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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1067–1075
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Impact of metabolic syndrome on elevated serum alanine aminotransferase levels in the Japanese population

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Received 12 January 2009; accepted 27 March 2009

Abstract

Measurement of the serum alanine aminotransferase (ALT) level is used as an initial test for detection of liver diseases, and recent studies have also highlighted its potential value as a measure of overall health and survival as a marker of an increased risk of metabolic disorder. This study was designed to clarify the prevalence of elevated ALT levels in the Japanese population and to assess factors associated with ALT elevation. The subjects were 2165 individuals aged 40 to 85 years who participated in a Japanese community-based study referred to as the *Takahata Study*. Serum ALT levels and factors associated with ALT elevation were investigated. Among 2087 subjects who were negative for hepatitis B and C, the rates of elevated ALT greater than 30 U/L in men and greater than 25 U/L in women were 217 (22.7%) of 957 and 239 (21.2%) of 1130, respectively. These ALT cutoff levels had a specificity of more than 80% for exclusion of subjects with none or 1 of 3 metabolic risk factors: hypertension, lipid metabolism abnormality, and hyperglycemia. Multivariate analysis revealed 5 factors with a significant association with ALT elevation in men (n = 957): high γ-glutamyltranspeptidase, low adiponectin, high low-density lipoprotein cholesterol, high body mass index, and high homeostasis model assessment insulin resistance index. Similarly, 4 factors were significantly associated with ALT elevation in women (n = 1130): high γ-glutamyltranspeptidase, low adiponectin, high body mass index, and high homeostasis model assessment insulin resistance index. These results suggest that elevated ALT levels in the Japanese population older than 40 years have a strong association with metabolic syndrome–related features including obesity and insulin resistance.

1. Introduction

Metabolic syndrome due to visceral fat obesity and increased insulin resistance has a risk for progression to a broad spectrum of metabolic syndrome–related diseases, including type 2 diabetes mellitus, hypertension, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD) [1,2], as well as to systemic cancer development [3]. There has been a worldwide increase in the number of obese individuals at risk of metabolic syndrome–related diseases, and determination of risk factors for metabolic syndrome is required to prevent further spread of these diseases through proper intervention in the general population.

Elevation of serum alanine aminotransferase (ALT) is a sign of possible underlying liver disease, but an unexplained prevalence of ALT elevation in the general population and a strong association of elevated ALT with NAFLD have also been reported in Western countries [4-8]. In addition, several studies have shown that elevated serum ALT levels have a positive association with metabolic syndrome–related diseases such as type 2 diabetes mellitus [9] and cardiovascular diseases [10]; and several prospective studies suggest that elevated ALT levels predict the development of metabolic syndrome [11,12]. A close relationship between elevated ALT and mortality has also been found in community residents [13]. These reports suggest that the ALT level is a good indicator of overall health, particularly in the context of

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0026-0495/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.03.008

lifestyle-related diseases in association with metabolic syndrome [14]. Thus, measurement of ALT may identify people in the general population with a risk of these diseases. However, to date, there have been few comprehensive studies of elevated ALT in association with many metabolic factors including an insulin-sensitive adipocytokine in a large population sample.

Recently, the number of people having metabolic syndrome has rapidly increased in many countries. In particular, Asian individuals have been observed to have a high prevalence of visceral fat accumulation [15]. To estimate the spread of metabolic risk for the occurrence of metabolic syndrome–related diseases in the population and to define preventive strategies, investigation of the prevalence of elevated ALT and determination of factors associated with elevated ALT are required in a large population sample. Therefore, we conducted a large-scale cross-sectional study of ALT levels and factors associated with elevated ALT in Japanese adult subjects representative of the general population.

2. Materials and methods

2.1. Subjects

This study was performed as a community-based survey and consisted of a self-administered questionnaire on lifestyle, measurement of physical status, and collection of blood samples from participants. The subjects were the general population aged 40 to 85 years in the town of Takahata, which is located in Yamagata Prefecture, approximately 350 km north of Tokyo. From June 2004 to November 2005, 2401 individuals (1055 men and 1346 women) took part in the research program. Of these people, 236 for whom data were incomplete were excluded from further analysis, leaving 2165 subjects (991 men and 1174 women) aged 40 to 85 years. We examined the prevalence of elevated ALT in a large sample population and determined the factors currently associated with elevated ALT in Japan. The study was approved by the institutional ethics committee, and written informed consent was obtained from all subjects.

2.2. Measurements

The subjects used a self-reported questionnaire to document medical history, current medication, family history, and clinical symptoms. The presence of a smoking habit (current smoker, nonsmoker, or past smoker) and alcohol intake (current drinker, nondrinker, or past drinker) were determined through an interview. Systolic and diastolic blood pressures were determined using a mercury manometer in a sitting position after resting for at least 5 minutes. These measurements were performed twice, and the mean was used for statistical analysis. Body mass index (BMI) was calculated from weight (in kilograms) divided by the height squared (in square meters), and *obesity* was defined as BMI of at least 25 kg/m^2. Blood samples were collected in the morning and shipped to a central laboratory to be assayed. Ordinary biochemical tests for serum levels of ALT, albumin, fasting blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, γ-glutamyl transpeptidase (γ-GTP), and cholinesterase were performed. Fasting insulin was measured using a chemiluminescent immunoassay kit (Kyowa Medics, Tokyo, Japan). Insulin resistance was calculated based on the homeostatic metabolic assessment method (HOMA-IR), as follows: HOMA-IR = fasting plasma insulin × fasting plasma glucose/405, where insulin is expressed in microunits per milliliter and glucose in milligrams per deciliter [16]. Insulin resistance was considered to have changed when HOMA-IR was greater than 2, as previously recommended [17]. Adiponectin was measured using an enzyme immunoassay kit (Human Adiponectin ELISA; Otsuka, Tokyo, Japan). Anti–hepatitis C virus (HCV) antibody, hepatitis B surface antigen, and antinuclear antibody were detected with a latex hemagglutination kit (Ortho HCVAb LPIA III; Ortho Clinical Diagnostics, Tokyo, Japan), a chemiluminescent immunoassay kit (Architect HBsAg QT; Abbott, Tokyo, Japan), and an enzyme immunoassay kit (MESACUP ANA Test; MBL, Tokyo, Japan), respectively.

2.3. Metabolic risk factors

According to the National Cholesterol Education Program Adult Treatment Panel III criteria [18] and the Japanese diagnostic criteria for metabolic syndrome published in April 2005 [19], we defined the metabolic risk for the occurrence of metabolic syndrome–related diseases as the presence of 2 or 3 of the following abnormalities: triglycerides of at least 150 mg/dL and/or HDL cholesterol less than 40 mg/dL, systolic blood pressure of at least 130 mm Hg and/or diastolic blood pressure of at least 85 mm Hg, and fasting glucose of at least 110 mg/dL.

2.4. Statistical analysis

Alanine aminotransferase levels were analyzed as the primary data to determine the prevalence of elevated ALT in the subjects. Analysis of the following 17 factors was performed to assess a potential association with elevated ALT levels in 2087 subjects (957 men and 1130 women) who were negative for viral markers for hepatitis B or hepatitis C: age, serum albumin, antinuclear antibody, γ-GTP, cholinesterase, adiponectin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, BMI, fasting glucose, fasting insulin, HOMA-IR, blood pressure, smoking habit, and drinking habit. The relationship of each factor with elevated ALT was assessed by univariate analysis with a χ^2 test or Fisher exact test for categorical variables, Mann-Whitney test for ordinal data, and unpaired t test for continuous variables. The factors of age and univariate predictors with P less than .10 were included in a multiple

Table 1
ALT levels and seroprevalence of viral hepatitis markers in the study population

	Male (n = 991)		Female (n = 1174)		Total (n = 2165)		*P* value	Test[a]
	n	(%)	n	(%)	n	(%)		
Age group								
40-49	93	(9.4)	128	(10.9)	221	(10.2)	.034	M
50-59	220	(22.2)	294	(25.0)	514	(23.7)		
60-69	338	(34.1)	383	(32.6)	721	(33.3)		
70-79	306	(30.9)	338	(28.8)	644	(29.7)		
>80	34	(3.4)	31	(2.6)	65	(3.0)		
Mean ± SD	64.1 ± 10.2		63.0 ± 10.1		63.5 ± 10.1		.011	T
Seroprevalence of hepatitis B and C								
Both negative	957	(96.6)	1130	(96.3)	2087	(96.4)	.217	F
Positive for HCVAb	12	(1.2)	24	(2.0)	36	(1.7)		
Positive for HBsAg	22	(2.2)	19	(1.6)	41	(1.9)		
Both positive	0	(0.0)	1	(0.1)	1	(0.0)		
ALT (U/L)								
Mean ± SD	24.9 ± 13.8		20.8 ± 11.0		22.7 ± 12.5		<.001	T
Median	21		18		19			
Minimum	6		4		4			
Maximum	122		115		122			

M indicates Mann-Whitney test; F, Fisher exact test; T, *t* test; HCVAb, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen.
[a] Comparison of male with female subjects.

logistic regression model to identify factors associated with elevated ALT levels. We estimated 95% confidence intervals (CIs) with maximum likelihood procedure. A backward-elimination procedure was adopted to remove the most insignificant variable in the regression model at each step until the *P* values for the variables that remained in the working model were all less than .10. The appropriateness of the logistic regression models was confirmed by the Hosmer-Lemeshow test. A 2-tailed *P* value less than .05 was considered statistically significant. Analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC) or SPSS version 15.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. ALT levels and seroprevalence of viral hepatitis markers in the study population

The characteristics of the subjects and ALT levels are shown in Table 1. Anti-HCV antibody and hepatitis B

Table 2
Association between the number of metabolic risk factors and ALT levels

No. of risk	Male			Female		
ALT (U/L)	2 or 3 n = 253 Sensitivity	0 or 1 n = 704 Specificity	Accuracy	2 or 3 n = 188 Sensitivity	0 or 1 n = 942 Specificity	Accuracy
≥17	83	28	43	73	42	47
≥18	78	36	47	69	49	53
≥19	72	41	49	63	56	57
≥20	66	47	52	58	62	61
≥21	61	52	54	52	67	64
≥22	56	58	57	48	71	67
≥23	53	62	60	43	75	70
≥24	50	66	62	37	78	72
≥25	46	69	63	34	81	74
≥26	43	72	64	30	84	75
≥27	38	75	65	28	86	76
≥28	36	77	66	25	87	77
≥29	34	79	67	23	88	77
≥30	32	81	68	20	89	78
≥31	29	83	68	19	90	78
≥32	28	85	70	17	92	79
≥33	27	86	70	16	93	80
≥34	26	88	71	15	94	80
≥35	24	88	71	13	94	81
≥36	24	89	72	11	95	81

Table 3
Prevalence of elevated ALT levels in the study population

	ALT ≧30		ALT ≧25				*P* value[a]
	Male (n = 957)		Female (n = 1130)		Total (N = 2087)		
	n	%	n	%	n	%	
Age groups							
40-49	29	31.5	18	14.4	47	21.7	.004
50-59	68	32.2	67	23.4	135	27.2	.032
60-69	72	22.3	94	25.5	166	24.0	.328
70-79	47	15.8	57	17.8	104	16.8	.591
≥80	1	2.9	3	10.0	4	6.3	.333
All ages	217	22.7	239	21.2	456	21.8	.281

[a] Fisher exact test for each age group and age-adjusted Cochran-Mantel-Haenszel χ^2 test for all ages.

surface antigen were positive in 36 (1.7%) and 41 (1.9%) of 2165 subjects, respectively; and 1 subject (1/2165, 0.0005%) was positive for both. The prevalence of anti-HCV antibody and that of hepatitis B surface antigen did not differ between men and women. The mean ALT levels in men and women were (mean ± SD) 24.9 ± 13.8 and 20.8 ± 11.0 U/L, respectively; and ALT was significantly higher in men than in women ($P < .001$).

3.2. Determination of normal ALT levels in subjects with a low potential risk for liver injury

Normal ALT levels were determined in subjects with a low potential risk of liver disease. These subjects met the following criteria: normal BMI, normal LDL cholesterol, and normal triglycerides, as described by van der Poorten et al [20]. Subjects with high systolic blood pressure, excessive alcohol consumption, and hepatitis B and C infection were excluded, as defined by Prati et al [21]. For the 120 men and 215 women in the study population who met these criteria, the mean ALT levels were 20.2 ± 7.4 U/L (median, 19) and 17.5 ± 7.7 U/L (median, 16), respectively; and the level was significantly higher in men than in women ($P < .001$).

3.3. Association between the number of metabolic risk factors and ALT levels

The cutoff values of ALT levels for effective screening for metabolic syndrome were determined based on the association between the number of metabolic risk factors found in 2087 subjects who were negative for viral markers for hepatitis B or C and ALT levels, as shown in Table 2. To determine the cutoff required to identify people with a risk of metabolic syndrome, we defined the *upper limit* of ALT as that required to exclude subjects with none or 1 of the 3 metabolic risk factors (as described above) with a specificity of more than 80%. These cutoff levels were determined to be 30 and 25 U/L for men and women, respectively. Using these proposed upper limits, the sensitivities for identifying subjects with 2 or 3 risk factors were 32% and 34% in men and women, respectively.

3.4. Prevalence of elevated ALT levels in the study population without hepatitis B or C

The rates of elevated ALT higher than the upper limits (30 U/L in men and 25 U/L in women) were 217 (22.7%) of 957 men and 239 (21.2%) of 1130 women. The prevalence of elevated ALT in women increased from 14.4% at 40 to 49 years old to 23.4% at 50 to 59 years old and to 25.5% at 60 to 69 years old, whereas those in men did not vary as much with age, with a similar rate of more than 30% at both 40 to 49 and 50 to 59 years old. The rate of elevated ALT was significantly higher in men than in women in the age groups of 40 to 49 ($P < .01$) and 50 to 59 years ($P < .05$) (Table 3).

3.5. ALT levels in subjects classified by the number of metabolic risk factors

The number of subjects with 2 or 3 of the 3 metabolic risk factors were 441 (21.1%) of 2087 total subjects, 253 (26.4%)

Table 4
ALT levels in subjects classified by the number of metabolic risk factors

	Male			Female		
	0 or 1 risk (n = 704)	2 or 3 risk (n = 253)	*P* value[a]	0 or 1 risk (n = 942)	2 or 3 risk (n = 188)	*P* value[a]
ALT (U/L)						
Mean	23.1	29.2	<.001	20.0	24.1	<.001
SD	11.3	17.9		9.9	13.4	
Median	20	24		18	21	
Minimum	6	9		4	8	
Maximum	116	122		111	115	

[a] *t* test (log-transformed value).

Table 5
Factors associated with elevated ALT levels in male subjects (elevated ALT, ≥30)

	Normal ALT n = 740		Elevated ALT n = 217		Univariate test	*P* value	Multivariate test			
							OR[a]	95% CI		*P* value
	n	(%)	n	(%)				Upper	Lower	
Age group										
40-49	63	(8.5)	29	(13.4)	M	<.001				
50-59	143	(19.3)	68	(31.3)						
60-69	251	(33.9)	72	(33.2)						
≥70	283	(38.2)	48	(22.1)						
Albumin (g/dL)										
Low (<3.7)	2	(.3)	0	(.0)	F	1.000				
Middle (3.7-5.5)	738	(99.7)	217	(100.0)						
High (>5.5)	0	(.0)	0	(.0)						
Antinuclear antibody										
Negative	632	(85.4)	183	(84.3)	C	.696				
Positive	108	(14.6)	34	(15.7)						
γ-GTP (U/L)										
Low (<60)	654	(88.4)	118	(54.4)	C	<.001	1.00			
High (≥60)	86	(11.6)	99	(45.6)			5.57	3.80	8.16	<.001
Cholinesterase (U/L)										
Low (<3500)	26	(3.5)	4	(1.8)	M	.165				
Middle (3500-8000)	707	(95.5)	210	(96.8)						
High (>8000)	7	(.9)	3	(1.4)						
Adiponectin (μg/mL)										
Mean ± SD	8.2 ± 4.2		6.1 ± 3.7		T	<.001	0.93	0.88	0.98	.010
Total cholesterol (mg/dL)										
Low (<150)	51	(6.9)	11	(5.1)	M	.005				
Middle (150-219)	568	(76.8)	152	(70.0)						
High (>219)	121	(16.4)	54	(24.9)						
LDL cholesterol (mg/dL)										
Low (<70)	29	(3.9)	8	(3.7)	M	.015	0.79	0.32	1.95	.612
Middle (70-139)	565	(76.4)	148	(68.2)			1.00			
High (>139)	146	(19.7)	61	(28.1)			1.58	1.06	2.35	.024
HDL cholesterol (mg/dL)										
High (≥40)	667	(90.1)	189	(87.1)	C	.200				
Low (<40)	73	(9.9)	28	(12.9)						
Triglyceride (mg/dL)										
Low (≤149)	618	(83.5)	142	(65.4)	C	<.001				
High (≥150)	122	(16.5)	75	(34.6)						
BMI										
Normal (<25)	554	(74.9)	113	(52.1)	C	<.001	1.00			
Obese (≥25)	186	(25.1)	104	(47.9)			1.85	1.28	2.68	.001
Fasting blood glucose (mg/dL)										
Low (<110)	649	(87.7)	176	(81.1)	C	.013				
High (≥110)	91	(12.3)	41	(18.9)						
Insulin (μU/mL)										
Low (<3)	149	(20.1)	16	(7.4)	M	<.001				
Middle (3-18)	584	(78.9)	194	(89.4)						
High (>18)	7	(.9)	7	(3.2)						
HOMA-IR										
0-1.9	630	(85.1)	138	(63.6)	M	<.001	1.00			
2.0-3.9	94	(12.7)	63	(29.0)			1.93	1.25	2.98	.003
≥4	16	(2.2)	16	(7.4)			2.94	1.26	6.86	.013
Blood pressure										
Normal	189	(25.5)	61	(28.1)	C	.449				
Hypertension	551	(74.5)	156	(71.9)						
Smoking habit										
Never	286	(38.6)	87	(40.1)	C	.469				
Current	250	(33.8)	64	(29.5)						
Former	204	(27.6)	66	(30.4)						
Drinking habit										
Never or former	209	(28.2)	54	(24.9)	C	.333				
Current	531	(71.8)	163	(75.1)						

(*continued on next page*)

Table 5 (*continued*)

	Normal ALT n = 740		Elevated ALT n = 217		Univariate test	*P* value	Multivariate test			
							OR[a]	95% CI		*P* value
	n	(%)	n	(%)				Upper	Lower	
Current medication[b]										
No	719	(97.2)	215	(99.1)	F	.132				
Yes	21	(2.8)	2	(0.9)						

C indicates χ^2 test.

[a] Multiple logistic regression analysis. Age group and the variables with *P* less than .1 on univariate analysis were included in the model.

[b] Current medication for hypertension, lipid metabolism abnormality, and diabetes was excluded.

Table 6
Factors associated with elevated ALT levels in female subjects (elevated ALT, ≥25)

	Normal ALT n = 891		Elevated ALT n = 239		Univariate test	*P* value	Multivariate test			
							OR[a]	95% CI		*P* value
	n	%	n	%				Upper	Lower	
Age group										
40-49	107	(12.0)	18	(7.5)	M	.521	1.00			
50-59	219	(24.6)	67	(28.0)			1.51	0.81	2.81	.196
60-69	274	(30.8)	94	(39.3)			1.71	0.94	3.12	.081
≥70	291	(32.7)	60	(25.1)			1.11	0.59	2.08	.756
Albumin (g/dL)										
Low (<3.7)	0	(.0)	0	(.0)	F					
Middle (3.7-5.5)	891	(100.0)	239	(100.0)						
High (>5.5)	0	(.0)	0	(.0)						
Antinuclear antibody										
Negative	697	(78.2)	191	(79.9)	C	.572				
Positive	194	(21.8)	48	(20.1)						
γ-GTP (U/L)										
Low (<60)	875	(98.2)	198	(82.8)	C	<.001	1.00			
High (≥60)	16	(1.8)	41	(17.2)			11.54	6.12	21.75	<.001
Cholinesterase (U/L)										
Low (<3500)	19	(2.1)	2	(.8)	M	.488				
Middle (3500-8000)	848	(95.2)	231	(96.7)						
High (>8000)	24	(2.7)	6	(2.5)						
Adiponectin (μg/mL)										
Mean ± SD	11.5 ± 5.5		9.5 ± 5.5		T	<.001	0.97	0.93	1.00	.047
Total cholesterol (mg/dL)										
Low (<150)	23	(2.6)	0	(.0)	M	<.001				
Middle (150-219)	597	(67.0)	137	(57.3)						
High (>219)	271	(30.4)	102	(42.7)						
LDL cholesterol (mg/dL)										
Low (<70)	11	(1.2)	2	(.8)	M	<.001				
Middle (70-139)	611	(68.6)	136	(56.9)						
High (>139)	269	(30.2)	101	(42.3)						
HDL cholesterol (mg/dL)										
High (≥40)	857	(96.2)	225	(94.1)	C	.165				
Low (<40)	34	(3.8)	14	(5.9)						
Triglyceride (mg/dL)										
Low (≤149)	794	(89.1)	194	(81.2)	C	.001				
High (≥150)	97	(10.9)	45	(18.8)						
BMI										
Normal (<25)	662	(74.3)	118	(81.2)	C	<.001	1.00			
Obese (≥25)	229	(25.7)	121	(18.8)			2.02	1.43	2.84	<.001
Fasting blood glucose (mg/dL)										
Low (<110)	834	(93.6)	199	(83.3)	C	<.001				
High (≥110)	57	(6.4)	40	(16.7)						
Insulin (μU/mL)										
Low (<3)	84	(9.4)	11	(4.6)	M	.003				
Middle (3-18)	801	(89.9)	222	(92.9)						

Table 6 (*continued*)

	Normal ALT n = 891		Elevated ALT n = 239		Univariate test	*P* value	Multivariate test			
							OR[a]	95% CI		*P* value
	n	%	n	%				Upper	Lower	
High (>18)	6	(.7)	6	(2.5)						
HOMA-IR										
0-1.9	731	(82.0)	130	(54.4)	M	<.001	1.00			
2.0-3.9	148	(16.6)	94	(39.3)			2.44	1.68	3.55	<.001
≥4	12	(1.3)	15	(6.3)			4.93	2.14	11.33	<.001
Blood pressure										
Normal	336	(37.7)	67	(28.0)	C	.006				
Hypertension	555	(62.3)	172	(72.0)						
Smoking habit										
Never	821	(92.1)	221	(92.5)	C	.494				
Current	44	(4.9)	14	(5.9)						
Former	26	(2.9)	4	(1.7)						
Drinking habit										
Never or former	760	(85.3)	210	(87.9)	C	.312				
Current	131	(14.7)	29	(12.1)						
Current medication[b]										
No	879	(98.7)	237	(99.2)	F	.746				
Yes	12	(1.3)	2	(0.8)						

[a] Multiple logistic regression analysis. Age group and the variables with *P* less than .1 on univariate analysis were included in the model.
[b] Current medication for hypertension, lipid metabolism abnormality, and diabetes was excluded.

of 957 men, and 188 (16.6%) of 1130 women. The ALT levels in these subjects were 29.2 ± 17.9 U/L in men and 24.1 ± 13.4 U/L in women; and thus, the mean levels were close to the cutoff values determined in this study. These values were significantly higher than those for subjects who had 0 or 1 metabolic risk factor for both men and women ($P < .001$) (Table 4).

3.6. Factors associated with elevated ALT levels

Factors associated with elevated ALT higher than the upper limits were investigated in 2087 subjects who were negative for anti-HCV antibody and serum hepatitis B surface antigen. The results for 957 men and 1130 women are shown in Tables 5 and 6, respectively. In men, 10 factors with a significant association with elevated ALT were identified in univariate analysis: age group, high γ-GTP, low adiponectin, high total cholesterol, high LDL cholesterol, high triglycerides, high BMI, high fasting glucose, high fasting insulin, and high HOMA-IR. In women, 10 factors associated with elevated ALT were identified in univariate analysis: high γ-GTP, low adiponectin, high total cholesterol, high LDL cholesterol, high triglycerides, high BMI, high fasting glucose, high fasting insulin, high HOMA-IR, and hypertension. A current drinking habit was not associated with elevated ALT in either men or women in univariate analysis. Multivariate logistic regression models were constructed for men and women using variables with low *P* values in univariate analysis. This analysis revealed 5 factors in men (high γ-GTP: odds ratio [OR], 5.57; 95% CI, 3.80-8.16; $P < .001$; low adiponectin: OR, 0.93; 95% CI, 0.88-0.98; $P < .02$; high LDL cholesterol: OR, 1.58; 95% CI, 1.06-2.35; $P < .03$; high BMI: OR, 1.85; 95% CI, 1.28-2.68; $P < .01$; and high HOMA-IR [2.0-3.9]: OR, 1.94; 95% CI, 1.26-2.98; $P < .01$; [≥4]: OR, 2.94; 95% CI, 1.26-6.86; $P < .02$) and 4 factors in women (high γ-GTP: OR, 11.54; 95% CI, 6.12-21.75; $P < .001$; low adiponectin: OR, 0.97; 95% CI, 0.93-1.00; $P < .05$; high BMI: OR, 2.02; 95% CI, 1.43-2.84; $P < .001$; and high HOMA-IR [2-3.9]: OR, 2.44; 95% CI, 1.68-3.55; $P < .001$; [≥4]: OR, 4.93; 95% CI, 2.14-11.33; $P < .001$) with a significant association with elevated ALT levels.

4. Discussion

Elevated serum ALT levels in the general population are closely associated with NAFLD, which is a liver phenotype of metabolic syndrome [4-8]. Alanine aminotransferase activities have also been shown to be useful as an indicator of general health [14], and ALT is a predictor of mortality in community residents [13]. Mortality may be due to unrecognized liver diseases, but may also be due to other causes of ALT elevation, such as atherosclerosis, hypertension, and type 2 diabetes mellitus, which are linked to nonliver health risks. This suggests the importance of determining the association of ALT levels with metabolic factors influencing the occurrence of metabolic syndrome–related diseases in a large population sample. Our results clearly indicate that elevated ALT levels unrelated to hepatitis virus infection are closely associated with metabolic syndrome–related features in a study population that is representative of the general Japanese population older than 40 years old. This suggests that measurement of ALT levels is likely to be a useful primary screening test for metabolic syndrome in the population.

In this study, the seroprevalences of hepatitis B and C were 1.7% and 1.9%, respectively, similar to the standard rates in the Japanese population [22]. Because hepatitis B and C infection is associated with elevated ALT levels, subjects positive for hepatitis markers were excluded from further analysis. To date, the upper limits of ALT levels in screening tests for the general population have not been established clearly; and therefore, we reevaluated these limits for effective screening of metabolic syndrome in the Japanese adult population. Previous reports have shown that sex has a significant influence on ALT levels [23,24]; and therefore, we assessed ALT levels separately for men and women. The ALT cutoff levels for effective screening of individuals with metabolic syndrome for men and for women were proposed in this study on the basis of the relationship between ALT levels and the number of the 3 major metabolic risk factors. Upper limits of 30 U/L in men and 25 U/L in women gave a good specificity of more than 80% for exclusion of subjects with none or 1 of the 3 metabolic risk factors: hypertension, lipid metabolism abnormality, and hyperglycemia. Using these cutoff values, we demonstrated that approximately 20% of the male and female subjects older than 40 years had ALT elevation. A current drinking habit was identified in 694 (72.5%) of 957 men and 160 (14.3%) of 1130 women, but a drinking habit itself was not significantly associated with elevated ALT in univariate analyses in this population, although there is no doubt that excess intake of alcohol causes liver injury in each individual. Multivariate analysis clearly showed that metabolic syndrome–related features that reflect obesity and insulin resistance, including high BMI, high LDL cholesterol, high HOMA-IR, and lower adiponectinemia, were associated with elevated ALT in the study population.

Elevated serum γ-GTP also showed a significant association with elevated ALT in both male and female subjects. These results were replicable in subjects without a history of alcohol consumption (data not shown). Previous studies have documented that elevated serum γ-GTP has a risk for metabolic syndrome and type 2 diabetes mellitus in middle-aged Japanese male office workers [25] and may represent an early marker of subclinical inflammation and increased oxidative stress in healthy individuals [26,27]. Our results are consistent with these studies, and we also found that elevated γ-GTP was associated with obesity and insulin resistance in both men and women. Therefore, γ-GTP is a promising marker for metabolic syndrome and particularly for prediction of development of metabolic syndrome–related diseases; and this warrants a further prospective study.

Because high serum ALT levels often reflect hepatic fat accumulation and inflammation, they are well correlated with the prevalence of NAFLD in the population in cases of unexplained ALT elevation. The importance of ALT activity as an indicator of NAFLD has been demonstrated in association with metabolic abnormalities caused by central obesity and insulin resistance [28-30]. Nonalcoholic fatty liver disease is classified into 2 categories: simple fatty liver and nonalcoholic steatohepatitis (NASH), which is intractable and progressive. The population with elevated ALT levels includes those with NASH [7,8,31] as a phenotype of metabolic syndrome in the liver. Fat droplets in liver tissue are often depleted in the advanced stage of NASH, and such cases may be diagnosed as cryptogenic liver cirrhosis or liver cancer [32]. In fact, the prevalence of obesity, hypertriglyceridemia, or type 2 diabetes mellitus is significantly higher in cases of liver cancer that develop from cryptogenic cirrhosis compared with those caused by HCV infection or excess intake of alcohol [33]. Because a cohort study showed prospectively that individuals with NAFLD had a higher mortality due to liver disease–related deaths [34], people in the general population with high ALT levels are of particular concern because those with NASH have a risk for progression to cirrhosis or cancer.

Individuals with minor elevation of serum ALT levels that are close to the upper limits of the reference range are also of concern because elevated ALT itself is closely associated with insulin resistance, even in the absence of NAFLD and obesity [35,36]. Recent studies have shown that elevated ALT could be a prognostic marker for development of metabolic syndrome [11,12]. Because individuals with ALT elevation have a potential risk for development of various metabolic syndrome–related diseases, including type 2 diabetes mellitus [9], cardiovascular disease [10], atherothrombosis [37], and obstructive sleep apnea [38], it may be worthwhile to notify those with minor ALT elevation of the risk of such diseases. In fact, in this study, we found that mean ALT activities in subjects with 2 or 3 metabolic risk factors were not particularly high, tending only to be close to the upper limit. Thus, minor ALT elevation is also an important feature for effective screening of metabolic syndrome. Elevation of ALT beyond the cutoff levels determined in this study was strongly associated with a broad spectrum of metabolic syndrome–related features, including obesity and insulin resistance. A prospective study of the association between elevated ALT levels and the occurrence of metabolic syndrome–related diseases is now in progress in this Takahata cohort, which includes more than 4000 people and is representative of the Japanese adult population.

In conclusion, the results of this study clearly show that elevated ALT levels in the Japanese population older than 40 years are associated with obesity and insulin resistance, which in turn are associated with metabolic syndrome. This suggests that, in addition to detection of liver disease, screening of serum ALT levels may contribute to identifying the potential risk of metabolic syndrome–related diseases in the general population.

Acknowledgment

This study was supported by a Grant-in-Aid from the Center of Excellence program of the Japan Society for the Promotion of Science.

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