Abstract

This study aimed to investigate the risk of metabolic syndrome (MS) in participants whose alanine aminotransferase (ALT) levels were within the normal range in the general population. A cross-sectional study was conducted using nationally representative samples from the Korea National Health and Nutrition Examination Survey 2007–2015. A total of 43,402 adults (men, 17,535; women, 25,867) with ALT < 40 U/L without a history of hepatitis B and C, liver cirrhosis, or liver cancer were analyzed. The risk of MS was evaluated according to the ALT level. The prevalence of MS significantly increased as the ALT levels increased. The proportions of MS in men were 12.6%, 25.2%, and 39.7% in the ALT levels of < 15, 15–30, and 30–40 U/L, respectively (p < 0.001), and those of women were 7.2%, 23.3%, and 44.7% in the ALT levels of < 10, 10–20, and 20–40 U/L, respectively (p < 0.001). There was an ALT-dependent relationship in the risk of MS in participants with normal ALT level after adjustment for age, alcohol intake, and body mass index. The adjusted odds ratio (aOR) of MS in men was 2.48 (95% confidence interval [CI], 2.16–2.85) in an ALT level of 30–40 U/L compared with that in ALT < 15 U/L (p < 0.001), and the aOR of MS in women was 2.67 (95% CI, 2.26–3.15) in an ALT level of 20–40 U/L compared with that in ALT < 10 U/L (p < 0.001). Although within the normal range of ALT, the risk of MS increases as the ALT levels increase. The ALT level in the general population without a history of chronic liver disease may be a useful marker to evaluate for MS.

Introduction

Metabolic syndrome (MS) is a cluster of conditions that predispose type 2 diabetes mellitus and cardiovascular disease. The prevalence of MS has increased in recent years worldwide [1]. It is noted for its clinical consequences because it is regarded as a precursor of cardiovascular
diseases such as coronary artery and cerebrovascular diseases and type 2 diabetes mellitus [2]. MS is an independent risk factor for various cardiovascular conditions such as microvascular dysfunction, coronary calcification and atherosclerosis, myocardial infarction, and heart failure [3].

The measurement of alanine aminotransferase (ALT) level is a fundamental test in screening for liver disease and assessing disease progression. Abnormal serum ALT levels are found in a variety of liver diseases such as viral hepatitis, alcoholic liver disease, or nonalcoholic fatty liver disease (NAFLD). The risk of cardiovascular disease such as ischemic heart disease or type 2 diabetes mellitus also increases in the case of elevated ALT levels [4, 5]. Furthermore, the risk of MS increases in participants with elevated ALT levels [6, 7]. The prevalence and development of MS are associated with the increased ALT levels independently of insulin resistance [8, 9].

Most clinicians carefully examine an abnormal ALT level, while they have little interest in an ALT level within the normal range. However, several studies were conducted to re-evaluate the upper limit of normal (ULN) of ALT and suggested that the new ULN of ALT should be lower than the conventional one (<40 U/L) [10–12]. Some studies suggested that the ULN of ALT in healthy participants are defined as 29–33 and 19–25 U/L in males and females, respectively [13–15]. Therefore, this study planned to investigate the risk of MS in participants with normal ALT levels in the Korean general population using a population-based nationwide data. Furthermore, we evaluated an ALT-dependent relationship in the risk of MS in participants with normal ALT levels.

Methods

Study population

This cross-sectional study was conducted using data from the Korea National Health and Nutrition Examination Survey (KNHANES) between 2007 and 2015. The KNHANES, a nationally representative survey, is performed by the Korea Centers for Disease Control and Prevention (KCDC). It is based on a complex, stratified, multistage, and probability cluster sampling of the noninstitutionalized population in Korea [16]. This survey consists of four parts: health interview, nutrition, health behavior, and health examination surveys. The health interview and examination are performed by trained medical staffs and interviewers at the mobile examination center. The KNHANES has been periodically performed since 1998. This study was conducted using KNHANES IV (2007–2009), V (2010–2012), and VI (2013–2015).

The target population of this survey was all noninstitutionalized Korean civilians older than 1 year of age. The survey was conducted with the sampling units based on gender, age, and geographic areas, which were determined according to the household registries of the Korea National Census Registry. Written informed consent was obtained from all participants in the survey. The KNHANES was approved by the Institutional Review Board of KCDC (2007-02CON-04-P, 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, 2013-12EXP-03-5C, and 2015-01-02-6C).

A total of 73,353 participants completed the survey through the mobile health exam units. First, we excluded 24,499 participants according to the following criteria: age under 19 years old (n = 17,314), absence of laboratory data (n = 6,337), and absence of alcohol intake history (n = 848). Of the remaining 48,854 participants, we additionally excluded 2,026 patients with hepatitis B (n = 1,757), hepatitis C (n = 174), liver cirrhosis (n = 79), and liver cancer (n = 16). A total of 46,828 participants without a history of viral hepatitis, cirrhosis, or liver cancer were determined. Finally, 43,402 participants whose ALT levels were within the normal range (≤40
U/L) were included in the final analysis, and we compared them to the remaining 3,426 with ALT level > 40 U/L (Fig 1).

Clinical variables

The information about alcohol consumption was obtained during the health interview survey. Alcohol consumption was evaluated by questioning the participants about their drinking behavior during the month just before the interview. They were asked for their average frequency (days per month) of alcoholic beverage consumption and average amount (units of drink/day) of alcoholic drinks ingested on a single occasion. Each unit was equivalent to approximately 10 g of alcohol intake.

Blood tests including aspartate aminotransferase (AST); ALT; total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; and triglyceride were checked after 12 h of fasting. Routine biochemical tests, including triglyceride; glucose; total, HDL, and LDL cholesterol; ALT; and AST, were performed by ADVIA 1650 analyzer (Bayer, Pittsburgh, PA, USA). Hepatitis B surface antigen was measured using an electrochemiluminescence immunoassay method with an E-170 automated analyzer (Roche, Penzberg, Germany). Chemiluminescent microparticle immunoassay was performed to check the antibody to hepatitis C virus (anti-HCV) using ARCHITECT Anti-HCV (ABBOTT Diagnostics Division, Korea/Germany). HCV RNA was measured by real-time polymerase chain reaction using the COBAS AmpliPrep/COBAS TaqMan HCV test (Roche, Penzberg, Germany). The hepatic steatosis index (HSI) was calculated to assess the relationship between the serum ALT levels and fatty liver grade [17]. High-risk alcohol consumption was defined as alcohol intake ≥ 7 drink-units one time and ≥ 2 times a week in men or ≥ 5 drink-units one time and ≥ 2 times a week in women. MS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III standards [18, 19].

Statistical analysis

All analyses were performed based on gender. Categorical variables are presented as frequencies and percentages, whereas continuous variables are demonstrated as mean value with standard deviation and median value with interquartile range. The linear trend was analyzed between clinical variables and ALT levels categorized by 3 groups (male, ALT, 0–15, 15–30, and 30–40 IU/L; female, ALT, 0–10, 10–20, and 20–40 IU/L). The ALT cutoff level was defined according to the quartile distribution of ALT level (< 25, 25–75, and ≥ 75 percentile). Continuous variables were analyzed by the weighted linear trend in the one-way ANOVA test, while categorical variables were analyzed by the linear-by-linear association in the chi-square test. A multivariable logistic regression model was used to investigate the influence of the ALT levels on MS. The risk of MS are presented as adjusted odds ratio (aOR). Three models were calculated according to each adjusting variable: age in model 1; age and alcohol consumption in model 2; age, alcohol consumption, and body mass index (BMI) in model 3. Multivariable analysis was performed using a forward conditional stepwise procedure to avoid multicollinearity. P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Window release 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the participants whose ALT levels were within the normal range (≤ 40 U/L)

Table 1 presents the baseline characteristics of the participants whose ALT levels were within the normal range (≤ 40 U/L). The mean ages and BMI values of male and female participants
Fig 1. Flow diagram of enrolled participants. Abbreviations: KNHANES, Korea National Health and Nutrition Examination Survey; ALT, alanine aminotransferase.
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were 50.5 and 49.5 years old and 23.8 and 23.3 kg/m², respectively. The systolic blood pressure (SBP) levels of male and female participants were 121.2 ± 15.9 and 116.4 ± 18.0, and their diastolic blood pressure (DBP) levels were 78.1 ± 10.6 and 73.6 ± 10.0, respectively. The ALT level of male participants was 20.8 ± 7.6 U/L, while that of females participants was 15.9 ± 6.5 U/L.

The mean levels of the HSI in male and female participants were 31.6 ± 4.5 and 32.0 ± 4.5, respectively. The prevalence rates of MS in male and female participants were 24.6% and 26.3%, respectively. The proportion of high-risk alcohol consumption in male participants was 18.9%, while that in female participants was 4.2%.

Table 2 demonstrates the changes of clinical variables according to the ALT level. There were dose-dependent increases of BMI, waist circumference, SBP, DBP, fasting blood glucose (FBS), total cholesterol, triglyceride, and HSI and prevalence rates of diabetes mellitus and MS as the ALT levels increased in both male and female participants. In addition, the HDL cholesterol level decreased as the ALT levels increased in both groups. In male participants, the proportion of high-risk alcohol consumption increased as the ALT levels increased, whereas that in female participants had an inverse correlation with the increase in the ALT levels.

Prevalence of MS in participants whose ALT levels were within the normal range

Fig 2 presents the prevalence of MS according to the ALT level. In male participants, the prevalence rates of MS were 12.6%, 25.2%, and 39.7% in the ALT levels of 0–15, 15–30, and 30–40
Table 2. Clinical characteristics of the participants according to the ALT level.

|                          | Male (n = 17,535) | Female (N = 25,867) |
|--------------------------|-------------------|---------------------|
|                          | 0–15              | 15–30               | 30–40   | P value for\(\text{trend}\) | 0–10   | 10–20   | 20–40   | P value for\(\text{trend}\) |
| Number of participants (No, %) | n = 3,927         | n = 10,916          | n = 2,692 | <0.001 | n = 3,193   | n = 1,6601 | n = 6,073 | <0.001 |
| Age (year, mean ± SD)     | 50.2 ± 19.5       | 51.1 ± 15.9         | 48.4 ± 14.7 | <0.001 | 37.6 ± 15.1 | 49.9 ± 16.4 | 54.8 ± 14.2 | <0.001 |
| BMI (kg/m\(^2\), mean ± SD) | 22.3 ± 2.7       | 23.9 ± 2.9          | 25.3 ± 3.0 | <0.001 | 21.4 ± 2.8 | 23.1 ± 3.2 | 24.9 ± 3.6 | <0.001 |
| Waist circumference (cm, mean ± SD) | 79.9 ± 8.3       | 84.4 ± 8.2          | 88.0 ± 8.1 | <0.001 | 72.9 ± 8.2 | 77.8 ± 9.2 | 83.2 ± 9.8 | <0.001 |
| SBP (mmHg, mean ± SD)     | 119.0 ± 16.5      | 121.6 ± 15.7        | 122.8 ± 15.3 | <0.001 | 107.6 ± 14.5 | 116.2 ± 17.9 | 121.7 ± 18.0 | <0.001 |
| DBP (mmHg, mean ± SD)     | 75.2 ± 10.3       | 78.5 ± 10.3         | 80.8 ± 10.8 | <0.001 | 69.8 ± 9.1 | 73.4 ± 9.9 | 76.1 ± 10.1 | <0.001 |
| AST (U/L, mean ± SD)      | 17.7 ± 4.1        | 22.1 ± 6.0          | 28.3 ± 10.8 | <0.001 | 14.8 ± 5.4 | 18.4 ± 3.9 | 24.7 ± 6.6 | <0.001 |
| ALT (U/L, mean ± SD)      | 11.8 ± 2.0        | 20.7 ± 4.1          | 34.1 ± 3.1 | <0.001 | 8.0 ± 1.2 | 14.0 ± 2.7 | 25.5 ± 1.1 | <0.001 |
| FBS (mg/dL, mean ± SD)    | 97.1 ± 22.9       | 100.4 ± 23.2        | 103.6 ± 26.0 | <0.001 | 90.1 ± 15.0 | 95.2 ± 19.7 | 102.0 ± 26.2 | <0.001 |
| Total cholesterol (mg/dL, mean ± SD) | 176.6 ± 32.2   | 187.0 ± 34.1        | 192.9 ± 37.7 | <0.001 | 176.4 ± 32.7 | 189.3 ± 35.2 | 197.0 ± 38.5 | <0.001 |
| HDL cholesterol (mg/dL, mean ± SD) | 48.4 ± 11.2   | 46.7 ± 10.9         | 45.2 ± 10.9 | <0.001 | 54.9 ± 11.6 | 52.3 ± 11.8 | 49.6 ± 11.6 | <0.001 |
| Triglyceride (mg/dL, mean ± SD) | 112.0 ± 75.1   | 151.2 ± 117.6       | 192.6 ± 144.6 | <0.001 | 84.7 ± 48.8 | 109.7 ± 70.3 | 144.7 ± 96.6 | <0.001 |
| Hepatic steatosis index   | 28.0 ± 3.2        | 31.9 ± 3.8          | 35.9 ± 4.3 | <0.001 | 28.0 ± 3.0 | 31.4 ± 3.8 | 35.7 ± 4.4 | <0.001 |
| High-risk alcohol consumption (N, mean ± SD) | 534 (13.6%) | 2121 (19.4%)        | 658 (24.4%) | <0.001 | 165 (5.2%) | 705 (4.2%) | 217 (3.6%) | 0.001 |
| Diabetes mellitus (N, %)  | 332 (8.5%)        | 936 (8.6%)          | 288 (10.7%) | <0.001 | 66 (2.1%) | 943 (5.7%) | 609 (11.5%) | <0.001 |
| Metabolic syndrome (N, %) | 495 (12.6%)       | 2,748 (25.2%)       | 1,069 (39.7%) | <0.001 | 231 (7.2%) | 3,862 (23.3%) | 2,716 (44.7%) | <0.001 |

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL, high-density lipoprotein; HSI, hepatic steatosis index.

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Fig 2. The prevalence of metabolic syndrome in patients with ALT \(\leq 40\) U/L: Male (A) and female (B). Abbreviation: ALT, alanine aminotransferase.

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A dose-dependent relationship between MS and ALT levels was noted in male participants whose ALT levels were within the normal range \((p < 0.001)\). In female...
participants, the prevalence rates of MS were 7.2%, 23.3%, and 44.7% in the ALT levels of 0–10, 10–20, and 20–40 U/L, respectively. A dose-dependent relationship between MS and ALT levels was also noted in female participants whose ALT levels were within the normal range (p < 0.001). We also examined the relationship between the score of MS components and ALT levels (Fig 3). Consequently, a positive correlation in the increase of ALT levels and that of MS components was found in both male and female participants, respectively (p < 0.001)

The relationship between the serum ALT levels and each component of MS in participants whose ALT levels were within the normal range

Table 3 shows the relationship between the serum ALT levels and each component of MS in participants whose ALT levels were within the normal range. In male participants, the serum ALT levels were significantly associated with waist circumference (r = 0.321, p < 0.001), SBP (r = 0.080, p < 0.001), DBP (r = 0.184, p < 0.001), FBS (r = 0.094, p < 0.001), and triglyceride (r = 0.234, p < 0.001). In female participants, the serum ALT levels were also significantly associated with waist circumference (r = 0.343, p < 0.001), SBP (r = 0.227, p < 0.001), DBP (r = 0.185, p < 0.001), FBS (r = 0.195, p < 0.001), and triglyceride (r = 0.269, p < 0.001). An

Table 3. Correlations between serum ALT and each components of metabolic syndrome.

| Variable                  | Male          | Female       |
|---------------------------|---------------|--------------|
|                           | r             | P            | r            | P            |
| Waist circumference (cm)  | 0.321         | <0.001       | 0.343        | <0.001       |
| SBP (mmHg)                | 0.080         | <0.001       | 0.227        | <0.001       |
| DBP (mmHg)                | 0.184         | <0.001       | 0.185        | <0.001       |
| FBS (mg/dL)               | 0.094         | <0.001       | 0.195        | <0.001       |
| Triglyceride (mg/dL)      | 0.234         | <0.001       | 0.269        | <0.001       |
| HDL cholesterol (mg/dL)   | -0.098        | <0.001       | -0.140       | <0.001       |

*Abbreviations: ALT, alanine aminotransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL, high density lipoprotein. ’r’ means the correlation coefficient.

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inverse correlation between HDL cholesterol and ALT activity was noted in both male ($r = -0.098$, $p < 0.001$) and female ($r = -0.140$, $p < 0.001$) participants.

Risk of MS in participants whose ALT levels were within the normal range

Table 4 presents the risk of MS in participants whose ALT levels were within the normal range. We assessed the risk of MS with or without adjustment for the clinical variables: unadjusted and models 1 (age), 2 (age and alcohol consumption), and 3 (age, alcohol consumption, and BMI).

In male participants, the risk of MS increased in the ALT level ranges of 15–30 and 30–40 U/L compared with that in ALT <15 U/L, respectively, in the unadjusted model (OR, 2.33 [95% confidence interval [CI], 2.10–2.56]; OR, 4.57 [95% CI, 4.04–5.16]). It also increased after adjustment for the clinical variables. In model 1, the risk of MS in these participants increased in the ALT level ranges of 15–30 and 30–40 U/L compared with that in ALT <15 U/L, respectively (aOR, 2.42 [95% CI, 2.18–2.69]; aOR, 5.31 [95% CI, 4.68–6.02]). In model 2, it increased in the ALT level ranges of 15–30 and 30–40 U/L compared with that in ALT <15 U/L, respectively (aOR, 2.20 [95% CI, 1.90–2.55]; aOR, 5.28 [95% CI, 4.53–6.15]). Moreover, in model 3, it increased in the ALT level ranges of 15–30 and 30–40 U/L compared with that in ALT <15 U/L, respectively (aOR, 2.42 [95% CI, 2.18–2.69]; aOR, 5.31 [95% CI, 4.68–6.02]).

In female participants, the risk of MS increased in the ALT level ranges of 10–20 and 20–40 U/L compared with that in ALT <10 U/L, respectively, in the unadjusted model (OR, 3.89 [95% CI, 3.38–4.47]; OR, 10.37 [95% CI, 9.00–11.97]). It also increased after adjustment for the clinical variables. In model 1, the risk of MS increased in the ALT level ranges of 10–20 and 20–40 U/L compared with that in ALT <10 U/L, respectively (aOR, 2.42 [95% CI, 2.18–2.69]; aOR, 5.31 [95% CI, 4.68–6.02]). In model 2, it increased in the ALT level ranges of 10–20 and 20–40 U/L compared with that in ALT <10 U/L, respectively (aOR, 2.20 [95% CI, 1.89–2.55]; aOR, 5.27 [95% CI, 4.52–6.15]). Moreover, in model 3, it increased in the ALT level ranges of 10–20 and 20–40 U/L compared with that in ALT <10 U/L, respectively (aOR, 1.58 [95% CI, 1.35–1.86]; aOR, 2.67 [95% CI, 2.26–3.15]).

Comparison of the risk of MS between the participants whose ALT levels were within and above the normal range

S1 and S2 Tables show the clinical characteristics of the participants with increased ALT levels (>40 U/L). In male participants, the prevalence rates of MS were 12.6%, 25.2%, 39.7%, and 50.8% in the ALT levels of <15, 15–30, 30–40, and >40 U/L, respectively. A dose-dependent
A dose-dependent relationship between MS and ALT levels was noted in these participants ($p < 0.001$). In female participants, the prevalence rates of MS were 7.2%, 23.3%, 44.7%, and 57.8% in the ALT levels of $<10$, $10–20$, $20–40$, and $>40$ U/L, respectively. A dose-dependent relationship between MS and ALT levels was noted in these participants ($p < 0.001$). Then, we compared the risk of MS between the participants whose ALT levels were within and above the normal range (S3 Table). In male participants, the risk of MS increased in the ALT level ranges of 15–30, 30–40, and $>40$ U/L compared with that in ALT $<15$ U/L, respectively, after adjustment for age, alcohol consumption, and BMI (aOR, 1.57 [95% CI, 1.40–1.76]; aOR, 2.54 [95% CI, 2.21–2.92]; and aOR, 3.63 [95% CI, 3.14–4.19], respectively). In female participants, the risk of MS increased in the ALT level ranges of 10–20, 20–40, and $>40$ U/L compared with that in ALT $<10$ U/L, respectively, after adjustment for age, alcohol consumption, and BMI (aOR, 1.59 [95% CI, 1.36–1.87]; aOR, 2.69 [95% CI, 2.28–3.18]; and aOR, 4.28 [95% CI, 3.46–5.31], respectively).

Discussion

The present study investigated the risk of MS in participants without chronic liver disease and whose ALT levels were within the normal range ($\leq 40$ U/L) in the Korean general population. The prevalence of MS significantly increased as the ALT levels increased. There was an ALT-dependent relationship in the risk of MS in participants with normal ALT levels after adjustment for age, alcohol intake, and BMI. The measurement of ALT, one of the many liver enzymes, is a widely used test for liver injury and applied in several clinical situations (acute and chronic liver disease, health checkup, preoperative examination, etc.). The ALT levels provide a basic clue to determine the presence of liver diseases including viral hepatitis, alcoholic liver disease, drug-induced liver injury, and NAFLD. Although ALT is perceived mainly as a liver enzyme, their increased levels are also associated with cardiovascular as well as liver diseases. In addition, such levels predict the development of type 2 diabetes mellitus and coronary heart disease [20,21] and are related to hypoxia in patients with obstructive sleep apnea [22] and associated with intracerebral hemorrhage [23].

MS is a cluster of clinical and laboratory findings consisting of high BMI, blood pressure, and glucose and triglyceride levels and low HDL level [24]. A meta-analysis showed that participants with MS have a twofold increased risk of cardiovascular disease, myocardial infarction, stroke, and cardiovascular disease-related mortality compared with those without MS [25]. MS is associated with increased ALT levels [8,9]. An Australian population-based cohort study showed that the ALT levels were strongly associated with the prevalence of MS [26]. A population-based Hispanic cohort study revealed that high prevalence rates of MS were observed in participants with increased ALT levels and male ones had increased ALT levels compared with the females [27]. A Chinese population-based cohort study demonstrated that the longitudinal increments of the ALT levels were related to an increased incidence of MS [28]. MS is related to an elevated ALT level in patients with diabetes mellitus [29]. Also, it is well known that MS is closely related to NAFLD. The prevalence of MS in patients with NAFLD increases as the BMI increases [30]. Furthermore, the increased ALT levels are significantly associated with MS in patients with NAFLD and viral hepatitis [31,32].

This study investigated the risk of MS in participants whose ALT levels were within the normal range ($\leq 40$ U/L). The prevalence rates of MS were 24.6% and 26.3% in male and female participants, respectively. Also, the proportions of MS in male and female participants whose ALT levels were within the ULN (male, 30–40 U/L; female, 20–40 U/L) were 39.7% and 44.7%, respectively. The prevalence rate of MS was approximately 40% in the Chinese general population.
population with an ALT level within the normal range (\( \leq 40 \text{ U/L} \)) [33]. The ALT level within the normal range (\( \leq 40 \text{ U/L} \)) is closely correlated with the severity of MS in a population-based cohort in Germany [34]. The risk of MS is associated with increased ALT levels within the normal range (\( \leq 43 \text{ U/L} \)) in the Korean population study [35]. Arterial stiffness and MS were related to the ALT levels within the normal range (\( \leq 40 \text{ U/L} \)) regardless of alcoholic consumption [36]. The present study also examined the relationship between the score of MS components and ALT levels within the normal range (\( \leq 40 \text{ U/L} \)). The ALT level significantly increased as the score of MS components increased. Considering the results of the aforementioned and present study, the risk of MS exists even in participants whose ALT levels were within the normal range. Moreover, there is an ALT-dependent relationship in the risk of MS in participants with normal ALT level. Similarly, the risk of liver disease can still exist even if the ALT level is within the normal range. The risk of disease progression is also still noted in patients with chronic hepatitis B or C despite having ALT levels within the normal range [10,11]. Also, the majority of patients with NAFLD (~80%) have ALT levels within the normal range levels [37]. Amarapurkar et al. reported that an abnormal ALT level is observed in 16% of patients with NAFLD diagnosed by ultrasonography [38].

This study has several limitations. Firstly, imaging study or liver biopsy was not checked. Therefore, this study has limitations in detailed information for liver diseases such as hepatic steatosis or liver cirrhosis. Secondly, the relationship between MS and the ALT level change was not evaluated because the present study was conducted based on a cross-sectional study design. Finally, the association between the serum ALT levels and inflammatory markers such as tumor necrosis factor-alpha, plasminogen activator inhibitor 1, interleukin-6, leptin, and adiponectin was not elucidated. In spite of these limitations, this study investigated the relationship between MS and a normal ALT level in a large-scale general population.

**Conclusions**

In conclusion, the risk of MS significantly increases as the ALT level increases within the normal ALT level. Even if the ALT level is within the normal range, it may be a useful marker to consider the presence of MS.

**Supporting information**

S1 Table. Baseline characteristics of the participants.

S2 Table. Clinical characteristics of the participants according to ALT level.

S3 Table. Risk of metabolic syndrome according to serum ALT level.

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References

1. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018; 20(2):12. https://doi.org/10.1007/s11906-018-0812-z PMID: 29480368; PubMed Central PMCID: PMC5866840.

2. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012; 59(7):635–43. https://doi.org/10.1016/j.jacc.2011.08.080 PMID: 22322788.

3. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res. 2017; 183:57–70. https://doi.org/10.1016/j.trsl.2017.01.001 PMID: 28130064; PubMed Central PMCID: PMC5393930.

4. Choi KM, Han K, Park S, Chung HS, Kim NH, Yoo HJ, et al. Implication of liver enzymes on incident cardiovascular diseases and mortality: A nationwide population-based cohort study. Sci Rep. 2018; 8(1):3764. https://doi.org/10.1038/s41598-018-19700-8 PMID: 29491346; PubMed Central PMCID: PMC5830612.

5. Liu J, Au Yeung SL, Lin SL, Leung GM, Schooling CM. Liver Enzymes and Risk of Ischemic Heart Disease and Type 2 Diabetes Mellitus: A Mendelian Randomization Study. Sci Rep. 2016; 6:38813. https://doi.org/10.1038/srep38813 PMID: 27996050; PubMed Central PMCID: PMC5171875.

6. Perera S, Lohsoonthorn V, Jiamjarasrangsi W, Lertmaharit S, Williams MA. Association Between Elevated Liver Enzymes and Metabolic Syndrome Among Thai Adults. Diabetes Metab Syndr. 2008; 2(3):171–8. https://doi.org/10.1016/j.dsx.2008.04.012 PMID: 25147585; PubMed Central PMCID: PMC4137970.

7. Saito T, Nishise Y, Makino N, Haga H, Ishii R, Okumoto K, et al. Impact of metabolic syndrome on elevated serum alanine aminotransferase levels in the Japanese population. Metabolism. 2009; 58(6):1067–75. https://doi.org/10.1016/j.metabol.2009.03.008 PMID: 19411086.

8. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D’Agostino RB Jr., Hoffner SM. Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study. Diabetes. 2005; 54(11):3140–7. https://doi.org/10.2337/diaabetes.54.11.3140 PMID: 16249437.

9. Yun JE, Kim SY, Kang HC, Lee SJ, Kimm H, Jee SH. Alanine aminotransferase is associated with metabolic syndrome independently of insulin resistance. Circ J. 2011; 75(4):964–9. https://doi.org/10.1253/circj.cj-10-0465 PMID: 21304212.

10. Tai DI, Lin SM, Sheen IS, Chu CM, Lin DY, Liaw YF. Long-term outcome of hepatitis B e antigen-negative hepatitis B surface antigen carrier in relation to changes of alanine aminotransferase levels over time. Hepatology. 2009; 49(6):1859–67. https://doi.org/10.1002/hep.22876 PMID: 19378345.

11. Tassopoulos NC. Treatment of patients with chronic hepatitis C and normal ALT levels. J Hepatol. 1999; 31 Suppl 1:193–6. https://doi.org/10.1016/s0168-8278(99)80400-0 PMID: 10622586.

12. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum alanine aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ. 2004; 328(7446):983. https://doi.org/10.1136/bmj.38050.593634.63 PMID: 15028636; PubMed Central PMCID: PMC404493.

13. Lee JK, Shim JH, Lee HC, Lee SH, Kim KM, Lim YS, et al. Estimation of the healthy upper limits for serum alanine aminotransferase in Asian populations with normal liver histology. Hepatology. 2010; 51(5):1577–83. https://doi.org/10.1002/hep.23505 PMID: 20162730.

14. Ruhl CE, Everhart JE. Upper limits of normal for alanine aminotransferase activity in the United States population. Hepatology. 2012; 55(2):447–54. https://doi.org/10.1002/hep.24725 PMID: 21987480; PubMed Central PMCID: PMC3268908.

15. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002; 137(1):1–10. https://doi.org/10.7326/0003-4819-137-1-200207020-00006 PMID: 12093239.

16. Kim Y. The Korea National Health and Nutrition Examination Survey (KNHANES): current status and challenges. Epidemiol Health. 2014; 36:e2014002. https://doi.org/10.4178/epih/e2014002 PMID: 24893580; PubMed Central PMCID: PMC4017741.

17. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010; 42(7):503–8. https://doi.org/10.1016/j.dld.2009.08.002 PMID: 19766548.
18. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285 (19):2486–97. https://doi.org/10.1001/jama.285.19.2486 PMID: 11368702.

19. Grundy SM, Brewer HB Jr., Cleeman JC, Smith SC Jr., Lenfant C, American Heart A, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109(3):433–8. https://doi.org/10.1161/01.CIR.0000112457.75752.C6 PMID: 14744958.

20. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002; 51(6):1889–95. https://doi.org/10.2337/diabetes.51.6.1889 PMID: 12031978.

21. Schindhelm RK, Dekker JM, Nipets G, Bouter LM, Stehouwer CD, Heine RJ, et al. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. Atherosclerosis. 2007; 191(2):391–6. https://doi.org/10.1016/j.atherosclerosis.2006.04.006 PMID: 16682043.

22. Norman D, Birdwell WA, Arosemena F, Nelesen R, Mills PJ, Loredo JS, et al. Serum aminotransferase levels are associated with markers of hypoxia in patients with obstructive sleep apnea. Sleep. 2008; 31 (1):121–6. https://doi.org/10.1093/sleep/31.1.121 PMID: 18220085; PubMed Central PMCID: PMC2225546.

23. Kim HO, Oh SM, Pan WH, Ushihama H, Gu D, Chuang SY, et al. Association between alanine aminotransferase and intracerebral hemorrhage in East Asian populations. Neuroepidemiology. 2013; 41 (2):131–8. https://doi.org/10.1159/000353186 PMID: 23980909.

24. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014; 43(1):1–23. https://doi.org/10.1016/j.ecl.2013.09.009 PMID: 24882088.

25. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 56(14):1113–32. https://doi.org/10.1016/j.jacc.2010.05.034 PMID: 20963953.

26. Olynyk JK, Knuijnen MW, Divitini ML, Davis TM, Beilby J, Hung J. Serum alanine aminotransferase, metabolic syndrome, and cardiovascular disease in an Australian population. Am J Gastroenterol. 2009; 104(7):1715–22. https://doi.org/10.1038/ajg.2009.229 PMID: 19491832.

27. Pan JJ, Qu HQ, Rentfro A, McCormick JB, Fisher-Hoch SP, Fallon MB. Prevalence of metabolic syndrome and risks of abnormal serum alanine aminotransferase in Hispanics: a population-based study. PLoS One. 2011; 6(6):e21515. https://doi.org/10.1371/journal.pone.0021515 PMID: 21720053; PubMed Central PMCID: PMC3123360.

28. Sun H, Liu Q, Wang X, Li M, Fan Y, Song G, et al. The longitudinal increments of serum alanine aminotransferase increased the incidence risk of metabolic syndrome: A large cohort population in China. Clin Chim Acta. 2019; 488:242–7. https://doi.org/10.1016/j.cca.2018.10.033 PMID: 30891232.

29. Esteghamati A, Jamalai A, Khalilzadeh O, Noshad S, Khalili M, Zandieh A, et al. Metabolic syndrome is linked to a mild elevation in liver aminotransferases in diabetic patients with undetectable non-alcoholic fatty liver disease by ultrasound. Diabetol Metab Syndr. 2010; 2:65. https://doi.org/10.1186/1758-5996-2-65 PMID: 21047423; PubMed Central PMCID: PMC2987914.

30. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003; 37(4):917–23. https://doi.org/10.1053/jhep.2003.50161 PMID: 12668987.

31. Chen ZW, Chen LY, Dai HL, Chen JH, Fang LZ. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. J Zhejiang Univ Sci B. 2008; 9(8):616–22. https://doi.org/10.1631/jzus.B0720016 PMID: 18763311; PubMed Central PMCID: PMC2491691.

32. Khalili M, Shuhart MC, Lombardo M, Feld JJ, Kleiner DE, Chung RT, et al. Relationship Between Metabolic Syndrome, Alanine Aminotransferase Levels, and Liver Disease Severity in a Multiethnic North American Cohort With Chronic Hepatitis B. Diabetes Care. 2018; 41(6):1251–9. https://doi.org/10.2337/dc18-0040 PMID: 29599296; PubMed Central PMCID: PMC5961397.

33. Chen S, Guo X, Yu S, Zhou Y, Li Z, Sun Y. Metabolic Syndrome and Serum Liver Enzymes in the General Chinese Population. Int J Environ Res Public Health. 2016; 13(2):223. https://doi.org/10.3390/ijerph13020223 PMID: 26901209; PubMed Central PMCID: PMC4772243.

34. Kalsch J, Bechmann LP, Heider D, Best J, Manka P, Kalsch H, et al. Normal liver enzymes are correlated with severity of metabolic syndrome in a large population based cohort. Sci Rep. 2015; 5:13058. https://doi.org/10.1038/srep13058 PMID: 26269425; PubMed Central PMCID: PMC4535035.

35. Suh SY, Choi SE, Ahn HY, Yang HM, Kim YJ, Sung NJ. The association between normal alanine aminotransferase levels and the metabolic syndrome: 2005 Korean National Health and Nutrition Examination
36. Fu S, Lin Y, Luo L, Ye P. The relationship of serum alanine aminotransferase normal-range levels to arterial stiffness and metabolic syndrome in non-drinkers and drinkers: a Chinese community-based analysis. BMC Gastroenterol. 2017; 17(1):49. https://doi.org/10.1186/s12876-017-0607-8 PMID: 28399807; PubMed Central PMCID: PMC5387349.

37. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40 (6):1387–95. https://doi.org/10.1002/hep.20466 PMID: 15565570.

38. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol. 2007; 6(3):161–3. PMID: 17786142.