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The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease

Se-Yong Oh[a], Yong-Kyun Cho[a,*], Mun-Su Kang[a], Tae-Woo Yoo[a], Jung-Ho Park[a], Hong-Joo Kim[a], Dong-Il Park[a], Chong-Il Sohn[a], Woo-Kyu Jeon[a], Byung-Ik Kim[a], Byung-Ho Son[b], Jun-Ho Shin[b]

[a]*Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 110-746, South Korea*
[b]*Department of Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 110-746, South Korea*

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Abstract

Nonalcoholic fatty liver disease (NAFLD) has been associated with metabolic disorders, including central obesity, dyslipidema, hypertension, and hyperglycemia. Metabolic syndrome, obesity, and insulin resistance are major risk factors in the pathogenesis of NAFLD. The aim of this study was to identify the relative contribution of the metabolic syndrome, obesity, and insulin resistance to alanine aminotransferase (ALT) activity in NAFLD. A total of 3091 subjects diagnosed with fatty liver by ultrasonography were enrolled. All components of metabolic syndrome criteria, anthropometric parameters, fasting insulin levels, high-sensitivity C-reactive protein (hs-CRP) as an inflammation marker, and ALT were measured in each subject. Homeostasis model assessment—insulin resistance (HOMA-IR) as a measure of insulin resistance and body mass index (BMI) as a measure of obesity were calculated. The prevalence of increased ALT levels (>40 IU/L) was 26.7%. Increased ALT activity was significantly associated with the following characteristics: male sex, young age, increased triglycerides, fasting glucose, fasting insulin, HOMA-IR, hs-CRP, waist circumference, BMI and diastolic blood pressure, and decreased high-density lipoprotein cholesterol (HDL-C). According to the increase in the number of metabolic syndrome components, BMI, HOMA-IR, and hs-CRP, the prevalence and odds ratio for having increased ALT activity were significantly increased. Central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose were strongly associated with increased ALT activity. In conclusion, a number of metabolic syndrome components, obesity, insulin resistance, and hs-CRP, are strong predictors of increased ALT activity in NAFLD. Central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose are metabolic syndrome components that contributed to increased ALT activity.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) comprises a large part of chronic liver disease in industrialized countries after excluding alcoholic and viral liver disease. As a result of a sedentary lifestyle and westernized food choices, metabolic syndrome and obesity are increasing in prevalence in Korea, and concomitantly there is an interest in NAFLD. Its presentation ranges from simple fatty liver without fibrosis or necroinflammatory changes to nonalcoholic steatohepatitis, with various degrees of fibrosis or intrahepatic necroinflammation, which can progress to liver cirrhosis or hepatocellular carcinoma [1].

The pathophysiology of NAFLD includes the intrahepatic accumulation of fat in the form of triglycerides, in which insulin resistance is believed to play an important role by facilitating the transport of free fatty acid into the liver from visceral fat stores or peripheral lipolysis [2]. Many studies show that several metabolic conditions, including obesity, diabetes mellitus, dyslipidemia, hypertension, and insulin resistance are strongly associated with NAFLD [3-5]. Metabolic syndrome represents a chronic inflammatory state that links insulin resistance, endothelial dysfunction, and cardiovascular disease, and it has also been reported in NAFLD [6,7]. This suggests that NAFLD may represent the hepatic manifestation of the metabolic syndrome [8].

* Corresponding author. Tel.: +82 2 2001 2080; fax: +82 2 2001 2610.
E-mail address: choyk2004.cho@samsung.com (Y.-K. Cho).

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The prevalence of unexplained hypertransaminasemia reported in the US population was 2.8% to 5.4% [9,10]. Approximately 80% to 90% of hypertransaminasemia may be explained by NAFLD, once other causes such as chronic viral hepatitis and alcohol-induced liver disease are excluded [11,12]. Therefore, nonalcoholic hypertransaminasemia, in which viral or other causes of liver disease are also excluded, has been used as a noninvasive surrogate marker for NAFLD.

The aim of this study was to identify the relative contribution of each component of the metabolic syndrome, obesity, and insulin resistance to increased alanine aminotransferase (ALT) activity in patients with NAFLD.

2. Materials and methods

2.1. Subjects

Kangbuk Samsung Hospital (Seoul, Korea), a tertiary care provider, runs a medical screening center with the aim of providing cutting-edge infrastructure to support early detection of health risk factors and eventually contributing to public health. The center accommodates about 60 000 to 70 000 people per year. Most examinees are employees of various companies and their spouses. Given their middle or higher income levels, they tend to be more attentive to their health status and undergo health checkup more often than other people of the same age range. Medical health checkup provided by the center includes urinalysis, blood cell counts, blood chemistry, measurements of hepatitis B surface antigen and hepatitis C antibody, electrocardiography, chest radiography, abdominal ultrasonography, upper and lower gastrointestinal endoscopy, and measurements of blood pressure and anthropometric parameters (height, body weight, waist circumference). A self-administered questionnaire is also served to measure medical history of the examinee and family, medication history, and lifestyles (smoking, drinking, diet and exercise). The center charges US $450 to men and US $500 to women. Employers usually pay this checkup fee, although there are some exceptions.

A total of 40 237 apparently healthy subjects who underwent a medical health checkup at the Kangbuk Samsung Hospital from January to December in 2004 were included in this study. Of those, 29 506 subjects who did not undergo ultrasonography, or who yielded abnormal ultrasonographic findings other than fatty liver, were excluded. A total of 10 731 subjects diagnosed with fatty liver by ultrasonography were included in the study. An additional 7640 subjects were excluded because of one of the following: a positive test for the hepatitis B surface antigen or hepatitis C antibody, a transferrin saturation of more than 50%, a daily alcohol intake of 20 g or more, drug-induced liver disease, or incomplete data for determination of the metabolic syndrome. Alcohol consumption was assessed by using a self-administered questionnaire concerning the amount and type of alcoholic beverages consumed per week, which was converted into the amount of pure alcohol per day. Taking drugs known to promote fatty liver disease in the past month was also surveyed by using the self-administered questionnaire. Data were not available to evaluate the presence of other less common liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Wilson disease. Ultimately, a total of 3091 subjects were enrolled in this study. The study protocol was approved by the institutional review board and the ethics committee of the Kangbuk Samsung Hospital, and it conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Assessment of hepatic steatosis

As liver biopsy in apparently healthy subjects is not ethical, and the sample size was very large, we used ultrasonography (ASPEN; Acuson, PA) as a noninvasive method to diagnose fatty liver disease. The presence of steatosis was assessed on the basis of ultrasonographic findings of a bright liver, increased echogenicity of the echotexture when compared with the kidneys, vascular blurring, and deep-echo attenuation, as previous described [13-16].

2.3. Measurement of anthropometric parameters

Anthropometric measurements of height, body weight, and waist circumference were made on the same day. The height was measured to the nearest 0.5 cm. The body weight was measured in light clothing and without shoes to the nearest 0.1 kg. The waist circumference was measured to the nearest 0.1 cm with flexible tape at the midpoint between the lower border of the rib cage and the iliac crest. The systolic and diastolic blood pressures were measured in the sitting position after at least 10 minutes of rest. During the 30-minute preceding the measurement, subjects were required to refrain from smoking or consuming caffeine. The blood pressure was measured twice and the mean value was recorded.

2.4. Measurement of biochemical items

For determination of plasma concentrations of fasting glucose, fasting insulin, high-density lipoprotein cholesterol (HDL-C), triglycerides, and ALT, blood was drawn in the morning after 12 hours of overnight fast from an antecubital vein into evacuated tubes containing EDTA. The fasting glucose level was measured using the hexokinase method. The fasting insulin level was measured by an immunoradiometric assay with a BioSource INS-IRMA Kit (BioSource, Belgium). The coefficient of variation was 1.6% to 2.2% for the intra-assay and 6.1% to 6.5% for the interassay. The triglycerides level was measured with an enzymatic calorimetric test. The HDL-C level was determined using the selective inhibition method. Serum iron and total iron binding capacity were measured by a colorimetric method using ferrozine and bathophenanthroline sulfonate, respectively. All biochemical items described above were measured in an automatic analyzer (Advia 1650; Bayer,

Fernwald, Germany). Hepatitis B surface antigen was assessed by chemiluminescent magnetic immunoassay technology, using the ARCHITECT i System (Abbott Laboratories, Abbott Park, IL). Hepatitis C antibody was assessed by radioimmunoassay using the RIAKEY Anti-HCV IRMA tube (Shin Jin Medics, Koyang, Korea). High-sensitivity C-reactive protein (hs-CRP) was measured by particle-enhanced immunonephelometry using the BN II System (N High Sensitivity CRP; Dade Behring, Marburg, Germany). The coefficient of variation was 3.1% to 3.8% for the intra-assay and 2.1% to 3.8% for the interassay. Serum transferrin saturation was calculated as [serum iron (μg/dL)/serum total iron binding capacity (μg/dL)] × 100. Increased ALT activity was defined as serum ALT above the upper limit of normal, that is, more than 40 IU/L.

2.5. Classification of the predictors of increased ALT activity

2.5.1. Metabolic syndrome

The metabolic syndrome was defined by the new International Diabetes Federation (IDF) definition [17].

1. Central obesity: waist circumference of 90 cm or more for Asian men and 80 cm or more for Asian women
2. Plus any 2 of the following 4 factors:
   - raised triglycerides: more than 150 mg/dL or specific treatment of this lipid abnormality;
   - reduced HDL-C: less than 40 mg/dL in males and less than 50 mg/dL in females, or specific treatment of this lipid abnormality;
   - raised blood pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg, or treatment of previously diagnosed hypertension;
   - raised fasting plasma glucose: 100 mg/dL or more, or previously diagnosed type 2 diabetes mellitus.

For analysis, subjects were divided into a noncentral obesity group and a central obesity group, according to central obesity to be certainly needed for diagnosis of metabolic syndrome. The central obesity group was classified into 5 subgroups based on additional metabolic syndrome components.

2.5.2. Obesity

The body mass index (BMI) was used to determine the degree of obesity and was calculated as the weight in kilograms divided by the square of height in meters. The BMI was classified into 4 groups based on the criteria of the Regional Office for the Western Pacific Region of WHO (WPRO) [18]:

- normal weight: less than 23 kg/m^2;
- overweight: 23 to less than 25 kg/m^2;
- obese I: 25 to less than 30 kg/m^2;
- obese II: 30 kg/m^2 or more.

Table 1
Clinical and metabolic characteristics according to ALT activity

Characteristic	ALT activity (N = 3091)		*P*
	Normal (≤40 IU/L) (n = 2266)	Increased (>40 IU/L) (n = 825)	
Percent of population (%)	73.3	26.7	
Sex (n [%])			<.001
Male	1381 (66.6)	694 (33.4)	
Female	885 (87.1)	131 (12.9)	
Age (y)	49.6 ± 10.4	44.8 ± 9.9	<.001
Triglyceride (mg/dL)[a]	163.0 (118.0-225.0)	210.1 ± 108.8	<.001
HDL-C (mg/dL)	55.9 ± 9.7	54.7 ± 9.6	.004
Fasting glucose (mg/dL)[a]	98.0 (91.0-107.0)	106.2 ± 27.6	.006
Fasting insulin (μIU/mL)[a]	10.70 (8.72-13.44)	12.91 ± 4.93	<.001
HOMA-IR[a]	2.64 (2.10-3.48)	3.42 ± 1.71	<.001
hs-CRP (mg/L)[a]	0.090 (0.050-0.170)	0.183 ± 0.214	<.001
Waist circumference (cm)	86.3 ± 7.1	90.4 ± 7.2	<.001
Body mass index (kg/m^2)	25.9 ± 2.5	27.1 ± 2.9	<.001
Systolic BP (mm Hg)	124.2 ± 16.1	124.1 ± 14.9	.927
Diastolic BP (mm Hg)	80.2 ± 9.8	81.2 ± 9.9	.013

Data are expressed as means ± SD, medians (interquartile ranges) for skewed variables, or proportions for categorical variables. Differences were assessed using *t* tests for continuous variables or χ^2 tests for categorical variables. BP indicates blood pressure.

[a] *t* Tests were performed on log transformations of skewed variables.

The underweight (<18.5 kg/m^2) category was combined with normal-weight category because of the small number of subjects in the underweight category.

2.5.3. Insulin resistance and hs-CRP

The homeostasis model assessment—insulin resistance (HOMA-IR) was used to determine the degree of insulin resistance using the following formula [19]: HOMA-IR = [fasting insulin (μIU/mL) × fasting blood glucose (mmol/L)]/22.5. For analysis, HOMA-IR and hs-CRP were categorized into quartiles of values.

2.6. Statistical analysis

Data are expressed as means ± SD, medians (interquartile ranges) for skewed variables, or proportions for categorical variables. Differences were assessed using *t* tests for continuous variables or χ^2 tests for categorical variables. The *t* tests were performed on log transformations of skewed variables. Linear increases in the prevalence of increased ALT activity, sorted by increasing numbers of metabolic syndrome components, BMI, HOMA-IR, and hs-CRP, were assessed using linear-by-linear association tests. The odds ratios and 95% confidence intervals (CIs) were assessed using multiple logistic regression analysis to determine the risk of increased ALT activity. Statistical analyses were performed with the SPSS 11.0 (SPSS, Chicago, IL) statistical package

Table 2
The association with increased ALT activity of the number of metabolic syndrome components, obesity, insulin resistance, and hs-CRP

Variable	No. of subjects (%), N = 3091	Increased ALT activity	
		Prevalence n (%)	Odds ratio (95% CI)
Metabolic risk factors		<.001[a]	
Noncentral obesity	1434 (46.4)	317 (22.1)	1
Central obesity + 0	167 (5.4)	28 (16.8)	0.66 (0.41-1.04)
Central obesity + 1	494 (16.0)	148 (30.0)	1.37 (1.05-1.81)
Central obesity + 2	628 (20.3)	202 (32.2)	1.53 (1.17-1.99)
Central obesity + 3	334 (10.8)	122 (36.5)	1.62 (1.17-2.22)
Central obesity + 4	34 (1.1)	8 (23.5)	1.49 (0.60-3.69)
Body mass index		<.001[a]	
<23	277 (9.0)	30 (10.8)	1
23 to <25	768 (24.8)	154 (20.1)	1.68 (1.09-2.59)
25 to <30	1785 (57.7)	518 (29.0)	1.94 (1.26-2.97)
≥30	261 (8.4)	123 (47.1)	3.17 (1.89-5.32)
HOMA-IR		<.001[a]	
First quartile	767 (24.8)	130 (16.9)	1
Second quartile	784 (25.4)	175 (22.3)	1.26 (0.96-1.64)
Third quartile	770 (24.9)	230 (29.9)	1.71 (1.32-2.22)
Fourth quartile	770 (24.9)	290 (37.7)	2.28 (1.75-2.98)
hs-CRP		<.001[a]	
First quartile	932 (30.2)	177 (19.0)	1
Second quartile	699 (22.6)	190 (27.2)	1.33 (1.04-1.70)
Third quartile	717 (23.2)	221 (30.8)	1.67 (1.31-2.14)
Fourth quartile	743 (24.0)	237 (31.9)	1.63 (1.27-2.09)

The odds ratios and 95% CIs were determined using multiple logistic regression analysis to determine the risk of increased ALT activity, adjusted for all other variables in the table, as well as for age and sex. Metabolic syndrome components were defined by the new IDF definition: noncentral obesity group, irrespective of the number of other 4 metabolic syndrome components; central obesity group, plus 0 to 4 according to the number of other 4 metabolic syndrome components. The body mass index was classified into 4 groups based on the criteria of the WPRO. HOMA-IR and hs-CRP were categorized into quartiles of values.

[a] Linear increases in the prevalence of increased ALT activity, sorted by increasing numbers of metabolic syndrome components, BMI, HOMA-IR, and hs-CRP, were assessed using linear-by-linear association tests.

for Windows. A P value of less than .05 was considered to be statistically significant.

3. Results

3.1. Prevalence of fatty liver disease on ultrasonography

Of the total 40 196 subjects (men/women, 24 863/15 333) except for 41 subjects who did not undergo ultrasonography, 10 731 (26.7%) were diagnosed as having fatty liver disease. Among these 10 731 subjects, 82.2% (8816) were men and 17.8% (1915) were women. Thus, 35.5% (8 816/24 863) of the men and 12.5% (1 915/15 333) of the women were affected.

3.2. Clinical and metabolic characteristics according to ALT activity

A total 3091 subjects except for 37 146 subjects who met exclusion criteria as previous described were left in the analysis. The mean age was 48.3 years (SD, 10.5 years; range, 19-86 years). Of the 3091 subjects, 2075 (67.1%) were men and 1016 (32.9%) were women. The prevalence of increased ALT levels was 26.7% (Table 1). Increased ALT activity was strongly associated with the following characteristics: male sex, young age, increased triglycerides, fasting glucose, fasting insulin, HOMA-IR, hs-CRP, waist circumference, BMI and diastolic blood pressure, and decreased HDL-C (Table 1).

3.3. Predictors of increased ALT activity

The prevalence of metabolic syndrome according to the new IDF definition was 32.2%. Of these, the prevalence of increased ALT levels was 33.3%. An increased prevalence of increased ALT levels was strongly associated with an increase in the number of metabolic syndrome components in the central obesity group (Table 2). The central obesity group, either with or without all the other metabolic syndrome components, was similar to the noncentral obesity group with regard to the prevalence of increased ALT levels. The prevalence of obesity, according to the WPRO criteria, was 66.1%. Of these, increased ALT activity was seen in 31.3%. An increased BMI was strongly associated with an increased ALT activity (Table 2). The increase in HOMA-IR and hs-CRP was strongly associated with increased ALT activity (Table 2). The prevalence of each of the metabolic syndrome components, according to the new IDF definition, was 53.6% for central obesity, 56.5% for raised triglycerides, 9.4% for reduced HDL-C, 47.5% for raised blood pressure, and 44.1% for raised fasting glucose. Among these, the prevalence of increased ALT levels was 30.7%, 32.0%, 22.6%, 28.1%, and 29.0%, respectively (Table 3). Of the 5 metabolic syndrome components, the presence of central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose were strongly associated with the increase of ALT levels (odds ratio [95% CI]: 1.99 [1.66-2.38], 1.64 [1.37-1.96], 1.62 [1.16-2.26], and 1.41 [1.19-1.69], respectively; Table 3).

4. Discussion

It is currently believed that the clinical diagnosis of NAFLD requires the exclusion of alcoholic, viral, autoimmune, genetic, and drug-induced liver disease determined in conjunction with laboratory testing and ultrasonographic or

Table 3
The association with increased ALT activity of metabolic syndrome components

Variable	No. of subjects (%), N = 3091	Increased ALT activity	
		Prevalence n (%)	Odds ratio (95% CI)
Central obesity	1657 (53.6)	508 (30.7)	1.99 (1.66-2.38)
Raised triglycerides	1745 (56.5)	558 (32.0)	1.64 (1.37-1.96)
Reduced HDL-C	292 (9.4)	66 (22.6)	1.62 (1.16-2.26)
Raised blood pressure	1467 (47.5)	412 (28.1)	1.10 (0.92-1.31)
Raised fasting glucose	1364 (44.1)	396 (29.0)	1.41 (1.19-1.69)

The odds ratios and 95% CIs were determined using multiple logistic regression analysis to determine the risk of increased ALT activity, adjusted for all other variables in the table, as well as for age and sex.

histologic evidence of hepatic steatosis [1]. Our study has a limitation in that liver biopsy was not performed to determine hepatic steatosis, inflammation, and fibrosis because most subjects had no clinical indication for liver biopsy. However, in other studies, ultrasonography was 87% to 100% sensitive and 84% to 89% specific in detecting fatty infiltration of the liver [14,15,20-22]. In our study, the prevalence of NAFLD diagnosed by ultrasonography was 7.7%. Male sex was significantly associated with NAFLD. In addition, we cannot state that the increased ALT levels associated with metabolic syndrome, obesity, insulin resistance, and hs-CRP were directly related to the degree of hepatic steatosis and inflammation. However, previous study has shown that most people (83%) with elevated ALT levels in the absence of alcoholic, viral, autoimmune, or genetic hepatitis have hepatic steatosis or steatohepatitis on liver biopsy [12]. In our present study, the prevalence of increased ALT levels in patients with NAFLD was 26.7%.

The pathogenesis of NAFLD is not clear, but it has been suggested that the presence of insulin resistance and visceral adiposity play a major role [23-25]. Recently, it has been reported that adipokines (such as leptin, adiponectin, and resistin) secreted in adipose tissue are closely related to insulin resistance, obesity, and a proinflammatory state in the pathogenesis of NAFLD [2]. Elevated C-reactive protein levels, an inflammation marker, have been reported in NAFLD as a subclinical inflammation state related to insulin resistance and has also been related to metabolic syndrome and elevated ALT levels [6,7,26]. In our study, the prevalence of metabolic syndrome in patients with NAFLD (32.3%) was higher than that of the general population (23.7%) reported in a previous study [27]. Patients with NAFLD with increased ALT activity were significantly associated with the following characteristics: male sex, young age, increased triglycerides, fasting glucose, fasting insulin, HOMA-IR, hs-CRP, waist circumference, BMI and diastolic blood pressure, and decreased HDL-C. By multiple logistic regression analysis to determine the risk of increased ALT activity, we found that increases in the number of metabolic syndrome components, BMI, insulin resistance, and hs-CRP, were strongly associated with increased ALT activity in patients with NAFLD. We also found that central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose were metabolic syndrome components strongly associated with increased ALT activity. In our study, the central obesity group, either with or without all the other metabolic syndrome components, was not different from the noncentral obesity group with regard to the prevalence of increased ALT levels. This might be explained by the fact that the number of subjects having all metabolic syndrome components is very small or might be because subjects with noncentral obesity may have other metabolic syndrome components affecting ALT levels, as previous described.

Our study has another limitation in that we could not rule out the presence of other, rarer causes of liver disease, such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Wilson disease. However, it is unlikely that they represent a significant number of patients with increased ALT levels.

In addition, because this study was conducted with apparently healthy Korean people who underwent health checkup at a hospital, results of the study cannot be generalized to the other groups and contexts.

In summary, this study suggests that a number of metabolic syndrome components based upon the new IDF definition, obesity, insulin resistance, and hs-CRP may be predictors of increased ALT levels in patients with NAFLD. Central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose are known metabolic syndrome components that may be predictors of increased ALT levels in NAFLD. The interpretation of results, combined with the metabolic syndrome, obesity, insulin resistance, and hs-CRP, may be useful for estimating the risk of progression of liver disease in the clinical setting and may be useful in the selection of patients with NAFLD who should be considered for liver biopsy and potential therapy.

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