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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1731 – 1736
Metabolism
Clinical and Experimental
www.metabolismjournal.com

The association between normal alanine aminotransferase levels and the metabolic syndrome: 2005 Korean National Health and Nutrition Examination Survey

Sang-Yeon Suh[a,*], Sung-Eun Choi[b], Hong-Yup Ahn[c], Hye-Min Yang[a], Yu-Il Kim[a], Nak-Jin Sung[a]

[a]*Department of Family Medicine, Dongguk University Ilsan Hospital, Goyang-si, Gyeonggi-do 410-773, Korea*
[b]*Department of Laboratory Medicine, University of Ulsan, College of Medicine and Asan Medical Center, Seoul, Korea*
[c]*Department of Statistics, Dongguk University, Seoul, Korea*

Received 29 September 2008; accepted 28 May 2009

Abstract

The metabolic syndrome is known to sometimes exist in the presence of normal aminotransferase levels. The purpose of this study was to determine the lowest sex-specific level of alanine aminotransferase associated with the metabolic syndrome in a nationwide, representative Korean population. We analyzed data from adults 20 years and older (n = 3405) assessed in the Third Korean National Health and Nutrition Examination Survey (2005). Participants were divided into 4 groups according to the quartiles of alanine aminotransferase levels for each sex. Logistic regression modeling was performed after adjustment for age, body mass index, waist circumference, smoking, ingested alcohol amount, and physical activity. Alanine aminotransferase level groups 3 and 4 in women (≥15 IU/L) and group 4 in men (≥27 IU/L) were significantly associated with the metabolic syndrome compared with the lowest alanine aminotransferase groups (<16 IU/L in men, <11 IU/L in women). In men, the odds ratio (95% confidence interval) of the metabolic syndrome was 2.71 (1.31-5.63) for alanine aminotransferase group 4 (≥27 IU/L). In women, odds ratios were 1.69 (1.02-2.80) and 2.06 (1.23-3.43) for alanine aminotransferase groups 3 (15 ≤ alanine aminotransferase < 19 IU/L) and 4 (≥19 IU/L), respectively. High-normal alanine aminotransferase levels (≥27 IU/L in men, ≥15 IU/L in women) were strongly associated with the metabolic syndrome in Korean adults.

1. Introduction

Hepatic aminotransaminases are indicators of hepatocellular health. Although multiple sources for alanine aminotransferase (ALT) are recognized, the highest concentrations of ALT are found in the liver [1,2]. Elevated ALT, even within the reference range, is known to be significantly correlated with increasing liver fat. Recent prospective studies have shown that elevations in ALT, including values less than the upper limit of the reference range, are associated with incident metabolic syndrome [3,4]. In fact, the importance of any variation within the "reference range" of liver enzyme activity is supported by several previous studies [3,5-8].

Most of the previous studies on liver markers and the metabolic syndrome have used population-based samples. However, a representative, national population deserves more complete investigation. Although Kim et al [5] demonstrated that even normal to near-normal ALT levels are associated with features of the metabolic syndrome in a nationally representative Korean sample, we believed that the most recent nationwide survey data merited more refined analysis. Kim et al analyzed data from the 1998 and 2001 nationwide surveys in Korea. However, the authors adopted the same lowest values of ALT associated with an increasing risk of the metabolic syndrome for each sex; and they did not suggest any rationale to define the lowest ALT values.

In this study, we explored the relationship between the metabolic syndrome and ALT levels in the reference range in the most recent (2005) nationwide representative sample of adult Koreans. We sought to determine the lowest sex-specific ALT level associated with an increased risk of the

* Corresponding author. Tel.: +82 031 961 7497; fax: +82 031 961 7977.
E-mail address: lisasuhmd@hotmail.com (S.-Y. Suh).

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doi:10.1016/j.metabol.2009.05.028

metabolic syndrome. This study was performed according to the guidelines of the Helsinki Declaration.

2. Methods

2.1. Study population

The Korea Centers for Disease Control and Prevention conducted the Third Korean National Health and Nutrition Examination Survey (Korean NHANES III) in noninstitutionalized Korean civilians in 2005. A stratified, multistage probability sampling design was used; and sampling units were based on geographic areas, sex, and age groups on household registries. The staff conducted household surveys by administering a questionnaire to each participant. The surveys investigated the demographic, socioeconomic, dietary, and medical histories of each respondent. The initial sample consisted of 5493 subjects older than 20 years who completed the health examination.

Subjects were excluded from analysis if their daily alcohol intake was more than 2 drinks (alcohol use ≥30 g/d) for men or more than 1.5 drinks (alcohol use ≥20 g/d) for women. Subjects with positive hepatitis B viral markers were also excluded from the study. The central laboratory of the Korean NHANES defines a *normal ALT level* as less than 43 IU/L for both sexes. In the interest of investigating the association between normal ALT levels and the metabolic syndrome, we excluded subjects with abnormal ALT levels (≥43 IU/L). We also excluded people who had a history of chronic hepatitis or liver cirrhosis, as well as those taking medications for any known diseases except diabetes and hypertension. The final sample consisted of 3405 subjects (1203 men and 2202 women).

2.2. Assessments and measurements

Height, weight, and blood pressure were measured; and body mass index (BMI) was calculated by dividing weight (kilograms) by height squared (square meters). Waist circumference measurements were taken at the end of normal expiration to the nearest 0.1 cm, measuring from the middle point between the lower border of the rib cage and the iliac crest at the midaxillary line.

Subjects were asked about their average frequency and amount of alcoholic consumption during the month before the interview. The average amount and number of alcoholic beverages consumed were converted into an amount of pure alcohol (grams) consumed per day.

Participants were divided into current smokers, past smokers, and nonsmokers. Exercise was ascertained by asking participants how often they engaged in exercise each week. Physical activities were assessed based on the frequency of exercise in leisure time. Participants were considered physically active if they exercised more than 3 times per week.

Blood samples were collected from an antecubital vein in the morning after the subjects had fasted for 12 hours overnight. The samples were subsequently analyzed at a central, certified laboratory. Plasma concentrations of glucose, triglycerides, high-density-lipoprotein (HDL) cholesterol, aspartate aminotransferase, and ALT were measured with an autoanalyzer (ADVIA 1650 autoanalyzer; Bayer, Pittsburgh, PA). The presence of hepatitis B surface antigen was assessing using the direct sandwich enzyme-linked electrochemiluminescence immunoassay method (E-170 automated analyzer; Roche, Penzberg, Germany).

2.3. Definition

The diagnosis of the metabolic syndrome was based on the presence of 3 or more of the following components, according to the revised Adult Treatment Panel III of the National Cholesterol Education Program [9], in which the criteria for abdominal obesity were specified in Asian populations [10]:

1. Abdominal obesity: waist circumference of at least 90 cm in men or at least 80 cm in women
2. High triglyceride: at least 150 mg/dL
3. Low HDL cholesterol: less than 40 mg/dL in men or less than 50 mg/dL in women
4. High blood pressure: at least 130/85 mm Hg or on antihypertensive drug treatment
5. High fasting glucose: at least 100 mg/dL or on drug treatment for elevated glucose

2.4. Statistical analysis

Data were expressed as the means ± standard error for continuous variables. For categorical variables, data were expressed as percentages ± standard error. All statistical analyses were performed using the survey analysis method.

Table 1
Subject characteristics

	Men	Women
Unweighted sample size	1203	2202
Age (y)	42.16 ± 0.49	42.53 ± 0.37
BMI (kg/m^2)	23.52 ± 0.11	22.91 ± 0.10
Waist circumference (cm)	81.84 ± 0.32	76.21 ± 0.28
Metabolic syndrome (%)	17.6 ± 1.4	15.8 ± 1.1
ALT (IU/L)	21.99 ± 0.31	15.74 ± 0.21
Smoking status (%)		
Nonsmoker	21.4 ± 1.3	91.6 ± 0.7
Ex-smoker	33.0 ± 1.5	3.9 ± 0.4
Current smoker	45.6 ± 1.6	4.5 ± 0.5
Alcohol intake (%)		
Nondrinker	33.0 ± 1.4	63.3 ± 1.2
Drinker	67.0 ± 1.4	36.7 ± 1.2
Regular physical activity (%)		
Active	39.6 ± 1.5	39.9 ± 1.3
Inactive	60.4 ± 1.5	60.1 ± 1.3

Results are weighted to represent the 1.82 million men and 2.95 million women, 20 years and older, in the present Korean population. Data are means or percentages ± standard error.

Table 2
Prevalence of each metabolic syndrome component within each sex, based on ALT group[a]

Metabolic syndrome component	Group 1	Group 2	Group 3	Group 4	*P* value[b]
High waist circumference (≥90 cm in men, ≥80 cm in women)					
Men	8.4 ± 1.4	12.7 ± 2.5	19.9 ± 2.6	27.8 ± 3.5	<.001
Women	16.2 ± 1.9	26.0 ± 2.1	36.6 ± 2.5	50.6 ± 2.8	<.001
High triglyceride (≥150 mg/dL)					
Men	16.3 ± 2.7	17.0 ± 2.8	30.3 ± 3.2	45.2 ± 3.6	<.001
Women	5.8 ± 1.0	9.7 ± 1.4	17.1 ± 1.9	29.3 ± 2.4	<.001
Low HDL cholesterol (<50 mg/dL in men, <40 mg/dL in women)					
Men	37.5 ± 3.4	43.7 ± 4.0	42.7 ± 3.3	47.4 ± 3.7	.243
Women	57.9 ± 2.6	58.1 ± 2.4	64.4 ± 2.4	67.5 ± 2.5	.011
High blood pressure (≥130/85 mm Hg or on antihypertensive drug treatment)					
Men	24.1 ± 2.6	27.0 ± 3.3	31.1 ± 3.3	41.3 ± 3.6	.001
Women	9.4 ± 1.3	14.8 ± 1.6	16.6 ± 2.0	24.2 ± 2.2	<.001
High glucose (≥100 mg/dL or on drug treatment for elevated glucose)					
Men	9.6 ± 1.6	10.5 ± 2.0	17.0 ± 2.3	21.3 ± 2.7	<.001
Women	5.8 ± 1.1	6.7 ± 1.0	12.0 ± 1.6	19.0 ± 2.1	<.001

Results are weighted to represent the 1.82 million men and 2.95 million women, 20 years and older, in the present Korean population. Data are percentages ± standard error.

[a] Group 1—ALT < Q_1 with ALT <16 IU/L for men and ALT <11 IU/L for women; group 2—Q_1 ≤ ALT < Q_2 with 16 ≤ ALT < 20 IU/L for men and 11 ≤ ALT < 15 IU/L for women; group 3—Q_2 ≤ ALT < Q_3 with 20 ≤ ALT < 27 IU/L for men and 15 ≤ ALT < 19 IU/L for women; group 4—Q_3 ≤ ALT with ALT ≥27 IU/L for men and ALT ≥19 IU/L for women.

[b] *P* value derived using the χ^2 test.

The χ^2 test was performed to demonstrate differences in the prevalences of the metabolic syndrome components by ALT categories. The general linear model was used to test the linear trend of ALT levels according to the number of components of the metabolic syndrome.

Quartiles Q_1, Q_2, and Q_3 of the ALT level were determined for each sex and used to divide subjects into the following 4 groups: group 1—ALT < Q_1 with ALT <16 IU/L for men or ALT <11 IU/L for women, group 2—Q_1 ≤ ALT < Q_2 with 16 ≤ ALT < 20 IU/L for men or 11 ≤ ALT < 15 IU/L for women, group 3—Q_2 ≤ ALT < Q_3 with 20 ≤ ALT < 27 IU/L for men or 15 ≤ ALT < 19 IU/L for women, and group 4—Q_3 ≤ ALT with ALT ≥27 IU/L for men or ALT ≥19 IU/L for women.

Logistic regression analysis for the metabolic syndrome was performed for each sex with the ALT group as a predictor variable after adjustment for age, BMI, waist circumference, amount of ingested alcohol, physical activity level, and smoking status.

All statistical analyses were performed with a statistical significance level of .05 by use of SPSS 16.0 for Windows (SPSS, Chicago, IL).

3. Results

Our study subjects consisted of 1203 men and 2202 women, the demographic and clinical characteristics of which are shown in Table 1. The sex-specific prevalences were 17.6% and 15.8% for the metabolic syndrome, 45.6% and 4.5% for smoking, and 39.6% and 39.9% for participation in active physical activities in men and women, respectively.

The prevalences for each component of the metabolic syndrome according to sex and ALT group are shown in Table 2. The prevalences of all 5 components of the metabolic syndrome increased with increasing ALT levels in both sexes. In both men and women, mean ALT levels increased with an increasing number of metabolic syndrome components (Table 3).

The association between ALT groups according to sex and metabolic syndrome risk is presented in Table 4. Group 1 (ALT <16 IU/L in men, ALT <11 IU/L in women) was set as the reference group. Odds ratios (ORs) were adjusted for age, BMI, waist circumference, smoking, alcohol consumption (grams per day), and physical activity. Independent of sex, the OR of the metabolic syndrome increased with ALT levels ≥ Q_3 (≥27 IU/L) in men and ALT levels ≥ Q_2 (≥15 IU/L) in women. The OR of having the metabolic syndrome was 2.71 (95% confidence interval [CI], 1.31-

Table 3
Mean ALT level according to the number of components of the metabolic syndrome

	No. of the metabolic syndrome components			
	0	1	2	≥3
Men				
Unweighted sample size	305	380	272	232
ALT (IU/L)	19.83 ± 0.45	21.43 ± 0.56	22.75 ± 0.69	25.97 ± 0.65
P for trend[a]	<.001			
Women				
Unweighted sample size	534	801	446	395
ALT (IU/L)	13.89 ± 0.28	14.70 ± 0.28	17.19 ± 0.49	19.47 ± 0.42
P for trend	<.001			

Results are weighted to represent the 1.82 million men and 2.95 million women, 20 years and older, in the present Korean population. Data are means ± standard error.

[a] *P* value derived by F test.

Table 4
Odds ratios of the metabolic syndrome in men and women according to ALT group

ALT level (IU/L)	Unweighted sample size	Prevalence of the metabolic syndrome (% ± SE)	OR (95% CI) for metabolic syndrome		
			Unadjusted	Model 1[a]	Model 2[b]
Men (mean ± SE of BMI: 23.52 ± 0.11)					
Group 1 (<16.00)	272	10.9 ± 3.0	1.00	1.00	1.00
Group 2 (≥16.00-<20.00)	287	12.8 ± 2.8	1.39 (0.66-2.92)	1.09 (0.49-2.42)	0.85 (0.39-1.88)
Group 3 (≥20.00-<27.00)	332	29.5 ± 3.6	2.87 (1.51-5.44)	1.91 (0.94-3.87)	1.64 (0.79-3.37)
Group 4 (≥27.00-<43.00)	312	46.8 ± 3.8	5.25 (2.74-10.04)	3.35 (1.59-7.05)	2.71 (1.31-5.63)
Women (mean ± SE of BMI: 22.91 ± 0.10)					
Group 1 (<11.00)	406	9.9 ± 1.9	1.00	1.00	1.00
Group 2 (≥11.00-<15.00)	686	16.4 ± 1.9	1.57 (0.98-2.53)	1.06 (0.61-1.83)	0.96 (0.55-1.70)
Group 3 (≥15.00-<19.00)	538	27.1 ± 2.6	3.51 (2.34-5.26)	1.81 (1.13-2.89)	1.69 (1.02-2.80)
Group 4 (≥19.00-<43.00)	572	46.7 ± 2.8	6.09 (4.00-9.27)	2.33 (1.43-3.78)	2.06 (1.23-3.43)

Results are weighted to represent the 1.82 million men and 2.95 million women, 20 years and older, in the present Korean population.
[a] Model 1: adjusted for age, body mass index, smoking, alcohol consumption (grams per day), and physical activity.
[b] Model 2: model 1 plus adjustment for waist circumference.

5.63) in men in the highest ALT group (≥27 IU/L). In women, the ORs were 1.69 (95% CI, 1.02-2.80) and 2.06 (95% CI, 1.23-3.43) for ALT group 3 (15 ≤ ALT < 19 IU/L) and group 4 (≥19 IU/L), respectively.

4. Discussion

We documented significant cross-sectional associations between high-normal ALT levels and the metabolic syndrome. High-normal ALT levels (≥27 IU/L in men, ≥15 IU/L in women) were strongly associated with the metabolic syndrome after controlling for confounding variables such as BMI, waist circumference, physical activity, and alcohol consumption. The highest ALT groups (≥27 IU/L in men, ≥19 IU/L in women) showed increased ORs for the metabolic syndrome of 2.71 and 2.06 in men and women, respectively.

A high prevalence of abnormal metabolic risk factors was observed among individuals with normal to slightly elevated ALT in the Korean population. As a consequence, clinicians should consider the possibility of the metabolic syndrome in people with high-normal ALT levels.

Although Kim et al [5] already found an association between normal aminotransferase levels and the metabolic syndrome in a nationally representative Korean sample, we postulated that an ALT level lower than 20 IU/L could be related to the metabolic syndrome and that the lowest ALT level associated with an increased risk of the metabolic syndrome may be sex specific. Kim et al reported an increased OR for the metabolic syndrome at 10-IU/L increments of ALT compared with levels less than 20 IU/L. They adopted the same lowest level (<20 IU/L) for both sexes; however, they did not present their rationale for the selection of the lowest ALT level or the categorization of ALT by 10-IU/L increments. In Korea, clinicians usually regard ALT levels less than 40 IU/L as normal for both sexes. The central laboratory of the Korean NHANES considers normal ALT levels to be less than 43 IU/L for both sexes. In a study similar to ours, Kim et al also analyzed the Korean NHANES data; however, subjects with hepatic steatosis or other liver diseases are likely to have been included because people with abnormally elevated aminotransferase levels were not excluded and the liver disease histories and physical activity levels of the participants were not assessed. The subject inclusion criteria in the study of Kim et al and our own study also differed in terms of the alcohol intake classification. We excluded men who consumed more than 2 standard alcoholic drinks per day (≥30 g/d) and excluded women who consumed more than 1.5 standard alcoholic drinks per day (≥20 g/d) based on a recent recommendation [11]. However, Kim et al set the exclusion limit at 50 g of alcohol per day for both sexes. Finally, our statistical models were fit for survey analysis because the weight estimation for association analysis was not given in the previous Korean NHANES.

A number of mechanisms may explain the association of ALT with the metabolic syndrome. Alanine aminotransferase activity is known to be significantly correlated with increased hepatic fat content [12], which worsens hepatic insulin resistance [13]. This association is probably reflective of a more generalized insulin resistance. Some investigators have insisted that higher ALT levels are associated with hepatic inflammation, which contributes to the development of the metabolic syndrome by promoting systemic inflammation [14]. Previous study has shown that aminotransferase levels in the reference range are associated with the development of the metabolic syndrome [3]. Some researchers have therefore suggested that ALT levels be used in further evaluation of the metabolic syndrome in the clinical setting [3,15,16].

Investigators have suggested various other roles for ALT as a metabolic indicator. Alanine aminotransferase activity is related to lipid and carbohydrate metabolism; and therefore, ALT has been suggested as an indicator for future metabolic derangement [17]. A prospective cohort study showed that ALT appears to be associated with both hepatic insulin resistance and later decline in hepatic insulin sensitivity [2]. According to a recent study, subtle

alterations in glucose tolerance and lipid metabolism exist in those patients with higher ALT, and this is not necessarily accompanied by hepatic steatosis [18]. Another recent prospective study suggested that ALT might be more than an indicator of liver injury due to hepatic steatosis; it might also be an early indicator of impaired insulin signaling [19]. Considering the simplicity of ALT measurement and its availability in clinical practice, the possible role of ALT as a surrogate marker for insulin resistance merits future research. Periodic health examinations routinely use liver enzyme assessment in Korea; thus, high-normal ALT values are commonly noted. Clinicians usually do not intervene in people with high-normal ALT levels. However, we showed that even normal ALT levels cannot guarantee the absence of metabolic abnormalities.

A strength of our study was the fact that our subjects were gathered from a nationwide representative sample and our data were adjusted for possible confounders. Although our Korean population was not obese by BMI criteria, the association between high-normal ALT levels and the metabolic syndrome still existed as expected. This relationship has been demonstrated in previous Korean studies [5,8]. It is well known that Asian people have higher percentage of body fat and more cardiovascular risk factors at lower BMIs and waist circumferences compared with Western people [20,21]. Therefore, we were able to demonstrate the relationship between high-normal ALT levels and the metabolic syndrome in a nonobese population.

Our study has several limitations. First, as this was a cross-sectional study, the causal relationship between the metabolic syndrome and ALT levels could not be examined. Furthermore, we did not exclude the possibility that patients had hepatitis C. However, the reported prevalence of hepatitis C has been shown to be very low in Korea: 1.7% [22]. We noted nonalcoholic fatty liver as one of the possible mechanisms behind elevated ALT levels in subjects with the metabolic syndrome. Because of the large sample size and ethical considerations, we could not perform liver biopsies. Ultrasonography is a useful tool to evaluate liver fat, but it requires significant financial cost. Therefore, it could not be done as part of routine nationwide examination. Moreover, we did not exclude the possible influence of antihypertensive and antidiabetes medications. People taking drugs for hypertension and diabetes were included in the study according to the definition of the metabolic syndrome. Finally, extrahepatic sources of ALT—most significantly skeletal muscle—were not considered. We adjusted the association between ALT and the metabolic syndrome for BMI, and we believe this corrected for some of the influence of skeletal muscle on ALT. However, precise measurements of skeletal muscle mass could not be performed on a nationwide level because the measurements required too much equipment and manpower.

In conclusion, we found a significant relationship between high-normal ALT levels and the metabolic syndrome in Korean adults. We suggest that Korean adults with high-normal ALT levels ($\geq$27 IU/L in men, $\geq$15 IU/L in women) be regarded as a group at elevated risk for the metabolic syndrome. Our findings may serve as base data to update the ranges for healthy ALT levels in Korea. In the future, a community-based cohort study should be performed to determine the optimal ALT cutoff value in the assessment of the metabolic syndrome in Korea.

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