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The association between non-alcoholic fatty liver disease and carotid atherosclerosis in subjects with within-reference range alanine aminotransferase levels

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Abstract. Our aim was to investigate whether the evaluation of non-alcoholic fatty liver disease (NAFLD) by ultrasound provides additional benefit in assessing carotid atherosclerotic burden in subjects with alanine aminotransferase (ALT) concentrations within the reference range. This was a cross-sectional analysis of 769 healthy individuals (326 men and 443 women) with an ALT concentration ≤ 40 IU/L and alcohol consumption < 140 g/week. Mean carotid artery intima-media thickness (C-IMT) was measured using ultrasound. NAFLD was defined as a mild or greater degree of hepatic steatosis on ultrasound. Although all subjects had an ALT concentration within the reference range, the prevalence of NAFLD increased with increasing quartiles of ALT concentration (27.1%, 40.0%, 54.7%, 75.3% in men, *P* for trend < 0.001; 22.0%, 34.4%, 35.7%, 55.0% in women, *P* for trend < 0.001). In the 3rd and 4th quartiles of ALT concentration, women with NAFLD had a significantly higher C-IMT than those without NAFLD (0.671±0.019 mm *vs*. 0.742±0.025 mm, *P*=0.023 in Q3; 0.651±0.023 mm *vs*. 0.737±0.021 mm, *P*=0.005 in Q4). These differences remained significant even after adjusting for a broad spectrum of potential confounders. In contrast, although men with NAFLD tended to have a higher C-IMT than those without NAFLD in each quartile, these differences were not statistically significant. Women with an upper normal range ALT concentration showed increased C-IMT only when they had NAFLD. Therefore, in women with an elevated ALT level within the reference range, further evaluation for NAFLD, such as liver ultrasound, could potentially identify those patients at high risk for cardiovascular disease.

Key words: Alanine aminotransferase, Intima-media thickness, Non-alcoholic fatty liver disease

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) is a slowly progressive condition and represents a spectrum of liver disease of varying severities, ranging from simple steatosis to cirrhosis [1]. Its prevalence parallels that of obesity and type 2 diabetes worldwide; in other words, it is increasing in incidence [2]. NAFLD is commonly associated with cardiovascular and metabolic diseases such as high blood pressure, dyslipidemia, type 2 diabetes, and metabolic syndrome [3-7]. Numerous epidemiological studies have reported an increased incidence of cardiovascular events in subjects with NAFLD compared to those without NAFLD [8-11].

The best diagnostic test to confirm NAFLD is a liver biopsy, but its use is limited because of medical and ethical considerations. Measurement of alanine aminotransferase (ALT) levels and hepatic ultrasound are the tools most commonly used to diagnose NAFLD, which is considered to be a risk factor for cardiovascular and metabolic disease [12, 13]. An elevated ALT level is a common laboratory abnormality found in patients with NAFLD, but the specificity of this test is low [14]. Although hepatic ultrasound is not sufficiently sensitive to detect liver inflammation and fibrosis, hepatic ultrasound results correlate well with the histological findings of NAFLD [15].

In practice, elevated ALT concentrations that fall within the reference range are interpreted to mean that the patient does not have liver problems; hepatic ultrasound is recommended only for patients with an ALT concentration outside of the reference range [16]. However, many studies have suggested that elevated ALT concentrations, even those within the reference range, are associated with atherosclerosis and cardiovascular disease. The results of ALT and hepatic ultra-

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sound are also often discordant [17-19].

Our aim in this study was to investigate whether NAFLD evaluation by ultrasound is associated with ALT concentration within the reference range and carotid atherosclerotic burden, to make recommendations as to when hepatic ultrasound is needed in patients with ALT levels within the reference range.

Materials and Methods

Subjects

A total of 1,244 patients who had undergone a medical check-up at the Korea Association of Health Promotion Center in Seoul, Korea were recruited consecutively. Anthropometric assessments were performed, blood pressure was measured, and laboratory tests and abdominal and carotid ultrasonography were performed in all study participants. Individuals with diagnosed or newly detected diabetes, history of coronary artery disease, stroke, other known liver disease, positive serologic finding for hepatitis B virus surface antigen, 140 g or more weekly alcohol consumption, elevated serum creatinine levels (>1.4 mg/dL), or elevated serum ALT levels (>40 IU/L) were excluded. Finally, 769 subjects (326 men and 443 women) were included in the analysis. The clinical characteristics of the study subjects are summarized in Table 1. All participants signed consent forms and the Institutional Review Board of Severance Hospital at Yonsei University College of Medicine approved this study.

Measurements

Body weight and height were measured in all subjects while wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Waist circumference was measured at the midpoint between the inferior border of the subcostal margin and iliac crest in the mid-axillary line after normal expiration with the subject standing. Blood pressure was measured using a mercury sphygmomanometer with the patient seated. Venous blood samples were obtained after an overnight fast of at least 8 hours and fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, aspartate aminotransferase (AST), ALT, and creatinine levels were measured.

Assessment of NAFLD and mean carotid artery intima-media thickness (C-IMT)

Trans-abdominal ultrasonography of the liver was performed using a high-resolution ultrasonographic system (SSD-5500; Aloka, Tokyo, Japan). The degree of steatosis was assessed semi-quantitatively (absent, mild, moderate, or severe) on the basis of hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring. NAFLD was defined as a mild or greater degree of hepatic steatosis on ultrasound.

C-IMT measurement was carried out according to a validated procedure using a high-resolution ultrasonographic system (SSD-5500) with a 7.5 MHz linear transducer. C-IMT was measured 1 cm proximal to the dilatation of the carotid bulb, at three points on the far wall of the mid and distal common carotid artery. C-IMT was defined as the distance between the lumen-intima interface and the media-adventitia interface. Mean values of six measurements from the right and left common carotid artery were used for the analysis. The same investigator took all measurements.

Table 1 Clinical and biochemical characteristics of study subjects

	Men	Women	*P*
N	326	443	
Age, y	51.1 ± 11.0	52.4 ± 9.5	0.074
Body mass index, kg/m^2	24.0 ± 2.7	24.6 ± 3.2	0.005
Waist circumference, cm	85.3 ± 7.5	81.8 ± 8.4	< 0.001
Systolic blood pressure, mm Hg	128.0 ± 17.8	130.3 ± 19.8	0.091
Diastolic blood pressure, mm Hg	79.4 ± 12.1	79.5 ± 12.8	0.854
Fasting blood glucose, mg/dL	93.1 ± 9.1	91.5 ± 9.1	0.012
Total cholesterol, mg/dL	197.5 ± 32.8	205.0 ± 36.0	0.003
Triglyceride, mg/dL	169.0 ± 117.7	138.1 ± 99.8	< 0.001
High density lipoprotein-cholesterol, mg/dL	43.6 ± 9.9	50.8 ± 13.4	< 0.001
Aspartate aminotransferase, IU/L	21.6 ± 5.1	20.4 ± 4.6	0.001
Alanine aminotransferase, IU/L	23.4 ± 8.0	18.8 ± 6.8	< 0.001
Anti-hypertensive medications, %	38 (11.7)	71 (16.0)	0.094
Statin, %	7 (2.1)	21 (4.7)	0.078
Non-alcoholic fatty liver disease, %	159 (48.8)	161 (36.3)	0.001

Data are expressed as the mean ± standard deviation or number (%).

Statistical analysis

Data for continuous variables are presented as means ± SDs or SEs and categorical factors are reported as percentages. The significance of differences in measurements among groups was tested using the independent sample *t*-test, chi-Square test, or one-way ANOVA followed by Scheffe's *post-hoc* test, as appropriate. Analysis of covariance was used to adjust for age, systolic blood pressure, triglyceride, HDL-cholesterol, and BMI in multivariate analysis. A P value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics (version 19.0; IBM Co., Somers, NY, USA).

Results

The clinical and biochemical characteristics of the study population are presented in Table 1. The mean age of men was 51.1 years while that of women was 52.4 years. Mean BMI was 24.0 kg/m^2 in men and 24.6 kg/m^2 in women. Despite having an ALT concentration within the reference range, 48.8% of men and 36.3% of women had NAFLD.

Study subjects' characteristics according to quartiles of ALT concentration and the presence of NAFLD within each ALT stratum are shown in Table 2 and 3 after separating the men and women. The prevalence of NAFLD

Table 2 Clinical and biochemical characteristics according to quartile of the alanine aminotransferase concentrations and the presence of non-alcoholic fatty liver disease in men

	ALT Q1 (4-17)		ALT Q2 (18-22)		ALT Q3 (23-28)		ALT Q4 (29-40)	
	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)
N, %	62 (72.9)	23 (27.1)	51 (60.0)	34 (40.0)	34 (45.3)	41 (54.7)	20 (24.7)	61 (75.3)
Age, y	54.0 ± 11.9	55.3 ± 7.1	51.5 ± 10.7	53.0 ± 8.9	46.8 ± 12.7	51.6 ± 12.2	46.9 ± 10.5	48.5 ± 9.6
Body mass index, kg/m^2	22.7 ± 2.5	25.1 ± 2.8	22.9 ± 2.1	24.2 ± 2.4	22.9 ± 2.3	24.5 ± 1.9	24.0 ± 2.8	25.8 ± 2.7
Waist circumference, cm	81.6 ± 7.1	88.3 ± 5.9[a]	81.8 ± 5.7	87.7 ± 6.4[a]	82.3 ± 7.3	86.6 ± 5.9	84.9 ± 7.4	90.5 ± 7.1
Systolic blood pressure, mm Hg	129.6 ± 17.0	124.1 ± 13.1	123.7 ± 15.1	133.4 ± 18.1	123.7 ± 17.0	130.5 ± 18.7	127.3 ± 21.3	129.3 ± 19.8
Diastolic blood pressure, mm Hg	79.6 ± 11.5	78.7 ± 10.6	76.7 ± 10.8	82.8 ± 12.6	77.7 ± 11.5	78.7 ± 11.9	79.0 ± 14.6	81.3 ± 13.3
Fasting glucose, mg/dL	90.6 ± 7.7	98.6 ± 9.1	91.1 ± 7.4	93.4 ± 9.4	90.5 ± 9.0	94.2 ± 10.5	91.3 ± 7.1	96.6 ± 9.6
Total cholesterol, mg/dL	191.1 ± 33.6	195.7 ± 35.1	198.6 ± 30.0	202.8 ± 31.4	186.8 ± 28.6	202.2 ± 32.1	203.7 ± 43.6	201.4 ± 32.2
Triglyceride, mg/dL	113.4 ± 55.1	162.5 ± 60.1	139.4 ± 90.1	204.0 ± 148.0	154.7 ± 65.6	165.5 ± 79.3	198.5 ± 212.8	233.7 ± 146.8
HDL-cholesterol, mg/dL	45.7 ± 10.2	41.5 ± 9.9	44.9 ± 10.8	40.5 ± 7.3	46.1 ± 11.7	44.3 ± 8.7	46.7 ± 9.7	40.3 ± 8.5
Aspartate aminotransferase, IU/L	18.7 ± 3.5	19.3 ± 6.4	20.1 ± 3.2	21.7 ± 3.5	22.6 ± 4.2	21.7 ± 4.8	25.2 ± 5.6	24.9 ± 5.9
Alanine aminotransferase, IU/L	14.0 ± 2.8	15.0 ± 2.1	19.8 ± 1.4	20.6 ± 1.1	25.5 ± 1.9	25.1 ± 1.7	33.8 ± 4.0	34.8 ± 3.8
Anti-hypertensive medications, %	6 (9.7)	2 (8.7)	2 (3.9)	5 (14.7)	1 (2.9)	5 (12.2)	3 (15.0)	14 (23.0)
Statin, %	1 (1.6)	0 (0)	1 (2.0)	1 (2.9)	0 (0)	0 (0)	1 (5.0)	3 (4.9)

ALT, alanine aminotransferase; Q, quartile; NAFLD, non-alcoholic fatty liver disease; HDL, high-density lipoprotein.
ALT represents interquartile range in each stratum. Data are expressed as the mean ± standard deviation or number (%).
[a] *vs*. subjects without NAFLD in same ALT stratum, P < 0.05.

Table 3 Clinical and biochemical characteristics according to quartile of the alanine aminotransferase concentrations and the presence of non-alcoholic fatty liver disease in women

	ALT Q1 (4-14)		ALT Q2 (15-17)		ALT Q3 (18-22)		ALT Q4 (23-40)	
	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)
N, %	96 (78.0)	27 (22.0)	63 (65.6)	33 (34.4)	74 (64.3)	41 (35.7)	49 (45.0)	60 (55.0)
Age, y	49.0 ± 10.7	53.7 ± 7.4	54.1 ± 10.0	52.9 ± 9.7	52.1 ± 8.0	55.4 ± 8.5	52.4 ± 9.4	53.6 ± 9.0
Body mass index, kg/m^2	23.1 ± 2.8	25.7 ± 3.2[a]	24.0 ± 2.6	25.4 ± 3.5	23.6 ± 2.7	26.3 ± 2.9[a]	24.2 ± 2.9	26.7 ± 3.2[a]
Waist circumference, cm	77.3 ± 7.9	86.1 ± 9.4[a]	80.3 ± 6.3	84.9 ± 8.3	79.0 ± 7.2	86.4 ± 6.7[a]	80.7 ± 6.7	88.3 ± 7.5[a]
Systolic blood pressure, mm Hg	124.3 ± 19.3	139.6 ± 18.1	129.1 ± 21.4	131.2 ± 19.5	132.0 ± 20.3	131.6 ± 16.7	127.8 ± 19.6	135.5 ± 18.9
Diastolic blood pressure, mm Hg	75.7 ± 12.1	85.0 ± 12.3	80.0 ± 13.8	81.1 ± 12.6	79.3 ± 13.2	81.0 ± 11.8	79.1 ± 13.5	81.8 ± 11.9
Fasting glucose, mg/dL	91.6 ± 8.8	95.3 ± 10.4	90.3 ± 6.8	93.2 ± 8.9	89.2 ± 8.2	92.2 ± 10.4	90.4 ± 10.4	92.9 ± 9.6
Total cholesterol, mg/dL	189.1 ± 30.9	211.6 ± 45.7	209.6 ± 31.9	216.3 ± 45.6	203.6 ± 33.6	209.9 ± 35.4	205.9 ± 37.0	214.0 ± 32.5
Triglyceride, mg/dL	102.9 ± 51.6	163.5 ± 72.4	117.8 ± 63.5	145.3 ± 61.0	128.5 ± 119.3	187.6 ± 145.5	138.4 ± 117.3	179.2 ± 111.8
HDL-cholesterol, mg/dL	50.7 ± 12.9	42.4 ± 11.0	55.5 ± 13.3	51.5 ± 13.9	53.3 ± 13.0	45.4 ± 12.8	54.7 ± 14.3	47.1 ± 11.3
Aspartate aminotransferase, IU/L	17.8 ± 4.1	17.2 ± 2.5	19.9 ± 2.8	18.7 ± 4.0	21.6 ± 4.8	20.7 ± 4.4	23.7 ± 4.2	23.2 ± 4.6
Alanine aminotransferase, IU/L	11.4 ± 2.3	12.3 ± 2.4	16.1 ± 0.8	16.2 ± 0.7	19.7 ± 1.4	19.9 ± 1.6	27.4 ± 4.6	28.9 ± 5.7
Anti-hypertensive medications, %	7 (7.3)	5 (18.5)	8 (12.7)	3 (9.1)	16 (21.6)	8 (19.5)	11 (22.4)	13 (21.7)
Statin, %	2 (2.1)	1 (3.7)	2 (3.2)	4 (12.1)	4 (5.4)	3 (7.3)	3 (6.1)	2 (3.3)

ALT, alanine aminotransferase; Q, quartile; NAFLD, non-alcoholic fatty liver disease; HDL, high-density lipoprotein.
ALT represents interquartile range in each stratum. Data are expressed as the mean ± standard deviation or number (%).
[a] *vs*. subjects without NAFLD in same ALT stratum, P < 0.05.

Table 4 Mean carotid artery intima-media thickness according to quartile of the alanine aminotransferase concentrations and the presence of non-alcoholic fatty liver disease

	ALT Q1		ALT Q2		ALT Q3		ALT Q4	
	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)	NALFD (-)	NAFLD (+)
Men								
C-IMT before adjustment								
	0.668 ± 0.021	0.735 ± 0.034	0.659 ± 0.023	0.707 ± 0.028	0.635 ± 0.028	0.716 ± 0.026	0.647 ± 0.037	0.708 ± 0.021
C-IMT after adjustment for age, systolic blood pressure, triglyceride, HDL-cholesterol								
	0.638 ± 0.018	0.709 ± 0.029[a]	0.662 ± 0.019	0.684 ± 0.024	0.674 ± 0.024	0.709 ± 0.021	0.686 ± 0.031	0.727 ± 0.018
C-IMT after adjustment for age, systolic blood pressure, triglyceride, HDL-cholesterol + body mass index								
	0.647 ± 0.018	0.699 ± 0.029	0.669 ± 0.019	0.685 ± 0.024	0.682 ± 0.024	0.704 ± 0.021	0.686 ± 0.031	0.713 ± 0.019
Women								
C-IMT before adjustment								
	0.632 ± 0.016	0.633 ± 0.031	0.673 ± 0.020	0.661 ± 0.028	0.671 ± 0.019	0.742 ± 0.025[a]	0.651 ± 0.023	0.737 ± 0.021[a]
C-IMT after adjustment for age, systolic blood pressure, triglyceride, HDL-cholesterol								
	0.660 ± 0.016	0.611 ± 0.029	0.662 ± 0.019	0.656 ± 0.027	0.668 ± 0.017	0.728 ± 0.023[a]	0.643 ± 0.021	0.726 ± 0.019[a]
C-IMT after adjustment for age, systolic blood pressure, triglyceride, HDL-cholesterol + body mass index								
	0.659 ± 0.016	0.611 ± 0.029	0.662 ± 0.019	0.657 ± 0.027	0.668 ± 0.017	0.729 ± 0.024[a]	0.643 ± 0.021	0.727 ± 0.020[a]

ALT, alanine aminotransferase; Q, quartile; NAFLD, non-alcoholic fatty liver disease; C-IMT, mean carotid artery intima-media thickness; HDL, high-density lipoprotein. Data are expressed as the mean ± standard error (mm).
[a] *vs*. subjects without NAFLD in same ALT stratum, $P < 0.05$

increased with increasing quartile of ALT concentration (27.1%, 40.0%, 54.7%, 75.3% in men, *P* for trend < 0.001; 22.0%, 34.4%, 35.7%, 55.0% in women, *P* for trend < 0.001). In the same ALT stratum, subjects with NAFLD tended to have a higher BMI and waist circumference than those without NAFLD, but this was only statistically significant in some quartiles of ALT concentration (BMI: Q1, Q3 and Q4 in women; waist circumference: Q1, Q2 in men; Q1, Q3 and Q4 in women). There were no differences in age, blood pressure, fasting blood glucose, total cholesterol, triglyceride, HDL-cholesterol, AST, ALT levels, and medications between quartiles, regardless of the presence of NAFLD.

C-IMT in the same ALT stratum did not differ according to the presence of NAFLD in women in the lower ALT quartiles (Q1 and Q2). However, in women in the higher quartiles (Q3 and Q4), those with NAFLD had a higher mean C-IMT value than those without NAFLD (0.671±0.019 mm *vs*. 0.742±0.025 mm, *P*=0.023 in Q3; 0.651±0.023 mm *vs*. 0.737±0.021 mm, *P*=0.005 in Q4). These differences remained significant after adjustment for age, systolic blood pressure, triglycerides, and HDL-cholesterol (0.668±0.017 mm *vs*. 0.728±0.023 mm, *P*=0.040 in Q3; 0.643±0.021 mm *vs*. 0.726±0.019 mm, *P*=0.004 in Q4). We obtained the same results when we performed an additional adjustment for BMI (0.668±0.017 mm *vs*. 0.729±0.024 mm, *P*=0.038 in Q3; 0.643±0.021 mm *vs*. 0.727±0.020 mm, *P*=0.004 in Q4). In men, after adjusting for aforementioned factors, subjects with NAFLD tended to have a higher C-IMT value than those without NAFLD in each quartile, but this was not statistically significant (Table 4).

Discussion

Several studies have documented an association between NAFLD and increased risk of cardiovascular morbidity [20-24]. The association between ALT concentration and cardiovascular disease has also been well documented [12, 13, 25]. However, few studies have investigated the relationship between NAFLD and cardiovascular risk in subjects with an ALT level within the reference range. In the present study, despite having an ALT concentration within the upper normal range (18~40 IU/L), women with NAFLD had a higher C-IMT than those without NAFLD. This finding means that women with an upper normal ALT concentration might be susceptible to carotid atherosclerosis if they have NAFLD. Therefore, in women with an ALT concentration ≥ 18 IU/L, NAFLD should be evaluated by liver ultrasound to screen for subjects at high risk for cardiovascular disease.

Although the best diagnostic tool for confirming NAFLD is liver biopsy, the most commonly used tools are ultrasound and measurement of ALT concentration [16]. The higher the ALT level, the higher the risk of NAFLD [26]. In contrast, if patients have an ALT concentration within the reference range, they are consid-

ered not to have liver disease. Consequently, hepatic ultrasound is generally recommended only for those patients with ALT concentrations outside the reference range. However, ALT concentrations within the reference range have been shown to be associated with NAFLD in some studies [27, 28]. A cross-sectional study of 1,346 Japanese subjects reported that ALT cutoff levels for ultrasound-diagnosed NAFLD were 25 U/L for men and 17 U/L for women [28].

In the present study, 65.4% of men and 45.1% of women in the higher ALT concentration quartiles also had ultrasound-diagnosed NAFLD, and the prevalence of NAFLD increased significantly with increasing quartiles of ALT concentration, even though these ALT levels were within the reference range. Therefore, patients with an upper normal ALT level should be evaluated further using techniques such as hepatic ultrasound. Furthermore, the reference range of ALT should be reconsidered.

The association between serum ALT concentration and cardiovascular and metabolic disease is well-established. Some studies have demonstrated that increased ALT, even within the reference range, may be related to increased risk of cardiovascular disease [17, 18, 29]. Accordingly, ALT concentrations currently regarded as within the normal range do not guarantee freedom from NAFLD and cardiovascular and metabolic disease; some authors have therefore suggested lowering the reference range of ALT. In Chinese adolescents (12-18 years), those in the highest ALT stratum within the normal range had more cardiovascular risk factors than those in the lower ALT strata [17]. A previous study by our group showed that ALT concentrations within the reference range were associated with increased C-IMT in healthy adults [18]. However, although serum ALT concentration is considered a marker of NAFLD, it is unclear whether elevated ALT level itself is sufficient to confirm the association between NAFLD and cardiovascular and metabolic disease or whether further evaluations, such as liver ultrasound, are needed. In the present study, we evaluated NAFLD by ultrasound and analyzed differences in C-IMT in the same ALT stratum according to the presence of NAFLD. In higher quartiles (Q3 and Q4), women with NAFLD had a higher C-IMT than those without NAFLD. Because medication history such as anti-hypertensive medications and statin was not different between each ALT stratum, this finding indicates that having an upper normal ALT level might be a risk factor for cardiovascular disease only when NAFLD is simultaneously present. Therefore, subjects with an ALT concentration in the upper normal range should undergo further evaluation for NAFLD and be screened for cardiovascular disease.

The difference in C-IMT in ALT strata according to the presence of NAFLD was significant only in women. One reason for this may be that more men had NAFLD in the higher ALT quartiles than women (54.7% *vs*. 35.7% in Q3, 75.3% *vs*. 55.0% in Q4). Moreover, because men may have less healthy lifestyles and worse metabolic profiles than women, the relationship between NAFLD and C-IMT in men might be weaker than that in women. Meanwhile, several studies demonstrated that women have much lower ALT cutoff value than men [27, 28]. In the present study, because we used same ALT cutoff value in men and women ($\leq$ 40 IU/L), women in the higher quartiles (Q3 and Q4) might have ALT concentration outside of reference range if ALT cutoff value would be redefined according to gender.

Our study had some limitations. First, no causal relationships among ALT concentration, NAFLD, and C-IMT could be established due to the cross-sectional nature of the study. Prospective studies are required to confirm our findings. Second, we did not completely exclude other hepatic diseases such as hepatitis C and autoimmune hepatitis because we did not check routinely for hepatitis C antibody or antinuclear antibody, as the prevalence of hepatitis C and autoimmune hepatitis is very low in the Korean population. The estimated prevalence of anti-HCV among Korean aged 40 years or older from 1995 to 2000 was 1.29% (95% CI, 1.12-1.48) [30]. Furthermore, we excluded alcoholic liver disease based on answers to a simple questionnaire, rather than using an objective index of alcohol intake. Finally, because NAFLD was not confirmed by liver biopsy for medical and ethical reasons, we could not determine whether there was a significant association between carotid atherosclerosis and the severity of liver histology among NAFLD patients. Several studies have demonstrated no difference between sonographically diagnosed and biopsy-confirmed NAFLD for cardiovascular risk factors and C-IMT [31, 32]. However, clarification of this aspect may help to explain the mechanisms underlying the association between NAFLD and increased risk of cardiovascular disease, and may be of clinical importance in planning preventive and therapeutic strategies.

In conclusion, women with an ALT level above the

middle of the reference range had a higher C-IMT value only when they also had ultrasound-diagnosed NAFLD. Therefore, subjects with high within-reference range levels of ALT should undergo further, more direct assessments of NAFLD to facilitate early identification of those subjects at high risk for cardiovascular disease.

Conflict of Interest

The authors declare that they have no conflict of interest.

Disclosure Summary

The authors have no conflicts of interest to disclose.

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