The relationship of alanine aminotransferase to metabolic syndrome in a Korean population

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ABSTRACT

Background/Aims: *Although associations between serum alanine aminotransferase and metabolic syndrome are well-recognized in Western countries, only a limited number of prospective studies have been performed in Asian populations. The aim of the study was to cross-sectionally and longitudinally examine whether serum alanine aminotransferase levels are associated with metabolic syndrome and its associated components in a Korean population.*

Materials and Methods: *A total of 31,832 subjects who received health screenings were included in cross-sectional analyses; a subgroup of 4.070 subjects without metabolic syndrome at baseline was included in the longitudinal analyses. The metabolic syndrome definition was based on the National Cholesterol Education Program Third Adult Treatment Panel criteria with modification on waist circumference cut-off to be more appropriate for an Asian population.*

Results: *In the cross-sectional analyses, serum alanine aminotransferase is positively associated with metabolic syndrome and its components. In the longitudinal analyses, the prevalence of metabolic syndrome increased across serum alanine aminotransferase quartiles in a dose-dependent manner after extensive adjustments (hazard ratios were 1.000, 1.609, 2.601, and 3.015 for quartiles, 1 through quartile 4; P for trend<0.001).*

Conclusion: *Our study confirmed a positive association between components of metabolic syndrome and elevated serum alanine aminotransferase in a Korean population.*

Keywords: *Alanine aminotransferase, liver enzymes, metabolic syndrome*

INTRODUCTION

Metabolic syndrome (MS) is a combination of a number of metabolic and physiological abnormalities, including increased blood glucose, elevated waist circumference, hypertriglyceridemia, increased blood pressure, and low high-density lipoprotein cholesterol (HDLC) (1). MS is associated with increased risk for developing cardiovascular diseases (2), type 2 diabetes (3), and chronic kidney disease (4). A number of studies have demonstrated that the prevalence of elevated alanine aminotransferase (ALT), widely used as a marker of liver damage (5), is higher in individuals with type 2 diabetes and MS (6). In addition, elevated ALT is independently related to the future risk of MS components such as obesity and diabetes (7). Furthermore, increased ALT is associated with diabetes-related morbidity and mortality as well as cardiovascular mortality (8).

Up to the present, a numbers of studies have conducted the prospective relationship between liver enzymes and risk of MS, but they have been predominantly performed in American and European populations (9-12); only, a limited number of prospective studies have been performed in Asian populations. For example, Suzuki et al. (13) studied the serial order of elevated ALT with features of MS and showed that elevated ALT is preceded by weight gain, whereas the other features followed the elevated ALT. However, this study targeted only nonalcoholic population and its results without adjusting for novel confounding factors such as serum γ-glutamyl transferase and uric acid. Nakanishi et al. (14) found that among the liver enzymes they studied, ALT is associated with risk of MS, but this study was confined to middle-aged Japanese men and used body mass index rather than waist circum-

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ference to define MS. Yu et al. (15) evaluated serum ALT as a risk marker for MS and its component disorders in a Chinese population over age 60 years old and they found that high-normal serum ALT is associated with increased risk of developing MS. To the best of our knowledge, no study has addressed the prospective relationship between ALT and MS in a general population-based study in Asia.

We hypothesized that increased serum ALT is connected with risk of MS. In addition, we based the study on the hypothesis that increased serum ALT should be considered to be associated with MS risk. The aim of the present study was to cross-sectionally and longitudinally examine whether serum ALT levels are correlated with MS and its associated components in a Korean population.

MATERIALS AND METHODS

Study population

We investigated 37,582 subjects who received health screenings at a health promotion center in Korea from January 1999 to December 2001 (for the first period of analysis) and 149,620 who received screenings from January 2006 to December 2014 (for the second period). If a subject received more than one screening during the first period, we used the first screening results; if a subject received a screening more than once in the second period, we used the last screening results.

For the cross-sectional study, subjects of the first period (n=37,582) were analyzed. We excluded 5.750 subjects for the following reasons based on their screenings: 271 had omitted data for any component of MS; 1,914 had a medical record of chronic hepatitis B, chronic hepatitis C, or liver cirrhosis, or they were taking medications that affect liver function (hepatotonics or herbs); 189 had a prior diagnosis of any malignancy; 407 had a diagnosis of cardiovascular disease (cerebrovascular, coronary, and peripheral artery disease and heart failure); 2.855 for excess alcohol consumption [>20 g/d in women or >30 g/d in men, which have been revealed to cause liver damage in prior studies (16, 17)]-we excluded these to avoid the presence of alcoholic liver disease in study sample. A total of 595 subjects had ALT levels above 2.5 times the upper level of the reference value (≥100 U/L)-we excluded these subjects to reduce confounding factors as a consequence of elevated ALT caused by toxic or viral agents. Finally, we included 31,832 subjects (16,017 women and 15,815 men).

For the longitudinal analysis, among subjects who were included for the cross-sectional study (n=31,832), 5.014 subjects who received health screenings in both periods (one baseline and one follow-up) were included. In addition, we applied the above exclusion criteria to the follow-up (n=501). Furthermore, we excluded subjects with MS at baseline (n=580) as well as subjects with any history in diagnosing or taking medications related with hypertension, hyperlipidemia, low HDLC, or glucose intolerance/diabetes mellitus either alone or in combination at baseline (n=665), and we finally included 4.070 subjects (1.891 women and 2.179 men).

Metabolic syndrome definition

We based our MS definition at baseline and follow-up screening on the Updated National Cholesterol Education Program Third Adult Treatment Panel criteria (18) with adjustment on waist circumference cutoff value to be more suitable for an Asian population (19). We considered a subject to have MS in three or more of the following cases: (i) blood pressure ≥130/85 mmHg or the subject was taking antihypertensive medications; (ii) waist circumference ≥80 cm in women and ≥90 cm in men; (iii) serum triglyceride ≥150 mg/dL (1.69 mmol/L); (iv) HDLC level <50 mg/dL (1.29 mmol/L) in women or <40 mg/dL (1.03 mmol/L) in men; or (v) fasting glucose ≥110 mg/dL (6.1 mmol/L) or verified diagnosis of type 2 diabetes.

Measurements

Before their blood samples were collected, each subject fasted for more than 10 hours. After the overnight fasting, skilled practitioners took venous blood sample to measure ALT, fasting blood glucose, uric acid, γ-glutamyl transferase, total cholesterol, triglycerides, HDLC, and low-density lipoprotein cholesterol. ALT, fasting blood glucose, uric acid, and lipid levels were assayed using a Toshiba- 200FR automatic analyzer (Toshiba Medical Systems, Tokyo, Japan). Serum γ-glutamyl transferase was assayed by the standard method recommended by the International Federation for Clinical Chemistry using L-γ-glutamyl-3-carboxy-4-nitroanilide as the substrate with a Toshiba 200FR autoanalyzer. Blood pressure was measured using a standard mercury manometer with

the subject in a sitting position for 5 min prior to measurement and expressed by rounding off; it was measured on three occasions and averaged for a final value. We used a self-reported questionnaire regarding diabetes, hypertension, alcohol consumption, and smoking status. Subject who had quit smoking for ≤1 or >1 month at the time of the baseline screening were considered to be current and former smokers, respectively. Alcohol consumption in subject was calculated and then altered to weekly consumption (grams of ethanol/week) using the graduated frequency method (20). To normalize their skewed distribution, amounts of alcohol were natural log-transformed.

Statistical analysis

First, we used simple descriptive analysis for the general characteristics, grouping the study populations into quartiles according to the levels of serum ALT; we assess the differences by quartile using ANOVAs. For the cross-sectional analyses, we used logistic regression models to determine the associations between MS and its individual components for each quartile compared with the reference group (the lowest quartile), adjusting for age, gender, serum γ-glutamyl transferase level, serum uric acid level, smoking status, and log-transformed alcohol consumption. We tested for linear trend across increasing ALT quartiles by regarding the quartiles as a continuous variable. We used Cox regression for the longitudinal analyses to assess the effects of serum ALT on the development of MS and its components. We performed all statistical analyses using Statistical Package for Social Sciences version 20.0 (IBM Corp.; Armonk NY, USA) and considered $p<0.05$ to be considered statistically significant. All participants provided written informed consent to participate in the survey. The Institutional Review Board of Ajou University Hospital (Suwon, Republic of Korea) approved the study (Approval No : AJIRB-MED-MDB-16-063).

RESULTS

The general characteristics of 31,832 subjects by serum ALT quartile are shown in Table 1. The mean (standard deviation) ALT levels for the subjects without MS was 27.4 (15.3) and for the subjects with MS was 37.5 (19.1) ($p<0.001$). The median (range) ALT levels for the first to the fourth quartiles were 12 (4-15), 18 (16-21), 26 (22-31), and 42 (32-99) IU/L, respectively. Subjects with higher serum ALT levels were more disposed to be current drinkers or smokers than those with lowest serum ALT levels. Almost the whole metabolic risk factors, including blood pressure, waist circumference, body mass index (BMI), fasting blood glucose, total cholesterol, and triglycerides, increased significantly with increasing serum ALT ($p<0.001$), whereas age did not significantly differ among quartiles. Elevated serum ALT is connected with an increased risk of MS in both univariate and multivariate analyses (Table 2). After we adjusted for age, gender, baseline γ-glutamyl transferase level, baseline uric acid level, smoking status, and log-transformed alcohol consumption, the hazard ratios (HR) for the highest and lowest serum ALT quartiles were significant in the presence of MS [Q1: 1.00; Q2: HR=1.151, 95% confidence interval (CI)=1.070-1.239, $p<0.001$; Q3: HR=1.342, 95% CI=1.247-1.444, $p<0.001$; Q4: HR=1.807, 95% CI=1.674–1.950, $p<0.001$) and its components.

The baseline subject characteristics for the longitudinal analysis are summarized in Table 3. There are similarities between the baseline characteristics for the longitudinal analysis and the general characteristics for the cross-sectional analysis. The mean follow-up period was 9.94 years (minimum, 4.08 y; maximum, 15.90 y; standard deviation, 3.10). Prevalence of MS and all of its components increased significantly with increased serum ALT level, whereas HDLC levels decreased markedly ($p<0.001$; Figure 1). The mean (standard deviation) ALT levels for the subjects with and without MS at follow-up study

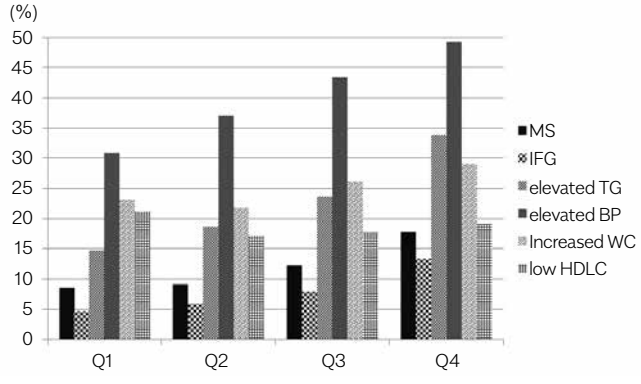

Figure 1. Prevalence of MS and its components at follow-up screening by serum ALT quartile at baseline. Prevalence of MS and all of its components except low HDLC show an increase by ALT quartile ($p<0.001$). BP, blood pressure; IFG, impaired fasting glucose; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; TG, triglyceride; WC, waist circumference.

Table 1. General characteristics of the study populations by serum ALT quartile

Variables*	Q1 (n=8.397) (ALT 12, 4-15IU/L)†	Q2 (n=7.247) (ALT 18, 16-21IU/L)†	Q3 (n=8.238) (ALT 26, 22-31IU/L)†	Q4 (n=7.950) (ALT 42, 32-99IU/L)†
Age (year)	54.27±8.72	56.93±9.22	58.35±8.88	56.86±8.39
BMI (kg/m^2)	21.72±2.42	22.70±2.74	23.63±2.66	24.73±2.74
Male (No., %)	313 (24.5)	569 (44.1)	867 (70.1)	1.042(82.4)
Waist circumference (cm)	71.76±6.95	76.72±8.23	81.47±8.06	85.58±8.09
GGT (IU/L)	13.70±6.33	19.07±9.50	28.82±18.21	49.13±40.24
Uric acid (mg/dL)	4.31±1.09	4.84±1.23	5.47±4.17	5.89±1.36
Total cholesterol (mg/dL)	174.94±32.78	182.31±32.73	191.25±34.12	197.40±34.94
Triglyceride (mg/dL)	90.89±50.70	111.68±66.96	135.46±83.54	174.70±117.46
HDLC (mg/dL)	53.77±11.72	51.86±12.07	49.10±11.45	46.30±10.86
LDLC (mg/dL)	105.14±28.85	109.80±28.57	116.70±30.94	117.81±32.82
SBP (mmHg)	110.84±14.57	115.23±15.72	119.74±16.01	122.90±15.23
DBP (mmHg)	69.42±9.74	71.58±10.22	74.29±10.72	76.33±10.56
FBS (mg/dL)	93.03±10.50	96.00±14.82	98.94±19.44	101.50±19.67
Smoking status				
None (No., %)	1.090 (85.22)	822 (66.61)	614 (49.64)	503 (39.79)
Former (No., %)	45 (3.52)	92 (7.46)	140 (11.32)	169 (13.37)
Current (No., %)	144 (11.26)	320 (25.93)	483 (39.05)	592 (46.84)
Alcohol consumption (g/week)	15.61±32.88	28.09±44.28	42.71±52.71	50.53±56.06

Data are shown as mean ± SD.

*p<0.001 - All values except age show statistical significance in the comparisons by quartiles.

†Data are presented as a median and ranges for the quartiles.

ALT: alanine aminotransferase; Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile; BMI: body mass index; GGT: γ-glutamyltransferase; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; None: non-smoker; Former: former smoker; Current: current smoker

were 20.3 (11.0) and 27.0 (13.2) (p<0.001), respectively. Table 4 reports the results for the Cox regression models that we used to evaluate the associations between MS, its components, and serum ALT levels. After we adjusted for the covariates mentioned previously in the cross-sectional analysis, the odd ratios (OR) for the highest and the lowest serum ALT quartiles were significant in the presence of MS (Q1: 1.00; Q2: OR=1.609, 95% CI=0.874–2.964, p=0.127; Q3: OR=2.601, 95% CI=1.451–4.663, p=0.001; Q4: OR=3.015, 95% CI=1.681–5.406, p<0.001) and its components, except for HDLC level (p=0.359, data not shown).

In the use of serum ALT as a test variable to predict MS, a receiver-operating characteristic (ROC) curve was prepared (Figure 2). The area under the ROC curve was 0.54 (95% CI: 0.41–0.50). On the basis of the ROC curve, the best serum ALT cutoff obtained was 21.5 IU/L with sensitivity of 58.1% and specificity of 51.0%

DISCUSSION

Our study reports that serum ALT level is positively associated with MS and its components (fasting glucose, triglyceride, blood pressure, and waist circumference), and this correlation remained statistically significant after we

Table 2. The association between serum ALT and MS and its components at baseline screening

	Q2 (n=7.247)	Q3 (n=8.238)	Q4 (n=7.950)
Total (n=31,832)	Hazard ratio (95% confidence interval; p value)		
MS			
Model 1	1.350 (1.305-1.396;<0.001)	1.656 (1.602-1.712;<0.001)	2.143 (2.072-2.216;<0.001)
Model 2	1.151 (1.070-1.239;<0.001)	1.342 (1.247-1.444; <0.001)	1.807 (1.674-1.950;<0.001)
Impaired fasting glucose			
Model 1	1.935 (1.694-2.210;<0.001)	2.917 (2.570-3.311;<0.001)	4.341 (3.841-4.907;<0.001)
Model 2	1.086 (0.848-1.391;0.514)	1.298 (1.017-1.656;0.036)	1.691 (1.315-2.174;<0.001)
Elevated triglyceride			
Model 1	2.073 (1.883-2.283;<0.001)	3.366 (3.607-3.695;<0.001)	6.834 (6.236-7.488;<0.001)
Model 2	1.273 (1.057-1.532;0.011)	1.457 (1.213-1.749;<0.001)	2.520 (2.090-3.039;<0.001)
Elevated blood pressure			
Model 1	1.696 (1.561-1.843;<0.001)	2.271 (2.093-2.465;<0.001)	2.946 (2.716-3.195;<0.001)
Model 2	1.132 (0.956-1.341;0.152)	1.280 (1.080-1.516;<0.001)	1.585 (1.329-1.890;<0.001)
Increased waist circumference			
Model 1	2.015 (1.825-2.225;<0.001)	3.150 (2.863-3.468;<0.001)	5.296 (4.823-5.816;<0.001)
Model 2	1.690 (1.360-2.098;<0.001)	2.515 (2.031-3.115;<0.001)	4.246 (3.410-5.287;<0.001)
Low high-density lipoprotein cholesterol			
Model 1	0.990 (0.915-1.070;0.793)	1.030 (0.953-1.114;0.458)	1.225 (1.133-1.323;<0.001)
Model 2	1.058 (0.898-1.247;0.500)	1.313 (1.112-1.550;0.001)	2.115 (1.780-2.513;<0.001)

Reference group: 1st quartile (n=8,397).
All p-values for trend<0.001
Model 1: before adjustment; Model 2: after adjustment for age, gender, serum γ-glutamyltransferase level, serum uric acid level, smoking status, and log-transformed alcohol consumption
ALT: alanine aminotransferase; MS: metabolic syndrome Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile

adjusted for gender, age, serum γ-glutamyl transferase level, serum uric acid level, smoking status, and log-transformed alcohol consumption.

The cross-sectional and longitudinal analysis results of our study coincide in previous studies that association between ALT and developing MS (9-12). Hanley et al. (10) studied the association between ALT developing MS in a cohort and documented that ALT is connected with MS risk. Goessling et al. (11) addressed that elevated levels of ALT are concerned with the development of various metabolic disorders in a Caucasian population, and Schindhelm et al. (12) proposed that higher ALT is correlated with an increased risk of MS in elderly Caucasians.

For the fourth quartile, we set ALT level cutoff >32 IU/L; a value of 40 IU/L is regarded as abnormal by most medical laboratories. The comments that the ORs of MS by serum ALT quartile were significantly high within the normal reference range of ALT levels suggest that ALT might be a risk marker for MS, in spite of the normal reference range. Furthermore, the best cutoff value of serum ALT was 21.5 IU/L in male and 20.5 in female, which are also in the reference range. These findings in the cross-sectional and longitudinal analyses in the

Table 3. Baseline characteristics of study populations by serum ALT quartile

Variables*	Q1 (n=966) (ALT 12, 4-14IU/L)†	Q2 (n=923) (ALT 17, 15-19IU/L)†	Q3 (n=1.052) (ALT 23, 20-28IU/L)†	Q4 (n=996) (ALT 38, 29-99IU/L)†
Age (year)	53.76±8.38	55.63±8.53	56.99±8.77	55.97±8.00
BMI (kg/m^2)	21.57±2.32	22.19±2.57	22.93±2.43	24.01±2.52
Male (No., %)	223 (23.1)	357 (38.7)	677 (64.4)	808 (81.1)
Waist circumference (cm)	71.23±6.43	75.47±7.62	79.31±7.52	83.20±7.40
GGT (IU/L)	12.89±5.53	17.18±7.49	24.47±15.71	41.98±34.77
Uric acid (mg/dL)	4.24±1.06	4.74±1.21	5.33±4.48	5.77±1.32
Total cholesterol (mg/dL)	173.87±32.51	180.65±31.02	186.87±32.66	195.48±33.70
Triglyceride (mg/dL)	85.83±40.33	102.87±57.72	114.02±61.88	144.76±94.63
HDLC (mg/dL)	30.88±28.20	40.90±24.89	41.28±22.25	39.69±21.12
LDLC (mg/dL)	104.48±28.80	109.64±27.50	115.07±30.33	120.18±31.36
SBP (mmHg)	110.01±14.06	113.26±14.77	116.05±14.14	119.00±13.36
DBP (mmHg)	68.99±9.46	70.37±9.75	72.13±9.63	73.61±9.30
FBS (mg/dL)	92.20±7.68	93.92±8.87	95.05±9.44	97.07±13.14
Smoking status				
None (No., %)	849 (87.89)	658 (71.29)	564 (56.31)	392 (39.36)
Former (No., %)	27 (2.80)	53 (5.74)	106 (10.08)	133 (13.35)
Current (No., %)	90 (9.32)	212 (22.97)	382 (36.31)	471 (47.29)
Alcohol consumption(g/week)	14.46±31.33	24.55±41.44	39.33±50.19	46.74±54.03

Data are shown as mean ± SD.

*p<0.001. All values except age showed statistical significance by quartiles.

†Data are presented as a median and ranges for the quartiles.

ALT: alanine aminotransferase; Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile; BMI: body mass index; GGT: γ-glutamyltransferase; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; Non: non-smoker; Former: former smoker; Current: current smoker

present study confirmed previous cross-sectional observations that suggested that increased serum ALT levels, even in the normal reference range, are connected with features of MS (21,22).

Although the mechanisms that underline the observed associations between serum ALT and MS are not yet fully understood, there are a number of possible explanations. One, ALT is associated with liver fat accumulation measured by proton magnetic resonance spectroscopy (23), and accordingly, it was supposed to reflect fat deposition in the liver, which is considered a feature of MS (24). This hepatic fat deposition may give rise to early insulin resistance (25), and actually, a previous study reported that hepatic fat content measured by proton magnetic resonance spectroscopy has relevance to insulin resistance, independent of obesity (26). Insulin resistance leads to increased free fatty acids that are absorbed by the liver. It is unclear if high plasma insulin is the primary disorder in the progression of events that results in hepatic steatosis. However, it might be the case that changes in the liver cells associated with fat accumulation affect insulin degeneration, resulting in delayed plasma insulin clearance and ensuing hyperinsulinemia (27).

Table 4. Cox regression analysis of MS and its components as independent variables and ALT quartiles as a dependent variable

	Q2 (n=1.105)	Q3 (n=1.001)	Q4 (n=988)
Total (n=4.070)	Hazard ratio (95% confidence interval; p value)		
Model 1			
MS	1.140 (0.854-1.522;0.374)	1.547 (1.172-2.042;0.002)	2.130 (1.643-2.761;<0.001)
IFG	1.357 (0.928-1.985;0.115)	1.870 (1.296-2.969;0.001)	2.926 (2.085-4.105;<0.001)
Elevated TG	1.346 (1.087-1.666 ;0.006)	1.755 (1.426-2.160;<0.001)	2.363 (1.943-2.874;<0.001)
Elevated BP	1.262 (1.078-1.477;0.004)	1.452 (1.252-1.684;<0.001)	1.612 (1.394-1.865;<0.001)
Increased WC	1.007 (0.840-1.208;0.936)	1.231 (1.030-1.741;0.022)	1.295 (1.088-1.541;0.004)
Low HDLC	1.076 (0.833-1.391;0.574)	1.067 (0.817-1.394;0.634)	1.133 (0.877-1.463;0.338)
Model 2			
MS	1.609 (0.874-2.964;0.127)	2.601 (1.451-4.663;0.001)	3.015 (1.681-5.406;<0.001)
IFG	1.411 (0.687-2.899;0.349)	2.349 (1.191-4.631;0.014)	3.189 (1.622-6.269;0.001)
Elevated TG	1.265 (0.876-1.828;0.210)	1.480 (1.036-2.114;0.031)	1.579 (1.109-2.247;0.011)
Elevated BP	1.467 (1.109-1.940;0.007)	1.612 (1.225-2.171;0.001)	1.384 (1.043-1.837;0.024)
Increased WC	1.335 (0.908-1.963;0.142)	1.970 (1.358-2.859;<0.001)	2.360 (1.614-3.450;<0.001)
Low HDLC	0.968 (0.591-1.584;0.897)	1.114 (0.679-1.828;0.670)	1.477 (0.906-2.409;0.118)

Reference group: 1st quartile (n=976).

Model 1, before adjustment; Model 2, after adjustment for age, gender, serum γ-glutamyltransferase level, serum uric acid level, smoking status, and log-transformed alcohol consumption.

MS: metabolic syndrome; ALT: alanine aminotransferase; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile; IFG: impaired fasting glucose; TG: triglyceride; BP: blood pressure; WC: waist circumference; HDLC: high-density lipoprotein cholesterol

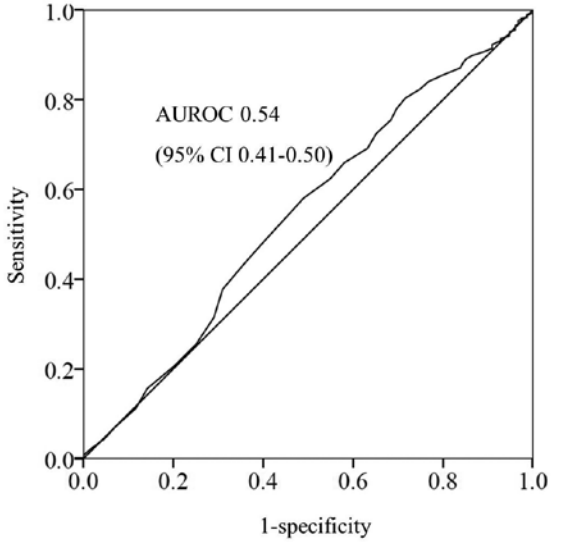

Figure 2. ROC curves of serum ALT level according to the presence of metabolic syndrome.
ROC: recieverr operateng characteristic; ALT: alanine aminotranüferase; CI: confidence interval; AUROC: area under the receiver operating characteristic

Elevated ALT levels might also indicate systemic inflammation and the interaction of visceral adipose tissue, stimulating hepatic C-reactive protein, which may bring about further metabolic derangement (28). These mechanisms could explain how elevated ALT levels increase the risk of developing MS. The present study pointed out that increased serum ALT predicts MS development even after we adjusted for γ-glutamyl transferase concentration, which also reflects metabolic disturbance (29). Therefore, this finding indicates that serum ALT levels may be a novel predictor of MS in Korean populations.

The strong points of our study are the long follow-up interval-9.95 years, large sample size, and its population-based design. In addition, we had access to detailed histories of the alcohol consumption, which is a strong confounding factor that might increase ALT elevation, is well-documented. Furthermore, we adjusted for exten-

sive covariates including novel confounding factors such as serum γ-glutamyl transferase and uric acid.

There are some limitations with this study. First, the participants of the present study consisted of a single health promotion center, and caution should be exercised in generalizing our findings to other populations. Second, serum ALT could be increased not only in liver disease but in other conditions, such as muscular diseases (30). However, the current study did not include these as confounders, as their prevalence is regarded to be very low. Third, it is unclear whether the analysis of our subject brought about selection bias.

In conclusion, our study reports positive associations between MS, its components, and increased serum ALT. These significant associations with serum ALT levels even within normal range seem to have an additional benefit in predicting the future development of MS. Thus, the current study suggests that elevated serum ALT is a novel biomarker for MS development in a Korean population.

Ethics Committee Approval: Ethics committee approval was received for this study from The Institutional Review Board of Ajou University Hospital (Decision Date: 28.04.2016/Decision No: AJIRB-MED-MDB-16-063)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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