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Severity of Nonalcoholic Fatty Liver Disease is Associated with Development of Metabolic Syndrome: Results of a 5-Year Cohort Study

Research Article

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Abstract

Aims: Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of metabolic syndrome (MS). However, a few studies have examined the effect of NAFLD on the development of MS. We evaluated the relationship between the development of MS and clinical severity of NAFLD according to alanine aminotransferase (ALT) levels.
Methods: A retrospective cohort study was conducted. Participants who underwent abdominal ultrasonography and blood samplings for health check-ups both in 2005 and 2010 were recruited. NAFLD was diagnosed if a person showed fatty liver on ultrasonography without significant alcohol consumption. Subjects with MS at baseline were excluded.
Results: A total of 2,728 subjects met the inclusion criteria. Fatty liver (FL) with normal ALT was found in 369 (13.5%) subjects and FL with elevated ALT in 328 (12.0%). During 5 years of follow up, 582 (21.3%) incident cases of MS developed between 2005 and 2010. The incidence of MS was higher in patients with NAFLD compared to control group (41.2% in FL with elevated ALT, 34.7% in FL with normal ALT and 15.7% in control, $p<0.001$). Multivariate analysis showed that odds ratio (OR) and 95% confidence interval (CI) for MS increased according to the severity of NAFLD [OR (95% CI), 1.29 (0.97−1.71) in FL with normal ALT and 1.54 (1.18−1.33) in FL with elevated ALT, $p=0.01$].
Conclusions: We have demonstrated that development of MS is significantly increased according to the clinical severity of NAFLD. These findings have implications in the clinical availability of NAFLD as a predictor of MS.

Keywords: Metabolic Syndrome; Non-Alcoholic Fatty Liver Disease; Liver Enzyme.

Abbreviations: ALT: Alanine Aminotransferase; BMI: Body Mass Index; HDL: High Density Lipoprotein; FL: Fatty Liver; MS: Metabolic Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of common causes of chronic liver disease, with increasing prevalence up to 20-30% worldwide [1]. NAFLD represents a group of conditions ranging from simple steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis [2]. Because the central pathogenesis of NAFLD is insulin resistance, NAFLD is considered to be a hepatic manifestation of metabolic syndrome (MS) [3]. In addition, NAFLD is closely linked to cardiovascular risk factors such as Type 2 diabetes, dyslipidemia and central obesity, which are components of metabolic syndrome [4, 5]. MS is related to atherosclerosis, cardiovascular disease, and as a result, increasing the development of diabetes and mortality of cardiovascular disease [6-8]. Many studies have shown the association between NAFLD and MS. A prospective observational study in Japan has identified MS as a strong predictor of NAFLD [9]. A recent study has found that the number of MS component was useful in predicting NAFLD [10]. However, a few studies have examined the effect of NAFLD the development of MS. Subjects with NAFLD and elevated liver enzyme was at an increased risk of developing MS [11]. A recent prospective cohort study showed that NAFLD was an independent risk factor for MS [12]. However, there is no data evaluating the development MS according to the severity of NAFLD including suspected simple steatosis and NASH based on general population. Therefore, the aim of this study was to determine the relationship between clinical severity of NAFLD according to ALT levels and the development of MS.

Patients and Methods

Study population

A retrospective cohort study was conducted to evaluate the association between NAFLD and the development of MS. The participants who underwent abdominal ultrasonography (US) and blood samplings at the Seoul National University Hospital Gangnam Healthcare Center, Seoul, Korea for routine health check-ups both in 2005 and 2010 were recruited. Most of the study population paid voluntarily for their health check-ups and some of them were supported by their company. 184 subjects positive for hepatitis B virus, 44 with positive hepatitis C virus, 754 subjects with alcohol consumption (>20 g/day for males and >10 g/day for females) and other hepatitis history were excluded. Among the 3,460 subjects enrolled, 732 subjects were excluded due to pre-existing MS. Finally, 2,728 subjects met inclusion criteria. This study was approved by the Institutional Review Board of the Seoul National University Hospital with a waiver of informed consent.

Clinical and laboratory assessments

Each subject completed a past medical history questionnaire and received an anthropometric assessment and laboratory and radiologic tests on the same day. Body weight and height were measured using a digital scale, and body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). Waist circumference was measured at the midpoint between the lower costal margin and the anterior superior iliac crest by a well-trained person using a tape. Systolic blood pressure and diastolic blood pressure were measured twice, and the mean values were reported. The laboratory tests included serum alanine aminotransferase (ALT), total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, fasting glucose, hepatitis B surface antigen and antibody to hepatitis C virus. Blood samples were collected before 10:00 AM after a 12-h overnight fast. All laboratory tests were carried out using standard laboratory methods.

Definitions

The presence of diabetes mellitus was defined as either a fasting serum glucose ≥ 126 mg/dL or use of anti-diabetic medication. The presence of hypertension was defined as having a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥90 mmHg or use of anti-hypertensive medication. Current smokers were defined as having smoked at least 1 cigarette/day during the previous year. Former smokers were defined as prior regular cigarettes smoking [13]. Abnormal liver enzyme levels were based on ALT elevation over the strict cut-off point based on the updated definitions by Prati et al. 30 IU/L for men and 19 IU/L for women [14].

NAFLD was defined as the presence of fatty liver disease as determined by ultrasonography in the absence of the following: 1) seropositivity for hepatitis B surface antigen or antibody to hepatitis C virus, 2) excessive alcohol intake (> 20g/day for males and >10 g/day for females), 3) other causes of liver disease, and 4) medications known to produce fatty liver disease.

MS was diagnosed when three or more of the five components were present, that is, (1) central obesity [waist circumference as defined by the Regional Office for the Western Pacific Region of the World Health Organization (WPRO) criteria, >90 cm (men) or >80 cm (women)]; (2) a triglyceride level ≥150 mg/dL (3) HDL-C <40 mg/dL (men) or <50 mg/dL (women); (4) fasting glucose ≥100 mg/dL or treatment for diabetes; (5) arterial pressure ≥130/85 mmHg or treatment for hypertension [15].

US assessments

US examination of the liver was performed by experienced radiologists who were unaware of the clinical information. The diagnosis of FL was performed by ultrasonography (Acusion, Sequioa 512, Siemens, Mountain View, CA) using previously described standardized criteria [16].

Statistical analysis

Comparisons of continuous variables between the two groups were performed with the Student's *t*-test, and categorical variables were compared using the chi-square test or Fisher's exact test. Variables that were statistically significant by univariate analysis and known risk factors were added to a multiple logistic regression model to identify independent predictors of the presence of NAFLD. Statistical analysis was performed with SPSS 19.0 (SPSS Inc.; Chicago, IL, USA). *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 2,728 subjects were finally analyzed. Their mean age was 47.5 ± 9.7 years and 50.4% were male. The anthropometric, clinical and laboratory characteristics of the subjects are shown in Table 1. FL with normal ALT was found in 369 (13.5%) and FL with elevated ALT in 328 (12.0%) subjects at baseline. BMI, waist circumference, ALT, and triglyceride level were higher in patients with NAFLD compared to the control group (p<0.001).

Development of the metabolic syndrome

During 5 years of follow-up between 2005 and 2010, 582 (21.3%) incident cases of MS developed. The incidence of MS was higher in patients with NAFLD compared to control group (41.2% in FL with elevated ALT, 34.7% in FL with normal ALT and 15.7% in control, p<0.001). Subjects who developed MS on follow-up were older with greater central obesity, dyslipidemia, and blood pressure at the time of baseline assessment compared to those who did not developed MS (p<0.001, Table 2).

To examine incident MS according to the NAFLD categories (control, FL with normal ALT and FL with elevated ALT), analysis was stratified according to baseline NAFLD categories (Table 3). In age and sex adjusted model, odds ratio (OR) and 95% confidence (CI) interval for MS increased according to the degree of NAFLD [1.99 (1.54−2.59) in FL with normal ALT and 3.09 (2.38−4.01) in FL with elevated ALT, p<0.001]. These associations were attenuated, but still remained significant, even after further adjustments for covariates, such as BMI, smoking, central obesity, hypertension, glucose, triglyceride and high-density lipoprotein cholesterol (model 2). [OR (95% CI), 1.29 (0.97−1.71) in FL with normal ALT and 1.54 (1.18−1.33) in FL with elevated ALT, p=0.01].

Table 1. Comparison of baseline characteristics in nonalcoholic fatty liver disease with or without elevated alanine aminotransferase versus control.

	Control (n=2,031)	FL with normal ALT (n=369)	FL with elevated ALT (n=328)	*p* for trend
Age, years	47.0 ± 9.7	49.8 ± 9.2	48.1 ± 9.6	<0.001
Male sex, %	843 (41.5)	292 (79.1)	239 (72.9)	<0.001
Smoking, %	252 (12.4)	74 (20.1)	71 (21.6)	<0.001
Body mass index, kg/m^2	21.9 ± 2.7	24.1 ± 2.1	22.6 ± 2.9	<0.001
Waist circumference, cm	80.9 ± 8.0	85.6 ± 5.4	87.2 ± 9.5	<0.001
ALT, IU/L	19.8 ± 11.9	20.1 ± 5.6	44.2 ± 23.0	<0.001
Fasting glucose, mg/dL	94.8 ± 11.3	102.2 ± 18.8	100.8 ± 15.8	<0.001
Triglycerides, mg/dL	83.5 ± 38.3	114.9 ± 51.7	120.5 ± 67.4	<0.001
HDL cholesterol, mg/dL	58.0 ± 13.2	51.0 ± 10.7	50.9 ± 11.4	<0.001
CRP, mg/dL	0.08 ± 0.21	0.09 ± 0.30	0.09 ± 0.23	0.316
Hypertension, %	186 (9.6)	56 (15.2)	50 (15.2)	<0.001
5_year metabolic syndrome development	319 (15.7)	128 (34.7)	135 (41.2)	<0.001

Data are presented as the mean ± SD

P-value by *ANOVA*-test for continuous variables and Chi square test for categorical variables

ALT, alanine aminotransferase; CRP, C-reactive protein; FL, fatty liver; HDL, high density lipoprotein;

Table 2. Baseline characteristics associated with development of metabolic syndrome over 5-year follow up period.

	MS absent at follow-up (n=2,146)	MS present at follow-up (n=582)	*p*
Age, years	46.5 ± 9.4	51.3 ± 9.7	<0.001
Male sex, %	959 (44.7)	415 (71.3)	<0.001
Smoking, %	273 (12.7)	74 (20.1)	<0.001
Body mass index, kg/m^2	22.1 ± 2.8	24.2 ± 2.7	<0.001
Waist circumference, cm	80.5 ± 7.9	86.1 ± 8.8	<0.001
ALT, IU/L	21.5 ± 14.7	27.2 ± 16.9	<0.001
Fasting glucose, mg/dL	94.8 ± 11.2	103.1 ± 18.3	<0.001
Triglycerides, mg/dL	87.4 ± 44.1	109.6 ± 53.5	<0.001
HDL-cholesterol, mg/dL	57.0 ± 13.4	53.4 ± 11.1	<0.001
Hypertension, %	141 (6.6)	151 (25.9)	<0.001

MS, metabolic syndrome; ALT, alanine aminotransferase; HDL, high density lipoprotein

Table 3. Age- and sex-adjusted and multivariable analyses of risk of metabolic syndrome in nonalcoholic fatty liver disease with or without elevated ALT versus control.

	Control (n=2,031)	FL with normal ALT (n=369)	FL with elevated ALT (n=328)	*p* for trend
Subjects who developed MS, n (%)	319 (15.7)	128 (34.7)	135 (41.2)	<0.001
Adjusted OR (95% CI)				
Model 1	1 (reference)	1.99	3.09	<0.001
		(1.54−2.59)	(2.38−4.01)	
Model 2,	1 (reference)	1.29	1.54	0.01
		(0.97−1.71)	(1.18−1.33)	

Model 1: adjusting for age and sex, Model 2: adjusting for age, sex, BMI, smoking, central obesity, hypertension, glucose, triglyceride and high-density lipoprotein. MS, metabolic syndrome; ALT, alanine aminotransferase; FL, fatty liver; OR, odds ratio; CI, confidence interval

We next investigated whether serum ALT threshold associated with the development of MS. Figure 1 illustrates that higher baseline ALT levels were significantly correlated with the development of MS in the subjects with NAFLD. Table 4 shows the effect sizes of NAFLD among groups divided according to each metabolic component for the development of MS. The effect of NASH on the development of MS was comparable to other components of MS except hypertension.

Discussion

The study showed that incidence of MS was increased in NAFLD patients according to the NAFLD categories (control, FL with normal ALT and FL with elevated ALT). These findings suggest an independent role of NAFLD in the development of MS. Consistent with our study, Adams et al. [11] reported that subjects with NAFLD and elevated ALT levels are at increased risk of developing MS. However, NAFLD was not a significant predictor of the development of MS in multivariate analysis in the study [11]. In addition, subjects with NAFLD and normal ALT levels were not included in the study, because definition of NAFLD was based only ALT levels. A case-control study [17] has shown that the presence of NAFLD may predict the development of metabolic disorders due to insulin resistance. However, the definition of metabolic disorders is was not clear and there was no data about NASH [17]. A recent prospective cohort study showed that the risk of MS independently increased according to the degree of NAFLD [12]. In this study, the subjects were confined to male and the degree of NAFLD was categorized by only US. Most studies using US refer to a three- score system for FL (mild, moderate and severe) based on echogenity of the liver [18, 19]. Although US is an established tool as a screening modality with acceptable sensitivity and specificity in detecting FL, US has limitations in grading the severity of NAFLD [20]. First, because of operator-dependency of US imaging, it is inaccurate in the quantification of fat accumulation. A retrospective study showed that the mean intra-observer agreement for severity of FL ranged from 55% to 68% [21]. Second, it is difficult to distinguish simple steatosis from steaohepatitis or fibrosis [22] as these have similar sonographic findings.

The presence of NAFLD on sonographic finding does not always indicate elevated ALT level. Only 16.5% of women and 14.5% of men above the 75th percentiles of ALT (≥19 for women and ≥23 for men) showed sonography findings of NAFLD [23]. Wang et al. [24] showed that coexistence of NAFLD and elevated ALT (>30) were associated with insulin resistance in young Han males, providing evidence of a relationship between NAFLD and elevated ALT level. In this study, we stratified subjects with NAFLD according to the ALT levels; NAFLD with normal ALT vs. NAFLD with elevated ALT (>30/19), which may reflect the presence of NASH, and development of MS was significantly higher according to the degree of NAFLD. As a result, the odds ratio of NASH on the development of MS was comparable to other components of MS, which suggests the role of a NASH as one component of MS. Using similar criteria for NAFLD categories to our study, Sung et al. [25] have shown that overall cardiovascular risk was significantly greater in NASH, defined as steatosis and an increased serum ALT, than either simple steatosis or raised ALT alone. Baumeister et al. [26] have identified that subjects with so-

Figure 1. Cumulative probability for the development of metabolic syndrome in 5-year follow-up in subjects with nonalcoholic fatty liver disease according to baseline ALT levels.

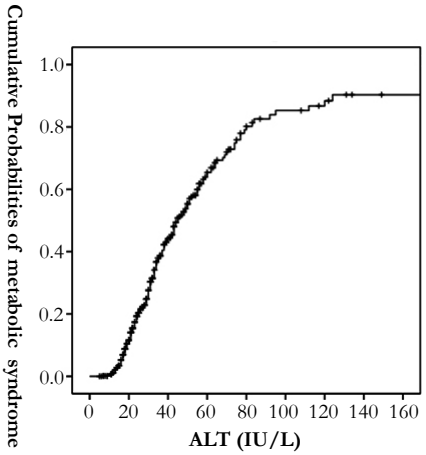

Table 4. The effect size of nonalcoholic fatty liver disease and groups divided according to each metabolic component for the development of metabolic syndrome. (Age, sex, body mass index and smoking adjusted).

	OR (95% CI)
Glucose > 100	2.00 (1.62−2.49)
Obesity	1.42 (1.08−1.88)
Hypertriglycemia	1.55 (1.13−2.11)
Low HDL	1.82 (1.31−2.54)
Hypertension	3.01 (2.42−3.74)
FL with normal ALT	1.47 (1.12−1.93)
FL with elevated ALT	1.84 (1.39−2.44)

ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; HDL, high density lipoprotein; FL, fatty liver

nographic FL and increased serum ALT levels had higher overall health care cost at 5-year follow up. These findings suggest that NAFLD categories used in this study are useful for predicting the prognosis of NAFLD.

In our study, development of MS was increased according to the increased ALT levels in subjects with NAFLD. The findings are in accordance with the two previous studies [27, 28]. An Australian population-based cohort study has found a strong association between ALT level and MS independent of insulin resistance [27]. Another study has suggested the role of ALT as an indicator for the 6-year risk of MS development in a general population of middle-aged Caucasians [28]. However, presence of NAFLD was not considered in these studies.

The strength of our study is that this is the first to determine the causal relationship between the severity of NAFLD and the development of MS providing substantial duration of follow-up. Moreover, the subjects in our study are representative of the general population due to the nature of a health check-up. Finally, the clinical diagnosis of NAFLD and suspected NASH used in this study may have implications for clinicians managing patients in the primary care center.

There are limitations of our study. First, hepatic sonography is used as a diagnostic tool for NAFLD, and this method cannot diagnose a small fatty infiltration below 30%. However, because of its relatively high sensitivity up to 84.8% and specificity up to 93.6%, hepatic ultrasound is widely used a diagnostic test for NAFLD [29, 30]. Although a biopsy was needed for grading for severity of NAFLD, we categorized NAFLD groups according to ALT levels. Actually, biopsies were not available in all subjects with NAFLD, and this grouping has been generally accepted. Second, there might be a selection bias, because this study was performed at a single health screening center and we did not evaluate whether the subjects were treated during the study period because of a retrospective design. Third, we cannot identify the effect of insulin resistance because there was no data regarding insulin levels in this study. However, a previous study in China established the association between NAFLD with elevated ALT with insulin resistance [24], supporting our results.

Conclusion

We have demonstrated that the development of MS is significantly increased according to the clinical severity of NAFLD during a 5-year follow-up. These findings have implications in the clinical availability of NAFLD as a predictor of MS.

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