, associated with elevated gamma-glutamyl transpeptidase (GGT) levels in Japanese women.

METHODS: From 4 366 women who received their annual health check-up, 4 211 women were selected for analysis. All 4 211 women were negative for both hepatitis B surface antigen and antibody to hepatitis C virus. Clinical and biochemical variables were examined by using univariate and multivariate analysis.

RESULTS: A raised GGT level (>68 IU/L) was seen in 258 (6.1%) of the 4 211 women. In univariate analysis, all variables examined (age, body mass index, blood pressure, hemoglobin concentration, fasting blood glucose, glycosylated hemoglobin A1c, cholesterol, triglyceride, and uric acid) were associated with the elevated GGT level, whereas in multivariate analysis, four variables (age ≧50 yr, hemoglobin ≧14 g/dL, triglyceride ≧150 mg/dL, and presence of diabetes) were significantly and independently associated with raised GGT level. Clinical variables predicting the presence of ultrasonographic evidence of fatty liver were also examined by multivariate analysis; four variables were associated with the presence of fatty liver: BMI ≧25 kg/m^2, hemoglobin ≧14 g/dL, triglyceride ≧150 mg/dL, and uric acid ≧7 mg/dL. There was no significant association between the raised GGT level and the presence of fatty liver. Hypertriglyceridemia was significantly and independently associated with both the raised GGT level and the presence of fatty liver.

CONCLUSION: Metabolic syndrome seemed to be directly, not indirectly through fatty liver, associated with the raised GGT level in Japanese women.

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INTRODUCTION

The prevalence of overweight persons is increasing in developed and developing countries[1-3]. Obesity is strongly associated with insulin resistance[4-6], which is known to be associated with an elevated gamma-glutamyl transpeptidase (GGT) level[7,8]. However, the mechanism of the relationship between insulin resistance and GGT elevation has not yet been clarified. Metabolic syndrome is associated with insulin resistant status[4-6], and is increasing recently in Japan together with an increase in the prevalence of obesity[2]. It is well known that insulin resistance is associated with fatty liver[9,10]. Furthermore, fatty liver is associated with elevated GGT levels[8]. Hence, the following question emerged: is insulin resistant status directly or indirectly, through fatty liver, associated with GGT elevation? Few population-based studies have been performed on the association between raised GGT level and metabolic syndrome[7,8]. Moreover, these studies usually dealt with men[8, 11]. It is well known that GGT elevation is frequently induced by habitual alcohol intake and drinkers are more frequently included among men than women. Most raised GGT levels seen in ordinary women are not caused by alcohol, because women with a history of regular alcohol intake in Japan are rare[12]. However, nonalcoholic steatohepatitis (NASH), a severe form of nonalcoholic fatty liver disease, is known to be associated with female gender, metabolic syndrome, and raised GGT level[10]. Hence, a general population study on the association of raised GGT level with risk factors of metabolic syndrome among women is urgently needed.

The aim of this study was to determine whether metabolic syndrome is directly or indirectly, through fatty liver, associated with GTP elevation in Japanese women.

MATERIALS AND METHODS

Subjects

From January 2000 to December 2000, 4 366 women received their annual health check-up at the Okinawa General Health Service Association. They were all Japanese aged between 21 and 88 years: 87% were 40 years of age or older.

Methods

For all women, the body mass index (BMI; kg/m^2) was calculated. Obesity was defined as BMI ≧25 kg/m^2 as recommended by the Japan Society for Obesity[13].

Laboratory tests included peripheral blood cell counts, liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, alkaline phosphatase (ALP), fasting glucose, cholesterol and triglyceride levels, uric acid, glycosylated hemoglobin A1c (HbA1c), hepatitis B surface antigen (HBsAg), and antibody to hepatitis C virus (anti-HCV).

Blood samples were obtained in the morning after an overnight fast. Standard liver tests were performed on a multichannel autoanalyzer (Hitachi 7250). HBsAg was measured by a commercially available enzyme immunoassay (Enzygnost, Berling, Germany). Anti-HCV was tested by a

second generation enzyme immunoassay (Ortho Diagnostics, Raritan, NJ).

Diagnosis of fatty liver was made using ultrasound according to Saverymuttu *et al*[14]. The criterion for fatty liver was hyperechoic liver tissue with fine, tightly packed echoes. The degree of fatty change was assessed by the fall in echo amplitude with depth, increasing discrepancy of echo amplitude between liver and kidney, and loss of echoes from the wall of the portal veins.

The presence of diabetes mellitus was defined as fasting blood glucose ≧126 mg/dL and/or HbA1c ≧6.1[15,16]. The presence of high blood pressure was defined as systolic blood pressure ≧140 mmHg and/or diastolic blood pressure ≧90 mmHg.

The main endpoint was the identification of the presence or absence of an elevated GGT level combined with clinically associated variables: age, BMI, hypertension, hemoglobin, total cholesterol, triglyceride, uric acid, diabetes mellitus, and fatty liver. All variables were included in a multivariate forward stepwise logistic regression analysis to find the independent predictors of the presence of an elevated GGT level.

Statistical analysis

The continuous variables were compared between the women with and without an elevated GGT level using the 2-tailed Student's *t* test. Correlation among these variables was analyzed by Pearson's correlation coefficient. Categorical variables were compared with Fisher's exact test. Multivariate analysis was tested using forward stepwise logistic regression analysis. The SPSS statistical software was used for statistical analysis. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Among 4 366 women who received a health check-up, 141 were positive for HBsAg and 14 were positive for anti-HCV (None was positive for both HBsAg and anti-HCV). Persons with either HBsAg or anti-HCV were excluded from this study; the data of the remaining 4 211 women was used for the analysis.

Factors correlated with GGT elevation

Univariate analysis Of the 4 211 women without hepatitis virus markers, 258(6.1%) showed an elevated GGT level (>68 IU/L, reference range: 10-68 IU/L). In comparison, the frequency of raised GGT level in 6 620 male health check-up participants (all were negative for both HBsAg and anti-HCV) was 30.2%. When classified into two categories (normal or abnormal, present or absent, above or below), several variables were associated with GGT elevation (Table 1).

Fatty liver was detected in 391(9.3%) of the 4 211 women by using ultrasound. Among the 391 women with fatty liver and 3 820 women without fatty liver, correlations of the GGT level with several quantitative variables were assessed. Among the women with fatty liver, age and BMI were not correlated with the GGT level, whereas all variables examined were correlated well with the GGT level in the women without fatty liver. The GGT level was strongly correlated with both AST and ALT, and the correlations were both stronger than that between GGT and ALP (Table 2).

When the women were divided into 2 groups according to the presence or absence of an elevated triglyceride level, the frequency of GGT elevation did not differ between the women with and without fatty liver. However, the mean GGT level in the women with fatty liver was significantly higher than that in the women without fatty liver (Table 3).

Multivariate analysis In multiple regression analysis, all independent variables but age were correlated with the GGT level. Although fatty liver was associated with GGT level, the association was weaker than those between the GGT level and the other independent variables (Table 4).

Table 1 Univariate analysis of the association between GGT elevation and different variables

Variable	Category	*n*	GGT>68 IU/L (%)	*P*
Age	≧50	2 342	181 (7.7)	<0.0001
	<50	1 869	77 (4.1)	
BMI	≧25	1 206	105 (8.7)	<0.0001
	<25	3 005	153 (5.1)	
Blood pressure	High	563	45 (8.0)	0.047
	Normal	3 648	213 (5.8)	
Hemoglobin	≧14	1 153	110 (9.5)	<0.0001
(g/dL)	<14	3 058	148 (4.8)	
Cholesterol	≧220	1 408	122 (8.7)	<0.0001
(mg/dL)	<220	2 803	136 (4.9)	
Triglyceride	≧150	667	89 (13.3)	<0.0001
(mg/dL)	<150	3 544	169 (4.8)	
Uric acid	≧7.0	154	16 (10.4)	0.025
(mg/dL)	<7.0	4 057	242 (6.0)	
Diabetes	Present	186	32 (17.2)	<0.0001
	Absent	4 025	226 (5.6)	
Fatty liver	Present	391	36 (9.2)	0.008
	Absent	3 820	222 (5.8)	

Table 2 Coefficients between GGT and several variables in women with and without fatty Liver (Pearson's correlation analysis)

Variable	Women with fatty liver (*n*=391)	*P* value	Women without fatty liver (*n*=3 820)	*P* value
Age	-0.035	0.485	0.091	<0.001
BMI	0.022	0.670	0.164	<0.001
SBP	0.078	0.122	0.131	<0.001
DBP	0.101	0.046	0.123	<0.001
Hemoglobin (g/dL)	0.140	0.006	0.100	<0.001
Blood sugar	0.129	0.011	0.195	<0.001
HbA1c (mg/dL)	0.108	0.032	0.186	<0.001
Total cholesterol (mg/dL)	0.187	<0.001	0.134	<0.001
Triglyceride (mg/dL)	0.226	<0.001	0.208	<0.001
AST (IU/L)	0.411	<0.001	0.455	<0.001
ALT (IU/L)	0.464	<0.001	0.524	<0.001
ALP (IU/L)	0.272	<0.001	0.363	<0.001
Uric acid (mg/dL)	0.188	<0.001	0.178	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Relationship between GGT and fatty liver in women with and without elevated triglyceride (TG) Level

	GGT>68 IU/l (%)	Mean of GGT (Geometric mean±SD)
Women with elevated TG level (*n*=667)	89 (13.5)	32.4±1.9
With fatty liver (*n*=137)	22 (16.1)	38.9±1.8
Without fatty liver (*n*=530)	67 (12.6)	30.9±1.9[b]
Women with normal TG level (*n*=3 544)	169 (4.8)	22.4±1.7
With fatty liver (*n*=254)	14 (5.5)	28.2±1.7
Without fatty liver (*n*=3 290)	155 (4.7)	22.4±1.7[b]

[b]*P*<0.001 when compared between with and without fatty liver.

Table 4 Multiple regression analysis of association between logarithmically transformed GGT level and independent variables

Variable	Regression coefficient	*T* value	*P* value
Age	-0.0007	-1.77	0.076
BMI	0.0058	4.82	<0.001
SBP	0.0007	3.36	0.001
Hemoglobin	0.0112	3.64	<0.001
Total cholesterol	0.0004	3.20	0.001
Triglyceride[a]	0.2160	11.38	<0.0001
Uric acid	0.0300	8.23	<0.0001
Diabetes	0.1140	6.45	<0.0001
Fatty liver	0.0340	2.60	0.009
R^2	0.1630		

a, logarithmically transformed triglyceride level.

Table 5 Factors contributing to elevated GGT level in women (*n*=4 211)

	Odds ratio	95% CI	*P*
Age ≧50 years	1.4	1.1-1.9	0.016
Hemoglobin ≧14 g/dL	1.6	1.3-2.1	<0.0001
Triglyceride ≧150 mg/dL	2.3	1.7-3.1	<0.0001
Diabetes	2.2	1.5-3.4	<0.0001

Table 6 Factors contributing to fatty liver in women (*n*=4 211)

	Odds ratio	95% CI	*P*
BMI ≧25 kg/m^2	3.3	2.8-3.9	<0.0001
Hemoglobin ≧14 g/dL	1.6	1.2-2.0	<0.0001
Triglyceride≧150 mg/dL	2.3	1.8-2.9	<0.0001
Uric acid ≧7.0 mg/dL	1.9	1.2-2.8	0.003

Although all variables were associated with GGT elevation in univariate analysis (Table 1), the stepwise logistic regression analysis indicated that four variables (age ≧50 years, hemoglobin ≧14 g/dL, triglyceride ≧150 mg/dL, and presence of diabetes) were significantly and independently associated with GGT elevation (Table 4). The presence of fatty liver was not independently associated with GGT elevation. In the women with fatty liver (*n*=391), only two variables, triglyceride ≧150 mg/dL and presence of diabetes, were significantly and independently associated with elevated GGT level (*P*=0.003 and *P*=0.023, respectively).

Clinical variables predicting the presence of ultrasonographic evidence of fatty liver were also examined by stepwise logistic regression analysis. In all women, four variables were independently associated with the presence of fatty liver: BMI ≧25 (*P*<0.0001), hemoglobin ≧14 g/dL (*P*=0.002), triglyceride ≧150 mg/dL (*P*<0.0001), and uric acid ≧7.0 mg/dL (*P*<0.0001). The elevated GGT level was not independently correlated with fatty liver.

DISCUSSION

GGT is one of the biliary enzymes, and is synthesized in epithelial cells of the intrahepatic bile duct[17]. A raised GGT level is usually seen in association with cholestasis and liver cell necrosis[17]. Although GGT is a biliary enzyme, the levels in this study were more strongly associated with transaminase levels, which are associated with liver cell necrosis, as compared with ALP.

Recently, an association between GGT and metabolic syndrome: hypertension[8], dyslipidemia[7], diabetes mellitus[11], has been reported. The mechanism of the association was still unknown, but one of the likely mechanisms proposed is that GGT is associated with fatty liver, which is also related to hepatic insulin resistance leading to insulin resistance syndrome[11].

In this study, the serum GGT level was correlated with metabolic syndrome (hypertension, diabetes mellitus, and dyslipidemia) and risk factors for metabolic syndrome (age, BMI, blood glucose level, and uric acid concentration) in the univariate analysis, whereas, in the multivariate analysis, only four variables were independently associated with the raised GGT level: age≧50 yr, hemoglobin≧14 g/dL, triglyceride ≧150 mg/dL, and presence of diabetes mellitus. Age ≧50 yr was one of the factors independently associated with GGT elevation, but the association was not seen in the multiple regression analysis. The reason for this discrepancy may be the unique distribution of the age-related prevalence of GGT elevation. The abnormally raised GGT level was most frequently seen in the women of 50-59 years of age.

A relationship between the ultrasonographic evidence of fatty liver and raised GGT level was seen in the univariate analysis, but the relationship was not observed in the multivariate analysis. The triglyceride level was strongly correlated with GGT level and also well associated with fatty liver. The association between the elevated GGT level and fatty liver might be influenced by the strong association between triglyceride and GGT and fatty liver. When the women were divided into two groups according to presence or absence of raised triglyceride level, the frequency of GGT elevation did not differ between the women with and without fatty liver. However, the mean GGT level in the women with fatty liver was significantly higher than that in the women without fatty liver, indicating the positive correlation between GGT level and fatty liver within its normal range.

Both hypertriglyceridemia and diabetes mellitus were independently associated with GGT elevation. Triglyceride level and diabetes mellitus are known to be strongly associated with insulin level and are included in metabolic syndrome[8,18]. Moreover, hyperinsulinemia was reported to be associated with raised GGT level[7]. Raised GGT level is associated with insulin resistance, which is related to an increase in oxidative stress, which leads to liver cell necrosis by stimulating inflammatory cytokines[10]. Fatty liver may not always mediate between insulin resistance and raised GGT levels. For example, diabetes mellitus is the representative condition of the sequelae of insulin resistance and independently associated with raised GGT level, but many diabetic persons do not have fatty liver.

In this study, GGT was correlated with an elevated hemoglobin level. Insulin resistance status increases delivery of free fatty acids to the liver[10], which leads to the formation of free radicals[10]. Formation of free radicals is also induced by iron overload[19], which is associated with insulin resistance[20,21]. Liver iron concentration is correlated with serum ferritin levels and peripheral hemoglobin concentration[21,22]. Obesity, which is linked with an elevated hemoglobin level, is associated with arterial hypoxemia, which may result from reduced pulmonary function[23,24]. Sleep apnea syndrome is frequently seen in obese persons[25,26], and is associated with hypoxemia and elevated levels of hemoglobin.

The serum GGT level is a well known indicator of excess alcohol intake. GGT is also raised in patients with various liver diseases: fatty liver, chronic viral hepatitis, drug-induced liver injury and primary biliary cirrhosis (PBC). These liver diseases are usually asymptomatic, and can be included in general-population studies[27]. Patients with chronic viral hepatitis were supposed to be excluded from this study because all women included in this study were negative for both HBsAg and anti-HCV. However, we did not take a history regarding past or current medication, nor did we examine anti-mitochondrial

antibody. Hence, our study population might contain patients with subclinical drug-induced liver injury and those with asymptomatic PBC. Neverthless, the influence of the presence of these liver diseases might be small because of the rarity of these liver diseases in a population-based study.

In this study, we enrolled only women, but the annual health check-ups include many men. General population studies from Japan showed that 73% of males having health check-ups drank alcohol and that 12.5% of them drank more than 453 mL/wk[8,10]. Obtaining information on alcohol intake from family members who are in close contact with each other is difficult in population-based studies. We therefore excluded male health check-up participants from this study to minimize the possibility of including alcohol-related liver disease. Most female health check-up participants had no regular alcohol intake. We previously interviewed 140 female health check-up participants who had an elevated GGT level and only two (1.4%) of them had a history of regular alcohol intake. The subjects of this study may have included some women with a history of regular alcohol intake, but the influence of alcohol might be quite small and might not affect the whole data.

In conclusion, GGT elevation was independently associated with hypertriglyceridemia and diabetes mellitus but not associated with the ultrasonographic evidence of fatty liver. Metabolic syndrome seemed to be directly, not indirectly through fatty liver, associated with the raised GGT level in Japanese women.

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