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World J Gastroenterol 2005;11(34):5314-5321
World Journal of Gastroenterology ISSN 1007-9327

• *CLINICAL RESEARCH* •

Severity of ultrasonographic liver steatosis and metabolic syndrome in Korean men and women

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Received: 2005-03-16 Accepted: 2005-04-02

Abstract

AIM: To evaluate the association between the severity of liver steatosis and metabolic syndrome in apparently healthy Korean adults.

METHODS: We examined 1 022 men and women, aged 30-79 years, who participated in a health screening test. A standard interview, anthropometrics, biochemical studies, and abdominal ultrasonography were conducted for each participant. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III, with a modification for the waist circumference cut-off level. The severity of liver steatosis was evaluated using liver ultrasonography, and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (γ-GT) levels were determined.

RESULTS: Ultrasonographic liver steatosis was strongly associated with metabolic syndrome and common metabolic abnormalities. Compared with people without steatosis, people with mild, moderate, and severe steatosis had adjusted odds ratios for metabolic syndrome of 1.72 (95%CI, 1.01-2.94), 2.89 (1.75-4.76) and 3.53 (1.25-9.98) in men, and 2.86 (1.64-5.01), 3.19 (1.80-5.65) and 3.70 (0.82-16.73) in women, respectively. The serum AST level was not associated with metabolic syndrome. The serum ALT and γ-GT levels were significantly associated with metabolic syndrome in men but not in women.

CONCLUSION: The occurrence of metabolic syndrome shows a stronger association with the severity of ultrasonographic steatosis than with the serum liver enzyme levels. The degree of fatty infiltration detected on ultrasonography can be used as an indicator of liver dysfunction attributable to metabolic abnormalities.

Key words: Metabolic syndrome; Liver steatosis; Non-alcoholic fatty liver disease; Ultrasonography

Kim HC, Choi SH, Shin HW, Cheong JY, Lee KW, Lee HC, Huh KB, Kim DJ. Severity of ultrasonographic liver steatosis and metabolic syndrome in Korean men and women. *World J Gastroenterol* 2005; 11(34): 5314-5321
http://www.wjgnet.com/1007-9327/11/5314.asp

INTRODUCTION

Non-viral non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized condition that accompanies an increase in obesity[1-3]. NAFLD is known to be associated with various metabolic abnormalities including central obesity, type 2 diabetes, dyslipidemia, and high blood pressure[2,4-9], which are also well-established cardiovascular risk factors. Recently, it was suggested that fatty liver disease can be considered to be the hepatic consequence of metabolic syndrome or of a cluster of metabolic disorders[10-14]. In a previous report, we showed that NAFLD is closely associated with various metabolic abnormalities even in non-obese non-diabetic Korean people[15].

NAFLD has a wide clinical spectrum, and its severity can be measured by several methods. Liver biopsy represents the best diagnostic test for staging liver steatosis, inflammation, and fibrosis, but medical and ethical considerations limit its use in subjects with non-progressive fatty liver conditions[14,16]. The severity of fatty liver disease can also be evaluated based on the serum levels of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (γ-GT)[1,2]. These enzymes are sensitive markers of liver cell damage, but they cannot provide information on the underlying causes of that damage. It has been shown that liver ultrasonography, although not sufficiently sensitive to detect liver inflammation and fibrosis, demonstrates a good correlation with histological findings of fatty infiltration, and international guidelines have been proposed for the diagnosis of different degrees of steatosis[17-19]. However, there are few data available on the

association of metabolic syndrome with the severity of liver steatosis assessed by ultrasonography.

Therefore, in the present study, we expanded our investigation to examine the sex-specific association between the severity of ultrasonographic liver steatosis and the presence of metabolic syndrome. In addition, we also examined the sex-specific association between the serum liver enzyme levels and metabolic syndrome.

MATERIALS AND METHODS

Subjects

This study was performed as part of the Korean metabolic syndrome study, which was undertaken to evaluate the role of metabolic syndrome as a risk factor for cardiovascular disease in Korean adults. We measured the metabolic profile, evaluated the cardiovascular risk factors, and performed abdominal ultrasonography scans on 1 244 men and women. The measurements were made over a 3-mo period (April-June, 2001) at a health screening center in Seoul, South Korea. All participants were healthy, independently functioning individuals who visited the health center for health-screening tests. From among the 1 244 initial volunteers, we selected 1 142 people who were between 30 and 79 years and who had completed anthropometric measurements, serum biochemistry profiles, and liver ultrasonography. We excluded 120 people who had a previous history of coronary heart disease or stroke and 35 people who tested positive for hepatitis B virus surface antigen (HBsAg). Ultimately 1 022 subjects (557 men and 465 women) were included in the analyses.

Measurements

Trained nurses interviewed all participants and obtained their medical history, family history of chronic disease, and information on life style factors, using a standardized questionnaire. The weight and height of each participant were measured while the participant was clothed only in a light gown, and the body mass index was calculated as body weight divided by height squared (kg/m^2). The waist circumference was measured midway between the lowest rib margin and the iliac crest in a standing position, by the same examiner. The percent body fat was measured by bioelectrical impedance analysis (Inbody 2.0, Biospace Co., South Korea). The participants were required to rest for at least 5 min prior to two repeated measurements of their blood pressure at an interval of at least 1 min. The mean value of these two measurements was used for the analyses. Blood samples were obtained from each participant after a fasting period of at least 8 h. The blood glucose level was measured using the glucose oxidase method. The serum insulin level was measured using a radioimmunoassay that had an interassay coefficient of variation of 4%. As an index of insulin resistance, we used the fasting insulin-glucose product. When divided by 22.5, this product is numerically equivalent to the homeostasis model assessment of insulin resistance (HOMA-IR)[20], which has been shown to correlate well with the results of the euglycemic hyper-insulinemic clamp in population-based studies[21]. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured on an autoanalyzer using enzymatic colorimetry. Serum levels of AST, ALT, and γ-GT were also measured using enzymatic methods.

The carotid arteries were evaluated by the same examiner using high-resolution B-mode ultrasonography with a 7.5-MHz probe. The carotid intima-media thickness (IMT) was obtained by measuring the distance between the first and second echogenic lines using a caliper. For each common carotid artery, three measurements were performed and the maximum IMT of each common carotid artery was selected. All measurements were made by the same examiner. Liver ultrasound scans were performed to assess the presence and degree of liver steatosis. All ultrasound scans were performed by the same operator, who was unaware of the participants' medical histories and laboratory findings, using a high resolution B-mode scanner (SSD-5500, Aloka, Tokyo, Japan). Liver steatosis was assessed semi-quantitatively on a scale of 0-3 (0, absent; 1, mild; 2, moderate; 3, severe), on the basis of abnormally intense, high-level echoes arising from the hepatic parenchyma, liver-kidney difference in echo amplitude, echo penetration into the deep portion of the liver, and clarity of the blood vessel structure in the liver (Figure 1)[17].

Metabolic syndrome was defined according to the criteria established by the National Cholesterol Education Program Adult Treatment Panel III (ATP III), except for the determination of abdominal obesity by waist circumference[22]. We used a waist circumference cut-off level of >90 cm in men and >80 cm in women, based on the report by the International Diabetes Institute/Western Pacific World Health Organization/International Obesity Task Force[23]. Hence, in this study, participants having three or more of the following five criteria were defined as having metabolic syndrome: high blood pressure (≥130/85 mmHg), elevated fasting blood glucose (≥110 mg/dL or 6.05 mmol/L), hypertriglyceridemia (≥150 mg/dL or 1.65 mmol/L), low HDL-cholesterol (men, <40 mg/dL or 1.05 mmol/L; women, <50 mg/dL or 1.30 mmol/L), and abdominal obesity by waist circumference (men, >90 cm; women, >80 cm). Participants taking anti-hypertensive or anti-diabetic medications were included in the high blood pressure group and the high fasting blood glucose group, respectively.

Statistical analysis

We reported the clinical and biochemical characteristics of the participants according to the severity of the liver steatosis on ultrasound examination, separating the data for the men and women. For each variable, the linear trend with the severity of ultrasound liver steatosis was tested. The prevalence of abnormal metabolic conditions and metabolic syndrome were calculated for each level of severity of liver steatosis, and the linear trends were also tested. In order to assess the independent association between liver steatosis and metabolic syndrome, age- and multivariate-adjusted logistic regression models were used. First, we estimated the age-adjusted odds ratios of having metabolic syndrome for each level of severity of liver steatosis. In the multivariate model, we estimated the corresponding odds ratios after adjustments for age, menopause (women only), body mass index, cigarette smoking, and alcohol intake. We also estimated the adjusted

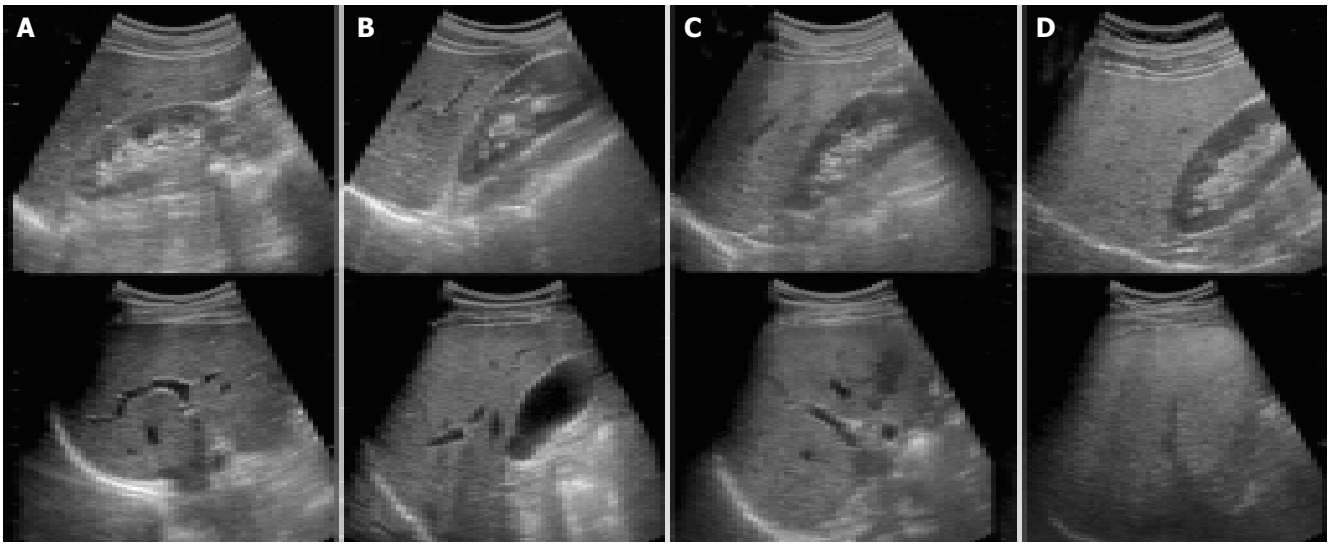

Figure 1 Ultrasonographic findings of liver according to the degree of steatosis. (**A**) Normal liver, (**B**) mild steatosis: a slight augmentation in liver echogenicity, a slight exaggeration of echogenic discrepancy between liver and kidney, and a relative preservation of echo line in the portal vein wall. (**C**) Moderate steatosis: a loss of echo line in the portal vein wall, particularly from the peripheral branches, resulting in a featureless appearance of the liver. (**D**) Severe steatosis: much greater reduction in echo penetration, a loss of echogenicity in most of the portal vein wall, including the main branches, and a large echo discrepancy between liver and kidney. Adapted from Saverymuttu *et al*.[17].

odds ratios of having metabolic syndrome for the different levels of the serum liver enzymes, AST, ALT, and γ-GT. For each enzyme, four categories were established using cut-off values determined by the level at which the number of individuals in each category was nearest to the number in the corresponding level of ultrasonographic severity. The SAS System version 8.01 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. All statistical tests were two-sided, and *P*-values less than 0.05 were considered statistically significant.

RESULTS

Among the 557 men and 465 women examined, ultrasonographic scans revealed mild steatosis in 133 (23.9%) men and 87 (18.7%) women, moderate steatosis in 165 (29.6%) men and 93 (20.0%) women, and severe steatosis in 19 (3.4%) men and 10 (2.2%) women. The clinical characteristics and laboratory data of the participants with different degrees of steatosis as detected on ultrasonography are shown in Table 1. In men, the mean age was similar among the groups with different severities of steatosis, but in women there was a positive association between age and liver steatosis. With increasing severity of liver steatosis, there were statistically significant progressive increases in mean body mass index, waist circumference, body fat percent, blood pressure, total serum cholesterol, and serum triglycerides, and there was a statistically significant decrease in mean HDL-cholesterol. A statistically significant increase was also observed in the mean fasting glucose and insulin levels, and in insulin resistance, as assessed by mean HOMA values. The levels of liver enzymes (AST, ALT, and γ-GT) and carotid IMT were also positively associated with the degree of fatty infiltration. In contrast, cigarette smoking and alcohol intake were not associated with liver steatosis.

In both men and women, fatty liver detected by ultrasonography was strongly associated with metabolic syndrome and the five metabolic abnormalities, which are criteria for its clinical diagnosis. Among the 515 people without liver steatosis, only 19.6% (16.3% for men and 22.6% for women) had metabolic syndrome, whereas almost half (48.3%; 41.0% for men and 60.5% for women) of those with liver steatosis had metabolic syndrome. In addition, the prevalence of metabolic syndrome and of each of the five metabolic abnormalities progressively increased with the severity of liver steatosis (Table 2).

In the age-adjusted logistic regression model, the participant group with liver steatosis had a significantly higher odds ratio of having metabolic syndrome than did the group without steatosis. The odds ratio also increased with increasing severity of liver steatosis. When we adjusted for age, menopause, body mass index, cigarette smoking and alcohol intake, the association between liver steatosis and metabolic syndrome was attenuated but still was highly significant (Table 3). To assess the possible confounding effects of alcoholic hepatitis, we examined the association between liver steatosis and metabolic syndrome by frequency of alcohol intake and found similar results regardless of the frequency of alcohol consumption (data not shown).

The possible associations of serum levels of AST, ALT, and γ-GT with metabolic syndrome were also examined. The serum AST level was not significantly associated with metabolic syndrome in either sex. Serum ALT and γ-GT levels were significantly associated with metabolic syndrome in men but not in women (Table 4).

DISCUSSION

Metabolic syndrome is very common in Western countries and is also increasingly frequent in most developing countries. Fatty liver is a common condition increasingly detected by

Table 1 Clinical and biochemical characteristics of 557 men and 465 women with different severities of ultrasonographic liver steatosis

Characteristics	Ultrasonographic liver steatosis									
	Men				*P* for trend	Women				*P* for trend
	Absent (*n* = 240)	Mild (*n* = 133)	Moderate (*n* = 165)	Severe (*n* = 19)		Absent (*n* = 275)	Mild (*n* = 87)	Moderate (*n* = 93)	Severe (*n* = 10)	
Age (yr)	51.6±11.0	50.0±9.9	51.4±10.6	49.2±11.2	0.521	51.5±9.4	52.7±9.5	55.5±7.8	55.9±9.1	<0.001
Body mass index (kg / m^2)	23.1±2.5	24.7±2.3	25.3±2.6	26.5±2.1	<0.001	23.6±2.7	25.8±3.1	26.6±3.0	27.5±4.0	<0.001
Waist circumference (cm)	83.0±6.9	88.0±6.5	89.2±6.3	92.1±6.8	<0.001	79.0±7.0	85.2±7.7	88.0±7.4	88.5±8.5	<0.001
Body fat percent	20.0±4.4	23.0±4.2	23.4±4.1	24.1±3.5	<0.001	30.1±4.7	33.2±5.4	34.8±4.9	36.1±3.8	<0.001
Systolic BP (mmHg)	126.7±16.9	129.4±16.0	133.9±18.8	133.7±10.7	<0.001	128.4±20.2	131.7±17.3	136.5±19.1	138.5±10.6	<0.001
Diastolic BP (mmHg)	78.2±11.5	79.9±11.1	83.0±12.2	84.2±7.9	<0.001	78.2±13.2	80.7±12.0	82.7±11.9	82.0±7.9	0.002
Total cholesterol (mg / dL)	194.5±32.2	200.6±33.4	205.3±34.6	204.7±25.1	0.001	201.3±33.0	208.3±37.3	217.0±36.9	225.4±28.2	<0.001
Triglyceride (mg / dL)	149.4±104.9	200.2±119.5	230.1±161.8	230.6±111.7	<0.001	123.5±93.1	164.5±115.3	188.6±122.0	184.0±80.1	<0.001
HDL-cholesterol (mg / dL)	46.2±10.4	43.7±9.6	41.3±8.3	41.7±8.8	<0.001	52.9±13.4	47.3±12.8	47.0±12.1	47.0±7.6	<0.001
Fasting glucose (mg / dL)	97.5±23.3	101.7±19.6	108.3±29.4	117.2±36.0	<0.001	92.7±21.2	102.9±36.3	103.4±27.4	109.7±17.7	<0.001
Fasting insulin (IU / L)	9.8±11.4	11.9±6.9	12.6±7.1	13.2±5.1	0.002	9.1±4.9	13.9±8.6	15.1±9.7	16.9±6.2	<0.001
HOMA-IR	2.6±5.4	3.0±1.9	3.3±2.0	3.9±1.8	0.037	2.1±1.4	3.5±2.3	3.8±2.5	4.5±1.5	<0.001
AST (IU / L)	22.4±7.2	25.0±10.0	27.5±21.5	29.5±8.0	<0.001	21.0±7.8	21.4±11.3	23.0±11.2	28.2±6.3	0.013
ALT (IU / L)	23.4±11.8	31.5±18.3	38.3±35.9	50.8±19.0	<0.001	19.2±13.5	21.8±13.8	26.8±17.4	34.8±12.9	<0.001
γ-GT (IU / L)	45.1±50.6	67.1±63.4	69.4±148.8	69.4±42.6	0.009	23.7±22.8	31.6±37.7	32.8±21.3	38.7±11.1	<0.001
Carotid IMT (mm)	0.71±0.19	0.75±0.21	0.79±0.26	0.73±0.13	<0.001	0.70±0.21	0.77±0.23	0.79±0.23	0.81±0.31	<0.001
Menopause (%)						58.2	60.9	81.5	90.0	<0.001
Current smoking	47.9	46.6	42.4	42.1	0.269	5.1	5.8	1.1	10.0	0.345
Alcohol intake≥4 / wk	55.6	60.9	53.0	42.1	0.387	13.2	17.2	9.7	-	0.314
Carotid IMT≥1.0 (mm)	10.0	10.5	17.0	5.3	0.143	6.6	12.6	8.6	20.0	0.145

Table 2 Sex-specific prevalence of metabolic disorders by the severity of ultrasonographic liver steatosis

	Severity of ultrasonographic liver steatosis				*P*
	Absent	Mild	Moderate	Severe	
Men (%)	(*n* = 240)	(*n* = 133)	(*n* = 165)	(*n* = 19)	
Waist circumference >90 (cm)	14.6	33.1	44.2	57.9	<0.001
Blood pressure≥130 / 85 (mmHg)[1]	51.7	52.6	72.1	84.2	<0.001
Fasting glucose≥110 (mg / dL)[2]	11.3	12.0	21.8	15.8	0.008
Triglyceride≥150 (mg / dL)	33.8	63.2	67.3	73.7	<0.001
HDL-cholesterol <40 (mg / dL)	30.4	39.8	42.4	36.8	0.020
Metabolic syndrome (≥3 of the above)	16.3	31.6	46.7	57.9	<0.001
Number of metabolic abnormalities, mean±SD	1.4±1.1	2.0±1.2	2.5±1.1	2.7±1.1	<0.001
Women (%)	(*n* = 275)	(*n* = 87)	(*n* = 93)	(*n* = 10)	
Waist circumference >80 (cm)	42.9	81.6	87.1	90.0	<0.001
Blood pressure≥130 / 85 (mmHg)[1]	56.4	64.4	73.1	100.0	<0.001
Fasting glucose≥110 (mg / dL)[2]	2.2	14.9	16.1	40.0	<0.001
Triglyceride≥150 (mg / dL)	22.9	34.5	47.3	60.0	<0.001
HDL-cholesterol <50 (mg / dL)	41.8	62.1	62.4	70.0	<0.001
Metabolic syndrome (≥3 of the above)	22.5	54.0	65.6	70.0	<0.001
Number of metabolic abnormalities, mean±SD	1.7±1.1	2.6±1.1	2.9±1.1	3.6±1.3	<0.001

HDL: high density lipoprotein. [1]Including subjects taking anti-hypertensive medication. [2]Including subjects taking anti-diabetic medication.

routine abdominal ultrasonographic examination; however, the spectrum of fatty liver varies from mild NAFLD to progressive non-alcoholic steatohepatitis (NASH). NAFLD is a benign fatty liver disease, which accounts for the majority of elevated aminotransferase levels in asymptomatic patients[24]. In contrast, NASH is a more progressive form of fatty liver disease that can progress to liver fibrosis and even cirrhosis[1,14,25]. It has been suggested that fatty liver develops as the result of various metabolic conditions that promote fat accumulation and inflammation in the liver[10-14].

Liver biopsy is the only diagnostic test that is able to differentiate benign NAFLD from progressive NASH, but

Table 3 Sex-specific associations between the severity of ultrasonographic liver steatosis and metabolic syndrome

Ultrasound liver steatosis	Number of people	Number with metabolic syndrome (%)	Age-adjusted odds ratio (95%CI)	Multivariate-adjusted odds ratio (95%CI)[1]
Men				
Absent	240	39 (16.3)	1.00	1.00
Mild	133	42 (31.6)	2.43 (1.47-4.01)	1.72 (1.01-2.94)
Moderate	165	77 (46.7)	4.54 (2.87-7.20)	2.89 (1.75-4.76)
Severe	19	11 (57.9)	7.32 (2.76-19.44)	3.53 (1.25-9.98)
Total	557	169 (30.3)	*P*<0.001	*P*<0.001
Women				
Absent	275	62 (22.6)	1.00	1.00
Mild	87	47 (54.0)	4.06 (2.41-6.83)	2.86 (1.64-5.01)
Moderate	93	61 (65.6)	5.81 (3.45-9.80)	3.19 (1.80-5.65)
Severe	10	7 (70.0)	7.07 (1.73-28.89)	3.70 (0.82-16.73)
Total	465	177 (38.1)	*P*<0.001	*P*<0.001

[1]Adjusted for age, menopause (in women), body mass index, cigarette smoking, and alcohol intake.

Table 4 Sex-specific associations between liver enzyme levels and metabolic syndrome

	AST (IU/L)	Multivariate-adjusted odds ratio (95%CI)[1]	ALT (IU/L)	Multivariate-adjusted odds ratio (95%CI)[1]	γ-GT (IU/L)	Multivariate-adjusted odds ratio (95%CI)[1]
Men						
	9-21	1.00	4-22	1.00	9-35	1.00
	22-25	0.69 (0.42-1.16)	23-31	1.76 (1.04-2.99)	36-52	1.66 (0.95-2.90)
	26-46	0.89 (0.54-1.45)	32-77	2.57 (1.54-4.29)	53-180	3.20 (1.87-5.47)
	47-278	1.81 (0.62-5.28)	78-421	5.23 (1.69-16.18)	181-1 885	3.33 (1.09-10.16)
		P = 0.953		*P*<0.001		*P*<0.001
Women						
	9-21	1.00	4-19	1.00	8-22	1.00
	22-24	0.58 (0.32–1.06)	20-24	1.22 (0.70-2.12)	23-31	1.87 (1.06-3.30)
	25-42	0.96 (0.54–1.70)	25-61	1.44 (0.83-2.50)	32-100	1.25 (0.72-2.19)
	43-117	0.68 (0.16–2.93)	62-172	0.87 (0.20-3.73)	101-323	1.46 (0.33-6.37)
		P = 0.475		*P* = 0.271		*P* = 0.230

AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GT: γ-glutamyl transferase. [1]Adjusted for age, menopause (in women), body mass index, cigarette smoking, and alcohol intake.

it should not be performed on the majority of patients with asymptomatic or mild fatty liver disease. Thus, the clinical evaluation of the severity of fatty liver disease in people with metabolic syndrome is usually based on a combination of ultrasonographic findings and laboratory tests. Liver ultrasonography is frequently used to assess fatty infiltration of the liver, but there is little information on the association between the metabolic diseases and the severity of fatty liver detected by ultrasonography. One previous study reported an association between common metabolic disorders and the severity of liver steatosis assessed by routine ultrasonography in 340 patients[14]. The present study showed that various metabolic abnormalities and metabolic syndrome were positively associated with the severity of ultrasonographic liver steatosis detected in 1 022 healthy people. Our findings suggest that liver ultrasonography can be used to monitor liver dysfunction that occurs in association with common metabolic abnormalities and metabolic syndrome.

Serum aminotransferase assays have also been widely used to detect and diagnose NAFLD[2,9], which is the most common cause of unexplained aminotransferase elevations in most Western populations and in some Asian populations. Thus, we assessed the associations between metabolic syndrome and the levels of several liver enzymes. In our data, metabolic syndrome showed a significant association with ALT and γ-GT levels only in men and showed no significant association with AST levels in either sex. For purposes of comparison, we categorized the enzyme levels so that the distribution of participants in the categories was similar to the distribution of subjects by ultrasonographic severity of steatosis; however, this type of categorization would not be relevant in clinical settings. Thus, we performed further analyses using different classification schemes and obtained similar findings.

The serum AST level is a sensitive marker of liver cell damage, but it has been less frequently used than ALT and γ-GT levels to monitor liver dysfunction because it is relatively non-specific for liver disease and correlates poorly with the clinical severity of liver disease[26]. Our findings support the use of serum ALT and γ-GT levels as indicators of the development of liver steatosis in men with metabolic syndrome. Recently, Jeong and colleagues reported that serum ALT levels were positively associated with metabolic disorders in a population, even when the levels were in the

normal range[27]. The results of that study differed from ours in that, the authors found a significant association in both sexes, although the association in women was weaker than that in men.

The sex-specific differences in the associations between liver enzyme levels and metabolic syndrome were not fully explained by the data. One contributing factor may be that, compared with men, women have relatively low ALT and γ-GT levels that fall within relatively narrow ranges[28,29]. Thus, serum enzyme levels in women might show a poor correlation with liver dysfunction. Another contributing factor to the sex-specific differences might be that the underlying causes of the enzyme elevation may differ by sex. For example, if central obesity is a major cause of enzyme elevation in men but not in women, the relationship between enzyme elevation and metabolic syndrome would likely differ by sex. Sakugawa *et al*., reported that serum γ-GT was correlated with the components of metabolic syndrome and its risk factors in the univariate analysis, but four variables were independently associated with γ-GT: age, hemoglobin, triglyceride, and diabetes[30]. The sex-specific differences shown by our analysis may also be attributable to chance observation. Thus, the association between the serum enzyme levels and metabolic syndrome in women requires further investigation.

The association between fatty liver disease and metabolic syndrome may be explained by several mechanisms. Type 2 diabetes (or insulin resistance) and central obesity have been frequently reported to be associated with both benign NAFLD and progressive NASH[2,4-9]. Insulin resistance is a key component of metabolic syndrome and is also a well-known risk factor for the development of NAFLD[31-33]. However, it is still controversial whether liver disease plays a primary role in the development of hyper-insulinemia and insulin resistance or is a consequence of insulin resistance. Recent studies have added evidence supporting the interpretation that insulin resistance is the primary phenomenon, by showing that hyper-insulinemia and insulin resistance do not stem from a reduction in hepatic insulin extraction, but from an enhancement in pancreatic insulin secretion that is compensatory to reduced insulin sensitivity[12,34-36].

Fatty liver disease has been reported to be closely related to indices of central obesity, such as waist circumference, waist-to-hip ratio, and visceral fat thickness[5,35,37]. Central obesity may contribute to insulin resistance, and increased visceral adiposity might be relevant in the pathogenesis of NAFLD[35,38]. Compared with adipose tissue in other sites, visceral adipose tissue is more resistant to insulin, exhibits greater lipolysis, and produces more free fatty acids[39]. The increased availability of substrates for lipogenesis and the relative hyperinsulinemia that accompany insulin resistance promote lipogenesis in the liver[40]. Visceral adipose tissue is also known to be a potent modulator of insulin action in hepatic glucose production and gene expression[41]. However, the significance of central obesity in the association between liver steatosis and metabolic syndrome may differ by ethnicity. It is well known that Asian people have lower body mass indices and waist circumferences than do Caucasians, but they have higher percent body fat and more cardiovascular risk factors for a given level of obesity[42,43]. In further analysis, we found that the association between liver steatosis and metabolic syndrome remained after additional adjustments were made for waist circumference; the odds ratios for mild, moderate, and severe steatosis were 1.37, 2.39, and 2.72 for men (P for trend <0.001), and 2.47, 2.57, and 3.27 for women (P for trend <0.001), respectively. Moreover, we have already reported that NAFLD was associated with various metabolic abnormalities in non-obese non-diabetic subjects[15]. Further studies will be required to investigate the ethnic and regional differences in the relationship between liver steatosis and metabolic syndrome.

Our study had several strengths. First, we showed an association between the degree of severity of liver steatosis detected by ultrasonography and the occurrence of metabolic syndrome in apparently healthy subjects. The progressive association between ultrasonographic liver steatosis and common metabolic diseases had previously been observed in data collected from patients, but had not yet been studied in the general population. Second, we were able to diminish the sources of inter-observer measurement error, for the liver ultrasonography in particular, because all of the measurements were performed by the same examiner in the same regulated setting, over a relatively short period (3 mo). Third, we were able to assess the association between metabolic syndrome and serum liver enzyme levels. Our data suggest that liver ultrasonography may be a better diagnostic tool than the determination of serum enzyme levels for monitoring liver function in people with metabolic syndrome.

We should point out some of the limitations of the present study. First, we could not assess the temporal relationship between fatty liver disease and metabolic syndrome because the study had a cross-sectional design. Although there is increasing evidence indicating that NAFLD is a hepatic consequence of metabolic syndrome[2,12,34,35], further prospective studies should be conducted to examine the temporal relationship between aminotransferase levels and metabolic syndrome in the general population. Second, we could not take into consideration any variation in the metabolic profile over time because we obtained only one measurement in each participant. Third, it is possible that we did not control entirely for confounding effects caused by viral and alcoholic liver diseases. We excluded subjects who were positive for HBsAg from the analyses because HBV infection is the most common liver disease in Korea, but we could not rule out the effects of other types of viral hepatitis. Alcoholic liver diseases are also common forms of chronic liver disease, but, in a further analysis, the association between liver steatosis and metabolic syndrome was not significantly affected by the level of alcohol intake. However, the possibility of residual confounding effects still exists because we measured alcohol intake with a simple questionnaire and did not use any objective index for alcohol intake. Finally, the study participants were apparently healthy members of the general population, but they were recruited from within a health screening center. Therefore, our study population was not necessarily representative of the general Korean population.

In conclusion, the present study showed a strong positive

association between the severity of ultrasonographic liver steatosis and the prevalence of metabolic syndrome in 1 022 apparently healthy Koreans. Our findings indicate that the degree of fatty infiltration detected on ultrasonography can be used as an indicator of liver dysfunction attributable to metabolic abnormalities. In addition, ultrasonography may be a better diagnostic tool than serum enzyme assays for monitoring liver function in people with metabolic syndrome.

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