Original Article

Serum alanine aminotransferase concentration as a predictive factor for the development or regression of fatty liver

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Serum alanine aminotransferase (ALT) concentration is the most commonly used marker for hepatocellular injury. We investigated the suitable cutoff value of serum ALT for the diagnosis or prediction of fatty liver. In 1578 Japanese adults (1208 men, 370 women; 35–69 years of age) who visited our center both in 2000 and between April 2007 and March 2008 (2007–2008), serum ALT concentration was an independent predictor of fatty liver in men in 2000 and in both sexes in 2007–2008. A significant increase in the frequency of fatty liver was detected in participants with elevated serum ALT concentrations, and serum levels of ALT in 2000 were associated with fatty liver in 2007–2008 when the cutoff value was set at 30 IU/L in men and 19 IU/L in women. The frequency of fatty liver in 2007–2008 was significantly lower in participants without fatty liver in 2000 whose serum ALT decreased between 2000 and 2007–2008. Our results suggest that serum ALT might be not only an indicator of fatty liver but also a predictor of the regression of fatty liver, and cutoff values of serum ALT of 30 IU/L in men and 19 IU/L in women are suitable for the screening of fatty liver.

***Key Words*: fatty liver, alanine aminotransferase, cutoff value, predictive factor**

Serum alanine aminotransferase (ALT) is a cytosolic enzyme that catalyzes the transfer of an amino group from alanine to ketoglutarate to form pyruvic acid and glutamate, respectively, and is the most commonly used marker for hepatocellular injury.[1,2] Although the absolute amount is less than that of aspartate aminotransferase (AST), a greater proportion is present in the liver compared with heart and skeletal muscles. Therefore, an increase in serum ALT concentration is more specific for liver damage than an increase in AST concentration.[3] In patients with alcoholic and non-alcoholic fatty liver disease (NAFLD), mild to moderate elevation of serum ALT concentration is usually seen.[3,4]

The upper normal limit for serum ALT concentration has usually been set around 40 IU/L, which was defined two decades ago by studying general populations that included covert liver pathological conditions such as chronic hepatitis C and NAFLD.[2] In 2002, Prati *et al.*[1] proposed new ALT upper normal limits for healthy men and women of 30 IU/L and 19 IU/L, respectively, by studying 6835 first-time blood donors who were negative for anti-hepatitis C virus (HCV) antibody and who had no contraindications to donation. Regarding NAFLD, Kunde *et al.*[2] supported this proposition because lowering the cutoff value of serum ALT significantly increased the detection of NAFLD in obese women. Chang *et al.*[5] also reported that increased serum ALT concentration, even below the usual upper normal limit, was an independent predictor of NAFLD in healthy, nondiabetic Korean men. However, the implication of serum ALT concentration in the prediction of development or regression of fatty liver is still unclear.

In the present study, we aimed to investigate whether the usually accepted upper normal limit of serum ALT concentration (around 40 IU/L) or recently proposed cutoff values (30 IU/L for men and 19 IU/L for women)[1] would be suitable as an indicator or predictor of fatty liver in 1578 participants who visited the Health Service Center, Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital, Nagasaki, Japan for a thorough medical examination between January and December 2000, and also re-visited the same center between April 2007 and March 2008.[6,7]

Materials and Methods

Study participants. As reported in our previous publications,[6,7] the participants in the present study were 1578 Japanese adults (1208 men and 370 women; mean age, 54.0 ± 4.7 years; range, 35–69 years) who visited the Health Service Center, Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital, Nagasaki, Japan for a thorough medical examination between January and December 2000 (in 2000), and also re-visited the same center between April 2007 and March 2008 (in 2007–2008). The medical examination was performed for subjects who visited the hospital voluntarily (most of them were employees or family members of employees) to promote public health through the early detection of chronic diseases. According to our inclusion criteria,[6,7] all participants were negative for hepatitis B surface antigen and anti-HCV antibody. They also underwent abdominal ultrasonography (USG) in both 2000 and 2007–2008. This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committees of Siebold University of Nagasaki and Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital. Informed consent was obtained from all participants.

Data collection and measurements. The medical examination was performed between 8:00–11:00 am after overnight fasting. The information obtained from the medical records for the present study included sex, age, height, body weight, history of alcohol intake, systolic blood pressure (SBP), diastolic blood

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pressure (DBP), serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGTP), total cholesterol (T.Chol.), triglyceride (TG), uric acid (UA), fasting blood glucose (FBG), percentage body fat (% fat volume), and liver status by USG in both 2000 and 2007–2008. In 2007–2008, information about the present physical exercise habit and history of medical treatment for hypertension, dyslipidemia, and/or diabetes mellitus was also obtained. Standard biochemical tests including those for liver enzymes were performed on a multichannel autoanalyzer.

Information on the history of alcohol intake, present physical exercise habit, and history of medical treatment for hypertension, dyslipidemia and/or diabetes mellitus was collected by a questionnaire. Different questionnaire formats were used in 2000 and 2007–2008. The history of alcohol intake was divided into two groups in 2000 as follows: non-drinker (never drink or occasionally drink 1–4 times per week) and daily drinker (at least 23 g/day of alcohol intake 5–7 times per week).[6] In 2007–2008, the history of alcohol intake was divided into three groups as follows: never drinker, heavy drinker (at least 70 g/day of alcohol intake more than 5 times per week), and moderate drinker (neither never drinker nor heavy drinker).[7] Regarding the present physical exercise habit, participants marked "yes" if they had a habit of physical exercise such as jogging, walking, or playing tennis, golf, or badminton. Regarding the history of medical treatment for hypertension, dyslipidemia and/or diabetes mellitus, participants marked "yes" if they had received medical treatment for any of the diseases.

The body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). Overweight was defined as a BMI $\geq$25 kg/m^2.[8] The percentage body fat measurement was performed using a bipedal bioimpedance instrument (Body Fat Analyzer TBF-210 and TBF-202; Tanita, Tokyo, Japan). Obesity was defined for Japanese adults as ≥25% body fat for men and ≥30% body fat for women.[6]

Abdominal USG was performed by clinical hepatogastroenterologists or trained technicians without knowledge of the anthropometric and laboratory data. When USG was performed by a trained technician, one hepatogastroenterologist reviewed the stored ultrasonographic images and made the final diagnosis. The diagnosis of fatty liver by USG (Aloka SSD-2000 and Aloka Pro Sound SSD-4000; Aloka, Tokyo) was based on the findings of "bright liver" (increased echogenicity) with "liver-kidney contrast" (increased echo level of the liver compared with the right kidney). "Vascular blurring" (blurring of the hepatic vein) and "deep attenuation" (attenuation of the echo level in the deep region of the liver) were also seen in many cases, but their absence did not exclude the diagnosis of fatty liver.

Because waist circumference and serum levels of high- and low-density lipoprotein (HDL and LDL) cholesterol were not available in our study participants, we defined a "tentative metabolic syndrome" as follows: BMI $\geq$25 kg/m^2 plus at least two of the following three factors: (1) a high serum level of triglyceride (≥150 mg/dL) or receiving specific treatment for triglyceride abnormality; (2) high blood pressure (SBP ≥130 mmHg and/or DBP ≥85 mmHg) or receiving specific treatment for hypertension; (3) high FBG concentration (≥110 mg/dL) or receiving specific treatment for glucose abnormality, as reported previously.[7]

Comparison of serum ALT data between 2000 and 2007–2008. In the comparison of each participant's serum ALT data between 2000 and 2007–2008, "ALT reduction" and "ALT elevation" were defined as "(serum level of ALT in 2007–2008) < (serum level of ALT in 2000)" and "(serum level of ALT in 2007–2008) ≥ (serum level of ALT in 2000)", respectively. "Change in ALT between 2000 and 2007–2008" was calculated as follows: (serum level of ALT in 2007–2008) – (serum level of ALT in 2000).

Statistical analysis. Data were expressed as mean ± standard deviation (SD) or as median (range). Differences between groups were examined for statistical significance using the two-tailed Mann Whitney *U* test, Kruskal-Wallis test followed by Bonferroni's multiple comparison test, chi-square test, or Fisher's exact probability test. Multivariate analysis was performed for variables that were significant in univariate analyses using logistic regression analysis. Correlations were examined by linear regression analysis using the coefficient of correlation. All data analyses were performed using IBM SPSS statistics, version 17.0 (IBM Co., Somers, NY) on a computer with a Windows operating system. A p value less than 0.05 was considered statistically significant.

Results

Clinical and laboratory features of participants in 2000 and 2007–2008. The median interval in thorough medical examinations between 2000 and 2007–2008 was 84.0 months (range, 76–98 months). The mean age of participants in 2000 was similar in men (47.1 ± 4.7 years; range, 34–62 years) and women (45.5 ± 4.6 years; range, 29–58 years), but in 2007–2008, the age was significantly higher in men (54.4 ± 4.7 years; range, 41–69 years) than in women (52.7 ± 4.6 years; range, 35–65 years) (p<0.001). The number and frequency of participants for each clinical and laboratory feature in 2000 and 2007–2008 are shown in Table 1. The frequency of participants with fatty liver in 2007–2008 (31.7%) was significantly higher than that in 2000 (22.7%). Fatty liver was more frequently seen in men than in women in both 2000 (26.2% vs 11.1, p<0.001) and 2007–2008 (35.3% vs 20.0%, p<0.001). The frequencies of participants with BMI excess (≥25 kg/m^2), diastolic hypertension, elevated AST, ALT, GGTP, T.Chol., TG, UA, and FBG levels, and tentative metabolic syndrome in 2007–2008 were also higher than those in 2000.

Body mass index, % fat volume, systolic and diastolic blood pressure, and serum levels of AST, ALT, GGTP, T.Chol, TG, UA, and FBG were higher in participants with fatty liver than in those without fatty liver in both 2000 and 2007–2008. Participants who had "tentative metabolic syndrome" in both 2000 and 2007–2008, and who had received treatment for hypertension, dyslipidemia, and/or diabetes mellitus in 2007–2008 were also more frequently found in the fatty liver group. In contrast, there were no significant difference in age or the proportion of alcohol drinker between the fatty liver and non-fatty liver groups of participants in both 2000 and 2007–2008. Habitual physical exercise was more common in the non-fatty liver group in 2007–2008[7] (data not shown).

Independent predictors of fatty liver in 2000 and 2007–2008 by logistic regression analysis. The logistic regression analysis showed that serum level of ALT was independent predictor of fatty liver in men in 2000 and in both sexes in 2007–2008. Serum levels of FBG and TG, and BMI were independent predictors of fatty liver in both sexes in 2000 and in men in 2007–2008. Additional independent predictors of fatty liver were serum level of UA in men in 2000, tentative metabolic syndrome in women in 2000, and % fat volume in both sexes in 2007–2008 (Table 2).

Serum ALT concentration and frequency of fatty liver. In both 2000 and 2007–2008, the frequencies of fatty liver in men whose serum level of ALT was ≤30 IU/L were significantly lower than those in men whose serum level of ALT was 31–42 IU/L. In 2000, the frequency of fatty liver in men whose serum level of ALT was 31–42 IU/L was also significantly lower than that in men whose serum level of ALT was ≥43 IU/L. However, there was no significant difference in the frequency of fatty liver between men whose serum ALT level was 31–42 IU/L and ≥43 IU/L in 2007–2008. In women, the frequencies of fatty liver whose serum level of ALT was ≤19 IU/L were significantly lower than those in women whose serum level of ALT was 20–42 IU/L, but there were no significant differences in the frequency of fatty liver between women whose serum ALT level was 20–42 IU/L and ≥43 IU/L in

Table 1. Number and frequency of participants for each clinical and laboratory feature in 2000 and 2007–2008 (n = 1578)

Feature	No. of subjects in 2000 (%)	No. of subjects in 2007–2008 (%)	p
Fatty liver by USG	358 (22.7)	501 (31.7)	<0.001
Alcohol consumption			
Non-drinker in 2000	705 (44.7)		
Daily drinker in 2000	873 (55.3)		
Never drinker in 2007–2008		365 (23.1)	
Light to moderate drinker in 2007–2008		1098 (69.6)	
Heavy drinker in 2007–2008		71 (4.5)	
nd		44 (2.8)	
Physical exercise habit			
Yes		536 (34.0)	
No		1031 (65.3)	
nd		11 (0.7)	
BMI $\geq$ 25 kg/m^2	314 (19.9)	414 (26.2)	<0.001
% fat volume excess (men and women)	441 (27.9)	596 (37.8)	<0.001
% fat volume $\geq$ 25% (men)	326 (27.0)	349 (28.9)	0.297
% fat volume $\geq$ 30% (women)	115 (31.1)	128 (34.6)	0.309
SBP $\geq$ 130 mmHg	523 (33.1)	505 (32.0)	0.494
DBP $\geq$ 85 mmHg	395 (25.0)	194 (12.3)	<0.001
AST $\geq$ 34 IU/L	103 (6.5)	145 (9.2)	0.005
ALT $\geq$ 43 IU/L	123 (7.8)	158 (10.0)	0.029
GGTP $\geq$ 48 IU/L	426 (27.0)	558 (35.4)	<0.001
T.Chol. $\geq$ 220 mg/dL	515 (32.6)	637 (40.4)	<0.001
TG $\geq$ 150 mg/dL	335 (21.2)	393 (24.9)	0.014
UA $\geq$ 7.6 mg/dL	104 (6.6)	167 (10.6)	<0.001
FBG $\geq$ 110 mg/dL	142 (9.0)	302 (19.1)	<0.001
Tentative MS	84 (5.3)	164 (10.4)	<0.001
Receiving treatment for HT, DL, and/or DM		430 (27.2)	

USG, ultrasonography; nd, not described; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma-glutamyl transpeptidase; T.Chol., total cholesterol; TG, triglyceride; UA, uric acid; FBG, fasting blood glucose; MS, metabolic syndrome; HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus.

Table 2. Independent predictors of fatty liver by logistic regression analysis

Variables	Regression coefficient	Standard error	p	Adjusted odds ratio	95% CI
In 2000					
Men (n = 1208)					
ALT	0.061	0.010	<0.001	1.062	1.042–1.083
BMI	0.436	0.056	<0.001	1.546	1.386–1.725
FBG	0.030	0.006	<0.001	1.030	1.017–1.043
UA	0.222	0.075	0.003	1.248	1.078–1.445
TG	0.002	0.001	0.017	1.002	1.000–1.004
Women (n = 370)					
BMI	0.779	0.156	<0.001	2.180	1.604–2.961
TG	0.023	0.006	<0.001	1.023	1.011–1.036
Tentative MS	−2.420	0.730	0.001	0.089	0.021–0.372
FBG	0.084	0.029	0.005	1.086	1.026–1.150
In 2007–2008					
Men (n = 1208)					
ALT	0.042	0.009	<0.001	1.042	1.024–1.061
% fat volume	0.099	0.025	<0.001	1.104	1.051–1.161
BMI	0.276	0.050	<0.001	1.317	1.195–1.452
TG	0.002	0.001	0.003	1.002	1.001–1.004
FBG	0.013	0.005	0.004	1.013	1.004–1.023
Women (n = 370)					
ALT	0.111	0.031	<0.001	1.117	1.052–1.187
% fat volume	0.197	0.061	0.001	1.218	1.080–1.374

CI, confidence interval. Refer to the legends of Table 1 for other abbreviations.

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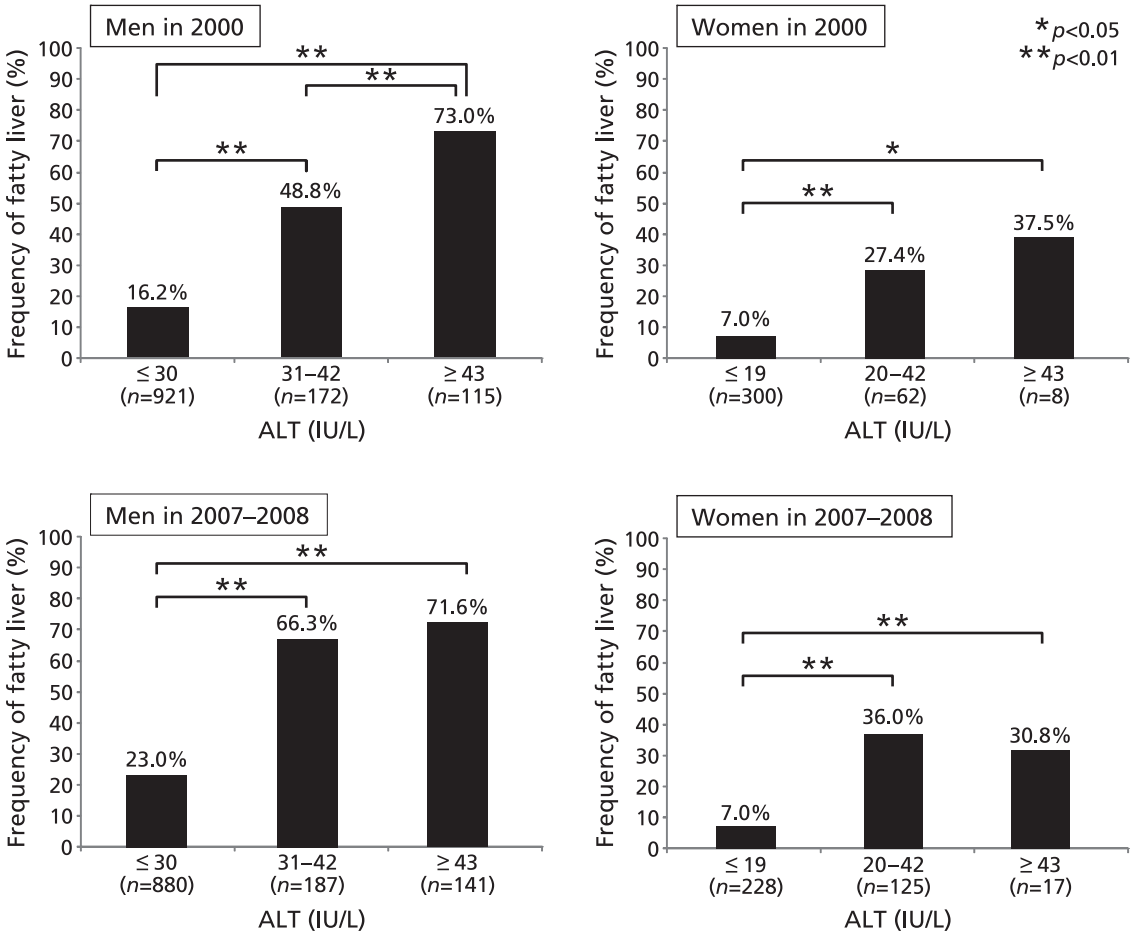

Fig. 1. Serum ALT concentration and frequency of fatty liver. ALT, alanine aminotransferase.

both 2000 and 2007–2008 (Fig. 1).

Serum ALT concentration in 2000 and frequency of fatty liver in 2007–2008. There was no significant difference in the frequency of fatty liver in 2007–2008 between men with fatty liver whose serum ALT level was ≤30 IU/L and ≥31 IU/L, and ≤42 IU/L and ≥43 IU/L in 2000, respectively. Also, there was no significant difference in the frequency of fatty liver in 2007–2008 between women with fatty liver whose serum ALT level was ≤19 IU/L and ≥20 IU/L, and ≤42 IU/L and ≥43 IU/L in 2000, respectively. Moreover, there were no significant differences in the frequency of fatty liver in 2007–2008 between both men and women without fatty liver whose serum ALT level was ≤42 IU/L and ≥43 IU/L in 2000. In contrast, the frequency of fatty liver in 2007–2008 was significantly lower in participants without fatty liver whose serum ALT level in 2000 was ≤30 IU/L in men and ≤19 IU/L in women compared with ≥31 IU/L in men and ≥20 IU/L in women, respectively (Table 3).

ALT reduction or elevation between 2000 and 2007–2008 and frequency of fatty liver in 2007–2008. There were no significant differences in the frequency of fatty liver in 2007–2008 between both men and women with fatty liver whose serum ALT reduced or elevated between 2000 and 2007–2008. However, the frequency of fatty liver in 2007–2008 was significantly lower in both men and women without fatty liver whose serum ALT concentration decreased than in those whose serum ALT concentration increased between 2000 and 2007–2008 (Table 4).

Change in ALT between 2000 and 2007–2008 and frequency of fatty liver in 2007–2008. Change in serum ALT concentration between 2000 and 2007–2008 was correlated with the frequency of fatty liver in 2007–2008, especially in both men and women without fatty liver in 2000. More than 50% of participants without fatty liver in 2000 whose serum ALT concentration increased more than 20 IU/L between 2000 and 2007–2008 were found to have fatty liver in 2007–2008, whereas the frequency of fatty liver in 2007–2008 was up to 20% in participants whose serum ALT concentration decreased more than 10 IU/L during the period in both sexes (Fig. 2).

Discussion

Measurement of serum ALT concentration is used as a primary screening test for the detection of liver diseases.[9] Alanine aminotransferase is a hepatic, glucogenic enzyme that has been reported to be related to visceral fat accumulation,[10] obesity,[11] metabolic syndrome,[9,12,13] and insulin resistance.[14,15] In alcoholic and nonalcoholic fatty liver disease, which is defined as an accumulation of fat (mainly triglyceride) in liver cells, elevated serum ALT concentration is considered to be a consequence of hepatocyte damage.[5] Tiikkainen *et al.*[16] reported that the change in serum ALT concentrations correlated with that in hepatic fat accumulation.

In the present longitudinal study, the frequency of participants with fatty liver in 2007–2008 (31.7%) was significantly higher than that in 2000 (22.7%), and the serum ALT concentration was an independent predictor of fatty liver in men in 2000 and in both sexes in 2007–2008. Kojima *et al.* reported that the prevalence of fatty liver rose gradually from 12.6% in 1989 to 30.3% in 1998;

Table 3. Relation between serum ALT concentration in 2000 and fatty liver in 2007–2008

Serum ALT concentration in 2000	No. of subject in 2007–2008		*p*
	Fatty liver (%)	Non-fatty liver (%)	
Men with fatty liver in 2000			
ALT ≤ 30 IU/L (*n* = 149)	117 (78.5)	32 (21.5)	0.889
ALT ≥ 31 IU/L (*n* = 168)	133 (79.2)	35 (20.8)	
ALT ≤ 42 IU/L (*n* = 233)	181 (77.7)	52 (22.3)	0.391
ALT ≥ 43 IU/L (*n* = 84)	69 (82.1)	15 (17.9)	
Women with fatty liver in 2000			
ALT ≤ 19 IU/L (*n* = 21)	15 (71.4)	6 (28.6)	0.093
ALT ≥ 20 IU/L (*n* = 20)	19 (95.0)	1 (5.0)	
ALT ≤ 42 IU/L (*n* = 35)	28 (80.0)	7 (20.0)	0.350
ALT ≥ 43 IU/L (*n* = 6)	6 (100)	0 (0)	
Men without fatty liver in 2000			
ALT ≤ 30 IU/L (*n* = 722)	139 (18.0)	633 (82.0)	<0.001
ALT ≥ 31 IU/L (*n* = 119)	38 (31.9)	81 (68.1)	
ALT ≤ 42 IU/L (*n* = 860)	169 (19.7)	691 (80.3)	0.399
ALT ≥ 43 IU/L (*n* = 31)	8 (25.8)	23 (74.2)	
Women without fatty liver in 2000			
ALT ≤ 19 IU/L (*n* = 279)	29 (10.7)	250 (89.3)	0.021
ALT ≥ 20 IU/L (*n* = 50)	11 (22.0)	39 (78.0)	
ALT ≤ 42 IU/L (*n* = 315)	37 (11.7)	278 (88.3)	0.392
ALT ≥ 43 IU/L (*n* = 14)	3 (21.4)	11 (78.6)	

ALT, alanine aminotransferase.

Table 4. Relation between ALT reduction or elevation between 2000 and 2007–2008 and frequency of fatty liver in 2007–2008

Change in serum ALT concentration between 2000 and 2007–2008	No. of subject in 2007–2008		*p*
	Fatty liver (%)	Non-fatty liver (%)	
Men with fatty liver in 2000			
ALT reduction (*n* = 169)	127 (75.1)	42 (24.9)	0.083
ALT elevation (*n* = 148)	123 (83.1)	25 (16.9)	
Women with fatty liver in 2000			
ALT reduction (*n* = 12)	8 (66.7)	4 (33.3)	0.165
ALT elevation (*n* = 29)	26 (89.7)	3 (10.3)	
Men without fatty liver in 2000			
ALT reduction (*n* = 381)	56 (14.7)	325 (85.3)	<0.001
ALT elevation (*n* = 510)	121 (23.7)	389 (76.3)	
Women without fatty liver in 2000			
ALT reduction (*n* = 99)	6 (6.1)	93 (93.9)	0.026
ALT elevation (*n* = 230)	34 (14.8)	196 (85.2)	

ALT, alanine aminotransferase.

this was mainly due to an increase in BMI.[17] Hamaguchi *et al.*[18] also reported that metabolic syndrome was a risk factor for the development of NAFLD. Because some metabolism-related factors such as BMI, % fat volume, and serum levels of FBG, TG, and UA were also independent predictors of fatty liver,[7] serum ALT concentration might be closely associated with metabolic syndrome as stated above.

Serum ALT elevation has been used as a surrogate biomarker for NAFLD.[19] Several studies have reported that elevated serum ALT concentration was closely associated with fatty liver even within the usually accepted normal reference interval.[1,2,5] Therefore, we investigated in the present study whether the usually accepted upper normal limit of serum ALT concentration (around 40 IU/L) or recently proposed cutoff values (30 IU/L for men and 19 IU/L for women)[1] would be suitable as an indicator of fatty liver or predictor of the development or regression of fatty liver. As a result, a significant increase in the frequency of fatty liver was detected in participants with elevated serum ALT concentrations when the cutoff value was set at 30 IU/L in men and 19 IU/L in women. We further found that serum ALT concentrations in 2000 were associated with fatty liver in 2007–2008 when the cutoff value was set at 30 IU/L in men and 19 IU/L in women. Moreover, the frequency of fatty liver in 2007–2008 was significantly lower in participants without fatty liver whose serum ALT reduced and the change in serum ALT concentration between 2000 and 2007–2008 was correlated with the frequency of fatty liver in 2007–2008 in a dose-dependent manner, especially in both men and women without fatty liver in 2000. These findings suggest that upper normal serum ALT concentrations of 30 IU/L in men and 19 IU/L in women are suitable for the effective screening of fatty liver and that serum ALT concentration might be not only an indicator of fatty liver, but also a predictor of the regression, rather than the development, of fatty liver.

The mechanism of the above findings is still unclear. Uslan

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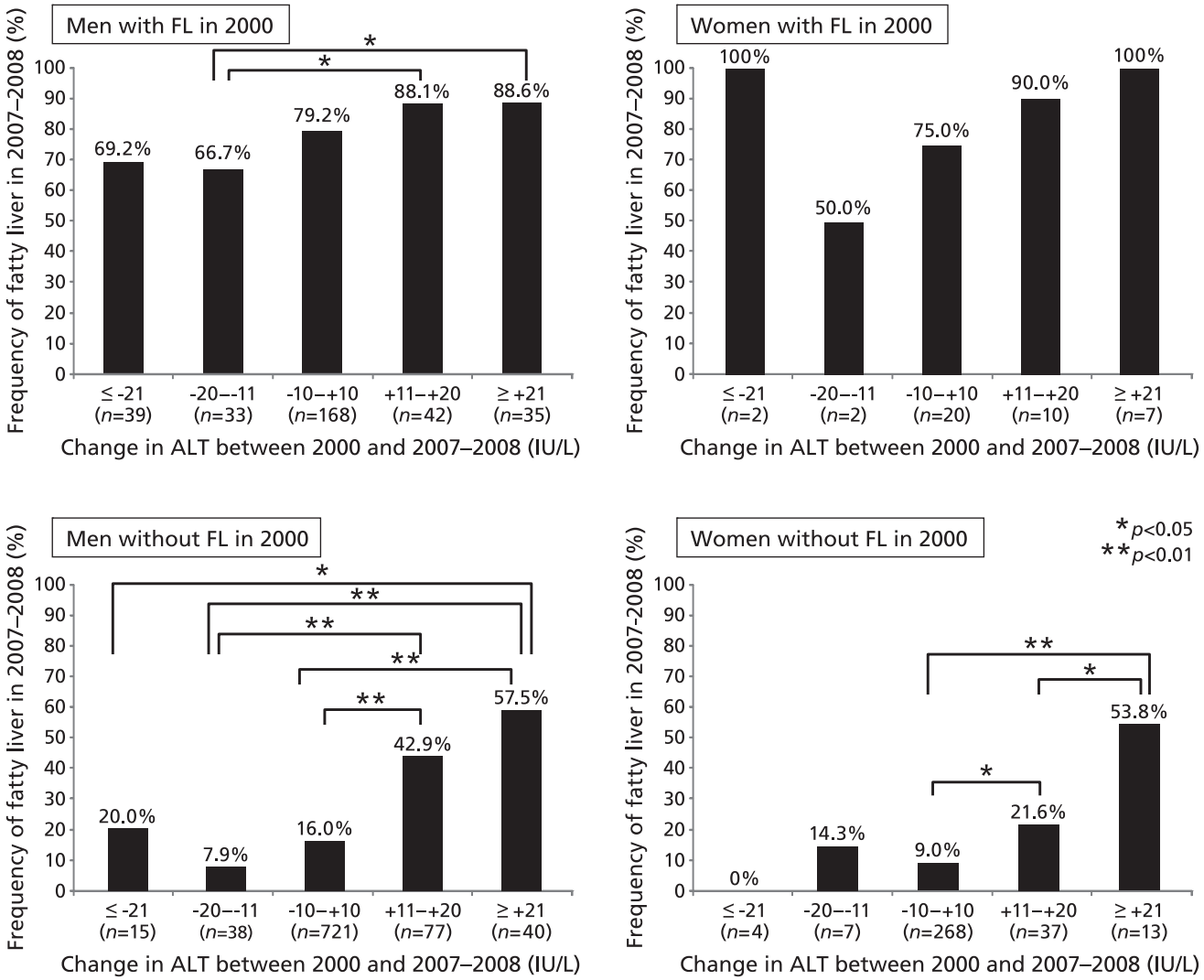

Fig. 2. Change in ALT between 2000 and 2007–2008 and frequency of fatty liver in 2007–2008. ALT, alanine aminotransferase; FL, fatty liver.

et al.[20] reported that weight loss in obese persons whose serum ALT concentrations were within usually accepted normal limit resulted in a decrease in serum ALT concentrations. Saito *et al.*[9] reported that upper normal limits of serum ALT concentration of 30 IU/L in men and 25 IU/L in women were suitable for the effective screening of individuals with metabolic syndrome in Japanese population. Wannamethee *et al.*[21] also reported that elevated serum ALT concentrations still within the normal range were an independent predictor of type 2 diabetes in older men. Oxidative stress plays a pivotal role in the pathogenesis of metabolic syndrome including type 2 diabetes and NAFLD or non-alcoholic steatohepatitis, and serum ALT concentration might be closely associated with metabolic syndrome.[22] Therefore, even a slight elevation of serum ALT concentration might reflect early stage of metabolic syndrome and subclinical, i.e., ultrasonographically undetectable, early hepatic fat accumulation.[5]

There were some limitations to the present study. First, fluctuation of serum ALT concentration is normally seen over the course of the day and ALT levels can also increase in response to strenuous physical exercise. However, we compared the serum ALT concentrations of only two timepoints in 2000 and 2007–2008 and the time-course of ALT concentrations during the follow-up periods was not included. Therefore, fluctuating serum ALT concentration was not considered. Second, liver biopsy, which is the standard to establish a histopathological diagnosis of fatty liver, was not performed. Whether early hepatic fat accumulation is present in patients whose serum ALT concentrations are slightly elevated would be of interest. Third, our criteria of "tentative metabolic syndrome" were different from the generally accepted criteria of metabolic syndrome.[7] A subsequent study should include a detailed evaluation of metabolic syndrome that includes the measurement of waist circumference and serum levels of HDL and LDL cholesterol.

In conclusion, our data demonstrate that serum ALT concentration might be not only an indicator of fatty liver but also a predictor of the regression of fatty liver and that the upper normal limits of serum ALT concentration of 30 IU/L in men and 19 IU/L in women are suitable for the effective screening of fatty liver. Our data might have clinical and public health implications because the measurement of serum ALT concentration is used as a primary screening test for the detection of liver diseases.[9] The exact mechanism of increased serum ALT concentration in fatty liver remained to be determined.

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