Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents¹,²

Hye Soon Park, Jee Hye Han, Kyung Mook Choi, and Seon Mee Kim

ABSTRACT

Background: Concern is growing about nonalcoholic fatty liver disease, not only because it is a common liver disorder but also because it is one of the leading causes of chronic liver disease. Unexplained elevations in aminotransferase concentrations have been strongly associated with adiposity and thus may represent nonalcoholic fatty liver disease.

Objective: We investigated the relation between nonviral or nonalcoholic elevations in alanine aminotransferase (ALT) and the metabolic syndrome in Korean adolescents.

Design: Data were obtained from 1594 subjects aged 10–19 y from the Korean National Health and Nutrition Examination Survey 1998, a cross-sectional health survey of a nationally representative sample of noninstitutionalized civilian South Koreans. Body mass index, waist circumference, blood pressure, fasting glucose, lipid profiles, and serum ALT were measured.

Results: The prevalence of elevated ALT (>40 U/L) was 3.6% in boys and 2.8% in girls. The prevalence of metabolic syndrome was 3.3% in both boys and girls. The components of the metabolic syndrome were significantly worse in the group with elevated ALT concentrations than in the group with normal ALT concentrations. The odds ratios (95% CIs) for elevated ALT were 6.6 (3.7, 11.8), 2.3 (1.2, 4.6), and 3.0 (1.6, 5.8) in the adolescents with abdominal obesity, high triacylglycerol concentrations, and low HDL-cholesterol concentrations, respectively. The odds ratios for elevated ALT were 1.5 (0.7, 3.1), 2.6 (1.1, 6.2), and 6.2 (2.3, 16.8) in the adolescents with 1, 2, and ≥3 risk factors (metabolic syndrome), respectively.

Conclusion: The metabolic syndrome was strongly associated with elevated ALT concentrations in Korean adolescents, and this association existed in a graded fashion across the number of metabolic components. Am J Clin Nutr 2005;82:1046–51.

KEY WORDS Nonalcoholic fatty liver disease, aminotransferase, metabolic syndrome, adolescents, Korea

INTRODUCTION

In the setting of nonviral and nonalcoholic elevation of liver enzymes, the most likely histologic diagnosis is large-droplet hepatic steatosis with or without fibrosis (1). Unexplained elevations in aminotransferase concentrations have been strongly associated with adiposity and thus may represent nonalcoholic fatty liver disease (NAFLD) (2). Although in most cases fatty liver does not progress to more severe liver disease, ≈20–30% of patients with the former have histologic signs of fibrosis and necroinflammation, which indicate the presence of nonalcoholic steatohepatitis (3, 4). In addition, these patients are at higher risk of developing cirrhosis (5) or hepatocellular carcinoma (6).

NAFLD is considered to be the hepatic manifestation of the metabolic syndrome (7). The rising prevalence of the metabolic syndrome and its adverse effects, most notably an increase in cardiovascular and total mortality (8), have prompted growing concern about this condition not only in adults (9, 10) but also in adolescents (11).

The incidence of NAFLD is increasing both in developed countries and in the newer industrial economies in the Asia-Pacific region. Lifestyle changes and the epidemics of obesity and type 2 diabetes in this region represent the key substrates for the rising prevalence of NAFLD (12). NAFLD in children and adolescents is likely increasingly prevalent in parallel with the increased prevalence of obesity (13). As a result of urbanization and economic development, the rates of overweight have doubled among Korean children and adolescents aged 5–20 y over the past 10 y (14), which may result in an increase in adverse metabolic outcomes.

A recent report showed that liver pathology in children with NAFLD is associated with insulin resistance and increased serum aminotransferase concentrations (15). Little is known, however, about the relation between NAFLD and the metabolic syndrome in adolescents. The purpose of the present study was to examine the prevalence of elevated alanine aminotransferase (ALT) as a surrogate marker for NAFLD and to investigate the relation between elevated ALT and the metabolic syndrome among Korean adolescents.

SUBJECTS AND METHODS

Study population

The Korean Ministry of Health and Welfare conducted the Korean National Health and Nutrition Examination Survey...
among noninstitutionalized Korean civilians in 1998. A stratified, multistage probability sampling design was used with selection made from sampling units based on geographic area, sex, and age groups with the use of household registries. The staff conducted surveys in households by administering questionnaires to the participants. Household surveys included the demographic, socioeconomic, dietary, and medical history of each respondent. The initial sample consisted of 1641 subjects aged 10–19 y. The study was performed according to the guidelines of the Helsinki Declaration.

Anthropometric measurements and nutritional assessment

Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained examiners. Height was measured to the nearest 0.1 cm with a portable stadiometer (850–2060 mm; Seriter, Bismarck, ND). Weight was measured in an upright position to the nearest 0.1 kg with a calibrated balance-beam scale (Giant-150N; HANA, Seoul, Korea). Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m²). Overweight adolescents were classified according to the international BMI cutoffs for overweight by sex, calculated to pass through a BMI of 25 at age 18 y, based on 6 nationally representative cross-sectional samples (16). Waist circumference measurements were taken at the end of normal expiration to the nearest 0.1 cm, measuring from the narrowest point between the lower borders of the rib cage and the iliac crest.

Dietary intake was assessed by use of a single 24-h dietary recall method. Experienced interviewers instructed the participants to recall and describe any foods and beverages consumed over the previous 24 h. The record for each subject was coded, and standard reference tables were used to convert household portions to gram weights. The nutrient content of the records was quantified by using a computer program (CAN; Korean Nutrition Society, Seoul, Korea). Alcohol consumption was assessed by asking the subjects about their average frequency and amount of alcoholic beverages ingested during the month before the interview. The average amount and number of alcoholic beverages consumed was converted into the amount of pure alcohol (in g) consumed per day.

Blood pressure measurements and biochemical analysis

A mercury sphygmomanometer (Baumanometer; WA Baum Co, Inc, Tokyo, Japan) was used to measure the blood pressure of each subject while in a sitting position after a 10-min rest period. During the 30 min preceding the measurement, the subjects were required to refrain from smoking or consuming caffeine. The appearance of the first sound (phase 1 Korotkoff sound) was used to define systolic blood pressure, and the disappearance of sound (phase 5 Korotkoff sound) was used to define diastolic blood pressure. Two readings each of systolic and diastolic blood pressure were recorded, and the average of each measurement was used for data analysis. If the first 2 measurements differed by >5 mm Hg, additional readings were obtained.

Blood samples were collected from an antecubital vein into evacuated tubes containing EDTA in the morning after the subjects had fasted for 12 h overnight. The samples were subsequently analyzed at a central, certified laboratory. Plasma concentrations of glucose, total cholesterol, triacylglycerols, HDL cholesterol, and ALT were measured with an auto analyzer (747 auto-analyzer; Hitachi, Tokyo, Japan). Hepatitis B surface antigen and antibody were tested by use of the direct sandwich enzyme-linked immunosorbent assay method (CODA automated EIA analyzer; Bio-Rad, Hercules, CA).

Definition of elevated ALT and metabolic syndrome in the study population

Elevated ALT was defined as enzyme activity >40 U/L. Because the criteria for metabolic syndrome have not been formally defined in children or adolescents, we modified the adult criteria by using similar patterns obtained from pediatric data. As described for adults (17), participants having ≥3 of the following 5 criteria were defined as having metabolic syndrome: abdominal obesity, high blood pressure, fasting blood glucose ≥ 6.05 mmol/L (110 mg/dL), serum triacylglycerols ≥ 1.54 mmol/L (140 mg/dL), or HDL cholesterol < 1.05 mmol/L (40 mg/dL). Because no reference values for waist circumference exist for abdominal obesity in children or adolescents, we analyzed all waist circumference data and classified subjects having a waist circumference at or above the 90th percentile value for age and sex from this sample population as having abdominal obesity. High systolic or diastolic blood pressure was defined as a value at or above the 90th percentile for age and sex. The cutoffs of ≥6.05 mmol/L (110 mg/dL) for high fasting blood glucose and ≥1.54 mmol/L (140 mg/dL) for high serum triacylglycerols were used as the mean values of the 90th percentile values for each age and sex. The cutoff of <1.05 mmol/L (40 mg/dL) for low HDL cholesterol was used as the mean value of the 10th percentile values for each age and sex.

Statistical analysis

Subjects were excluded from the statistical analysis if they had a history of alcohol intake (>9 g/d; n = 5) or if they tested positive for hepatitis B viral markers (n = 42). The final sample consisted of 1594 subjects.

Statistical analyses were conducted by using SAS version 8.1 (SAS Institute Inc, Cary, NY). Descriptive data were expressed as mean values with SDs for continuous variables. Student’s t test was used to compare differences in variables between sexes or between the group with elevated ALT concentrations and that with normal ALT concentrations. Post hoc analysis was conducted by stratification into a younger group, aged 10–14 y, and an older group, aged 15–19 y, on the basis of the significance of interaction between 2 independent variables. The general linear model was used to test the linear trend of ALT concentrations according to the number of components of the metabolic syndrome. Logistic regression analysis was performed to determine the risks of elevated ALT according to the presence of each component of the metabolic syndrome. The adjusted odds ratios (ORs) for elevated ALT according to the number of components of the metabolic syndrome after adjustment for age and BMI are presented together with their 95% CIs. The linear trend in odds was evaluated by using the trend test. All analyses were two-tailed and P < 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

The characteristics of the study population are presented in Table 1. Of the study participants, 811 (50.9%) were boys and
TABLE 1
Characteristics of the study population, Korean National Health and Nutrition Examination Survey 1998

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boys (n = 811)</th>
<th>Girls (n = 783)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–14 y</td>
<td>419 (51.7)</td>
<td>361 (46.1)</td>
</tr>
<tr>
<td>15–19 y</td>
<td>392 (48.3)</td>
<td>422 (53.9)</td>
</tr>
<tr>
<td>Overweight [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>139 (17.1)</td>
<td>115 (14.7)</td>
</tr>
<tr>
<td>No</td>
<td>672 (82.9)</td>
<td>668 (85.3)</td>
</tr>
<tr>
<td>Residential area [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large city</td>
<td>316 (39.0)</td>
<td>308 (39.3)</td>
</tr>
<tr>
<td>Medium-sized city</td>
<td>256 (31.6)</td>
<td>232 (29.6)</td>
</tr>
<tr>
<td>Rural area</td>
<td>239 (29.5)</td>
<td>243 (31.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.0 ± 3.3</td>
<td>20.1 ± 3.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–14 y</td>
<td>66.5 ± 9.1</td>
<td>65.7 ± 8.3</td>
</tr>
<tr>
<td>15–19 y²</td>
<td>74.3 ± 8.3</td>
<td>69.4 ± 7.3</td>
</tr>
<tr>
<td>Total energy (kcal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–14 y</td>
<td>2305 ± 830</td>
<td>1941 ± 686</td>
</tr>
<tr>
<td>15–19 y²</td>
<td>2417 ± 926</td>
<td>1823 ± 749</td>
</tr>
<tr>
<td>Carbohydrate (% of energy)</td>
<td>64.6 ± 8.4</td>
<td>64.8 ± 8.9</td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>20.6 ± 7.7</td>
<td>20.5 ± 8.4</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>13.8 ± 3.6</td>
<td>13.8 ± 4.5</td>
</tr>
</tbody>
</table>

1 Overweight was defined according to international BMI cutoffs for overweight by sex, which were calculated to pass through a BMI of 25 at age 18 y on the basis of 6 nationally representative cross-sectional samples (reference 16). Subgroup analysis was done on waist circumference and total energy on the basis of a significant interaction between age and sex (P < 0.05).

2 Significant difference between boys and girls, P < 0.05 (chi-square test for categorical variables and Student’s t test for continuous variables).

3 x ± SD (all such values).

783 (49.1%) were girls. The prevalence of overweight was 17.1% for boys and 14.7% for girls. Total calorie intake was significantly higher in boys than in girls. Waist circumference was significantly higher in boys than in girls among the older group (aged 15–19 y). BMI and percentages of energy from carbohydrate, fat, and protein were not significantly different between boys and girls.

Metabolic variables according to the presence of elevated ALT

As shown in Table 2, 3.2% of the participants had elevated ALT concentrations. The subjects with elevated ALT concentrations were significantly older and had a higher mean BMI, waist circumference, systolic blood pressure, diastolic blood pressure, and triacylglycerol, total cholesterol, and LDL-cholesterol concentrations and significantly lower HDL-cholesterol concentrations than did the subjects with normal ALT concentrations.

Relation between elevated ALT and each component of the metabolic syndrome

The associations between each metabolic variable and the risk of elevated ALT are shown in Table 3. The odds ratio for elevated ALT in the subjects having overweight, abdominal obesity, high triacylglycerols, low HDL cholesterol, high total cholesterol, and high LDL cholesterol was significantly higher than in the subjects not having these metabolic variables, whereas the associations between high blood pressure or high fasting glucose and elevated ALT were not significant.

Relation between elevated ALT and the number of components of the metabolic syndrome

The relations between the clustering of metabolic syndrome components and the risk of elevated ALT in the participants are shown in Table 4. The prevalence rates of elevated ALT were 1.8%, 3.3%, 7.2%, and 16.7% in the subjects with 0, 1, 2, and ≥3 risk factors, respectively. The adjusted odds ratios for elevated ALT were 1.5 (95% CI: 0.7, 3.1), 2.6 (95% CI: 1.1, 6.2), and 6.2 (95% CI: 2.3, 16.8) for the subjects with 1, 2, and ≥3 risk factors, respectively. We observed a prominent direct relation across the number of components of the metabolic syndrome, and the linear trend was significant (P < 0.0001 from the trend test). Mean ALT concentrations according to the number of components of the metabolic syndrome are shown in Figure 1. ALT concentrations showed a significant linear increase (P < 0.0001 from the general linear model) according to the number of metabolic syndrome components in the younger (aged 10–14 y) and older (aged 15–19 y) groups.

DISCUSSION

We found that the metabolic syndrome is an important cause of elevated ALT concentrations in adolescents. Our findings agree with previous findings that, in children, NAFLD occurs most commonly in conditions associated with insulin resistance (15, 18, 19). Our results show that the risks for elevated ALT increase with the number of components of the metabolic syndrome, although the odds ratio does not represent exact biological aggravation of liver function.

Overweight adolescents were much more likely to have elevated ALT concentrations than normal-weight adolescents in our study, a finding that agrees with the results of the third National Health and Nutrition Examination Survey (NHANES III; 20). In that study, the prevalence of elevated ALT (>30 U/L) in overweight children was 5.0% (20), whereas the prevalence of elevated ALT (>30 U/L) in overweight children in our study was
ELEVATED ALT AND METABOLIC SYNDROME IN ADOLESCENTS

TABLE 3
Odds ratios (ORs) for elevated alanine aminotransferase (ALT) according to the presence of each component of the metabolic syndrome among Korean adolescents, Korean National Health and Nutrition Examination Survey 1998

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of subjects</th>
<th>Elevated ALT (ALT &gt; 40 U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1340)</td>
<td>27 (2.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 254)</td>
<td>24 (9.5)</td>
<td>5.1 (2.9, 8.9)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1425)</td>
<td>30 (2.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 169)</td>
<td>21 (12.4)</td>
<td>6.6 (3.7, 11.8)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1378)</td>
<td>40 (2.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 216)</td>
<td>11 (5.1)</td>
<td>1.8 (0.9, 3.6)</td>
</tr>
<tr>
<td>High fasting glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1468)</td>
<td>44 (3.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 126)</td>
<td>7 (5.6)</td>
<td>1.9 (0.8, 4.3)</td>
</tr>
<tr>
<td>High triacylglycerols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1403)</td>
<td>39 (2.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 191)</td>
<td>12 (6.3)</td>
<td>2.3 (1.2, 4.6)</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1425)</td>
<td>38 (2.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 169)</td>
<td>13 (7.7)</td>
<td>3.0 (1.6, 5.8)</td>
</tr>
<tr>
<td>High total cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1370)</td>
<td>37 (2.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 224)</td>
<td>14 (6.3)</td>
<td>2.4 (1.3, 4.5)</td>
</tr>
<tr>
<td>High LDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1301)</td>
<td>34 (2.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes (n = 293)</td>
<td>17 (5.8)</td>
<td>2.3 (1.3, 4.2)</td>
</tr>
</tbody>
</table>

1 Variable definitions are as follows: overweight, defined according to international BMI cutoffs for overweight by sex, which were calculated to pass through a BMI of 25 at age 18 y on the basis of 6 nationally representative cross-sectional samples (reference 16); abdominal obesity, a waist circumference at or above the 90th percentile value for age and sex from this sample population; high blood pressure, a value at or above the 90th percentile of systolic or diastolic blood pressure for age and sex; high fasting glucose, ≥6.05 mmol/L (110 mg/dL); high triacylglycerols, ≥1.54 mmol/L (140 mg/dL); low HDL cholesterol, < 1.05 mmol/L (40 mg/dL); high total cholesterol, ≥4.54 mmol/L (190 mg/dL); high LDL cholesterol, ≥2.86 mmol/L (110 mg/dL). ORs and 95% CIs were calculated by performing logistic regression analysis to determine the risk of elevated ALT according to the presence of each component of the metabolic syndrome.

25 in children and adolescents. The cutoff for waist circumference in older adolescents used in the study in New Zealand (23) is similar to the cutoff used in our study. There is still a need for normative data in the Korean population. Waist circumference should be measured in adolescents being evaluated for nonviral and nonalcoholic elevation of aminotransferase concentrations.

Hyperlipidemia, especially elevated triacylglycerol concentrations, is a primary risk factor for NAFLD (18) and is also an outcome of NAFLD. We found that high triacylglycerol concentrations, as well as low HDL-cholesterol, high total cholesterol, and nonalcoholic elevation of aminotransferase concentrations.

1 Participants having ≥3 of the following 5 risk factors were defined as having the metabolic syndrome: abdominal obesity, high blood pressure, high fasting glucose, high triacylglycerols, or low HDL cholesterol. The adjusted ORs and 95% CIs were calculated by performing logistic regression analysis to determine the risk of elevated ALT according to the number of components of the metabolic syndrome after adjustment for age and BMI.

2 Trend test to show linear increase in OR according to the number of components of the metabolic syndrome.
or high LDL-cholesterol concentrations, were significantly associated with elevated ALT in the subjects. In a prospective study of adults undergoing obesity surgery, perisinusoidal fibrosis was independently predicted by hypertension (26). However, our results showed that the associations between high blood pressure or high fasting glucose and elevated ALT were not significant.

The prevalence of the metabolic syndrome among Korean adolescents aged 10–19 y was 3.3%, a finding that does not greatly differ from the 4.2% reported among American adolescents aged 12–19 y in NHANES III (27). Our results suggest that the metabolic syndrome, a clinical manifestation of insulin resistance, might be predictive of NAFLD independent of obesity even in adolescents.

Our study had some limitations. We used elevation of ALT as a surrogate marker for NAFLD in this population. In asymptomatic subjects with suspected liver disease, a liver biopsy is the only way to establish the type and severity of liver lesions (28). NAFLD may account for ≈80% of individuals with elevated liver enzyme concentrations (29), and in children, ALT could be significantly correlated with portal inflammation, portal fibrosis, and perisinusoidal fibrosis (15). In addition, ALT concentrations were more sensitive than those of AST (30), and ALT was shown to be useful as a screening test for fatty liver in children (31).

An additional limitation of our study is concerned with the selection of appropriate cutoffs for risk factors of the metabolic syndrome among adolescents. Because there are no standard criteria for the metabolic syndrome in adolescents, we adopted a modified version of the National Cholesterol Education Program Adult Treatment Panel III guidelines to fit Korean adolescents. We used the 90th percentile of individual metabolic variables as the cutoff for metabolic syndrome. Accordingly, only 10% of cases were selected for each variable, and subjects falling into this 10% for 3 or more variables were considered to have the metabolic syndrome. This criterion is remarkably different from that used in adults, in whom the prevalence of positive individual features is much higher than 10%. As shown in a study of children and adolescents in the United States, which also used the 90-95th percentile of individual metabolic variables for the cutoff (11, 27), we used the 90th percentile because no clear-cut ranges for normality have been defined. The cutoffs used for high fasting glucose and low HDL cholesterol correlate with the cutoffs for these risk factors in a recent study based on NHANES III (27). In that study, the cutoff for high triacylglycerols for adolescents was ≥110 mg/dL, which is 30 mg/dL lower than the cutoff we used. Therefore, it is unlikely that we overestimated the prevalence of the metabolic syndrome in our adolescent population.

Another limitation of the present study was our inability to completely exclude other types of hepatitis among adolescents. We did not check for anti-hepatitis C virus in this population, which may have influenced our results, even though the prevalence of hepatitis C in adolescents has been shown to be very low (32–34). Other limitations include recall bias. Diet survey from which may have influenced our results, even though the prevalence of hepatitis C in adolescents has been shown to be very low (32–34). Other limitations include recall bias. Diet survey from the single 24-h recall method and assessment of alcohol consumption cannot be corrected for intra-individual daily variation in consumption. Although the variation in intake might in fact be under- or overestimated (35), single recalls are useful for estimating population means.

In summary, we showed a strong relation between elevated ALT concentrations and the metabolic syndrome in adolescents. Adolescents being evaluated for NAFLD should be screened for waist circumference, blood pressure, fasting glucose, and serum lipid profiles. Assessment and management of the metabolic syndrome in adolescents is needed to improve abnormalities in non-viral and non-alcoholic liver enzymes in adolescents.

We thank the members of the Korea Institute for Health and Social Affairs, who conducted the national survey, and everyone who contributed to this project.

HSP was involved in the conception and design of the study; SMK, KMC, and JHH contributed to data analysis; HSP, SMK, KMC, and JHH contributed to interpretation of data; and HSP drafted the manuscript. All authors participated in critically revising the manuscript and approved the final version of the manuscript. None of the authors had a conflict of interest in any company or organization sponsoring this study.

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