Prevalence of Metabolic Syndrome Increases with the Increase in Blood Levels of Gamma Glutamyltransferase and Alanine Aminotransferase in Japanese Men and Women

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Abstract

Background Gamma glutamyltransferase (GGT) or alanine aminotransferase (ALT) is reported to be an independent risk factor of diabetes and cardiovascular disease and proposed as a component of metabolic syndrome (MS). However, there are few studies examining the direct association between MS and GGT or ALT in Japanese men and women.

Methods Direct associations between GGT or ALT and MS defined by revised NCEP criteria for Japanese and between GGT or ALT and Japanese MS (JMS) defined by the Examination Committee for the Criteria of Metabolic Syndrome were examined using medical check-up data from 1,880 men and 1,079 women.

Results The prevalence of MS and JMS was significantly higher in subjects with the highest quartile of GGT or ALT than the subjects with the lowest quartile of GGT or ALT ($p < 0.0001$ in men and $p < 0.0001$ for MS and $p < 0.001$ for JMS in women). The optimal cutoff points of GGT and ALT for diagnosing MS or JMS were 42 U/L or 41 U/L, respectively for GGT and both 25 U/L for ALT in men and 21 U/L or 23 U/L, respectively for GGT and 20 U/L or 25 U/L, respectively for ALT in women.

Conclusion The prevalence of MS and JMS increases with the increase in blood levels of GGT or ALT even through the normal range of GGT or ALT in Japanese men and women.

Key words: metabolic syndrome, gamma glutamyltransferase, alanine aminotransferase, fatty liver

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Introduction

Fatty liver is proposed to be a novel component of metabolic syndrome (MS) (1) and nonalcoholic fatty liver disease is reported to be more tightly associated with insulin resistance and with markers of oxidative stress and endothelial dysfunction than MS in nonobese nondiabetic subjects (2). Gamma glutamyltransferase (GGT), a marker of fatty liver disease and alcohol consumption, is reported as an independent risk factor of MS (3-5), diabetes (3, 4, 6) and cardiovascular disease (7, 8) and proposed as a component of MS (4). Alanine aminotransferase (ALT), another marker of fatty liver, was also reported as an independent risk factor of

MS (9), diabetes (9), and cardiovascular disease (10). However, there are few studies examining the direct association between MS and GGT or ALT in Japanese. We examined the direct association between GGT or ALT and MS defined by revised National Cholesterol Education Program (NCEP) criteria (11) for Japanese (12) and Japanese MS (JMS) defined by the Examination Committee for Criteria of Metabolic Syndrome (13) in Japanese men and women.

Methods

Subjects

Between April 1 and November 30 in 2008, 1,928 men

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and 1,113 women visited our medical check-up center for “Ningen Dock”, one of our medical check-up programs. Visitors were all required to fill out a questionnaire made by Ministry of Health, Labor, and Welfare for the purpose of “Special Health Examination and Instruction” including questions about the history of stroke, ischemic heart disease, chronic renal failure, smoking status, antihypertensive, antidiabetic, and antihyperlipidemic medication, and alcohol consumption. Among the total subjects, 9 men and 13 women without signed consent, 10 men and 10 women lacking respiratory function data, 3 men and a woman lacking body fat % (BF%) data, a man and a woman lacking renal function data, and 25 men and 9 women with high-sensitivity C-reactive protein (hs-CRP) levels higher than 10 mg/L were excluded from the present study, resulting in 1,880 men and 1,079 women. The protocol for the present study was approved by the ethics committee of Tachikawa Medical Center and signed informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were obtained to measure blood levels of routine medical check-up tests: glucose, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c, uric acid, blood cell counts, electrolytes, liver and kidney function tests including GGT, ALT, creatinine, and hs-CRP. Simple qualitative urinalyses were performed with test papers. Chemical measurements were all performed at BML Nagaoka (Nagaoka, Niigata, Japan) except for hs-CRP which was measured at BML General Laboratory (Tokyo, Japan) with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and the value of hs-CRP less than the measurement limit was considered as 0.01 mg/L. Respiratory function tests were performed with Autospirometer System 7 (Minato Medical Science, Osaka, Japan). Estimated glomerular filtration rate (eGFR) was calculated as $eGFR (mL/min/1.73 m^2) = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ in men, and $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ in women according to the Japanese Society of Nephrology. Body fat % was measured with bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated from two measurements with the subjects in a sitting position after 5 min rest. Heart rate was automatically recorded with electrocardiograms. Body weight was measured with the subjects wearing light clothes provided by our center and the weight of the clothes was subtracted from the measured body weight. Waist circumference was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Statistical analysis

MS was defined by revised NCEP criteria (11) as three or

more of five components where the cut-off point of waist circumference was modified for Japanese as $90 \geq$ cm in men and ≥ 80 cm in women according to the recommendation by International Diabetes Federation (IDF) (12). The cut-off points of the other components were systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg for blood pressure, ≥ 150 mg/dL for triglyceride, < 40 mg/dL in men and < 50 mg/dL in women for HDL cholesterol, and ≥ 100 mg/dL for fasting glucose. Subjects receiving antihypertensive or antidiabetic medication were considered to have the respective component. JMS defined by the Examination Committee for Criteria of Metabolic Syndrome (13) was also examined. The criteria of JMS is visceral adipose tissue area ≥ 100 cm² or waist circumference ≥ 85 in men and ≥ 90 in women, and 2 or more of the following 3 components; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg for blood pressure, triglycerides ≥ 150 mg/dL and/or HDL cholesterol < 40 mg/dL, and fasting glucose ≥ 110 mg/dL. Diabetes was defined as fasting glucose ≥ 126 mg/dL and/or with antidiabetic medication. Blood levels of MS-related risk factors, and heart rate were compared between MS and non-MS subjects and the prevalence of diabetes, MS, and JMS, and blood levels of MS-related risk factors, and heart rate were compared by the quartile of GGT. The prevalence of MS, JMS, and diabetes was also compared by the quartile of ALT. The prevalence of diabetes, MS, and JMS by the quartile of GGT or ALT was reexamined in everyday drinkers and in subjects excluding everyday drinkers separately. Area under curve (AUC) and optimal cut-off points of GGT and ALT as optional components of MS or JMS were obtained using receiver operating characteristic curves with Dr SPSS-2. Partial correlation coefficients between GGT or ALT and MS-related risk factors controlling for age and excluding subjects with antihypertensive, antidiabetic, or antihyperlipidemic medication were calculated with Dr SPSS-2. The results are presented as mean $\pm$ SEM. Statistical differences between the means of various groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's test. Data were considered statistically significant at *p* values of less than 0.05.

Results

Basal data are shown in Table 1 and Table 2. BMI, body fat %, waist circumference, SBP, DBP, fasting glucose, triglycerides, hs-CRP, GGT, ALT, LDL cholesterol, uric acid, white blood cell count, and heart rate were significantly higher and HDL cholesterol was significantly lower in MS subjects than in non-MS subjects. The prevalence of diabetes and current smoker was significantly higher in MS subjects than in non-MS subjects among men ($p < 0.0001$ and $p < 0.01$, respectively). The prevalence of diabetes was significantly higher in MS subjects than in non-MS subjects among women ($p < 0.0001$). The diagnostic agreement between MS and JMS (MS and JMS/MS or JMS) was 57% in men and 26% in women. Table 3 and Table 4 show data by

Table 1. Basal Data according to MS or Non-MS in Men

n	MS		non-MS		p
	277	1603	mean	SD	
age years	52.9	8.5	50.9	9.2	<0.001
body mass index kg/m ²	26.7	3.0	22.7	2.6	<0.0001
body fat %	27.4	4.6	21.2	4.6	<0.0001
waist circumference cm	94.3	6.7	82.6	7.2	<0.0001
systolic blood pressure mmHg	134.6	16.0	120.1	16.6	<0.0001
diastolic blood pressure mmHg	84.6	10.2	76.4	10.2	<0.0001
fasting glucose mg/dL	108.3	21.5	93.8	12.4	<0.0001
triglycerides mg/dL	198.8 (171)	122.4	108.0 (95)	61.1	<0.0001
HDL cholesterol mg/dL	47.5	10.5	59.3	14.2	<0.0001
hs-CRP mg/L	1.17 (0.62)	1.45	0.54 (0.28)	0.91	<0.0001
GGT U/L	73.2 (53)	65.0	47.8 (33)	47.9	<0.0001
ALT U/L	37.8 (31)	23.7	24.9 (21)	16.0	<0.0001
LDL cholesterol mg/dL	126.3	30.1	119.2	28.5	<0.001
uric acid mg/dL	6.6	1.4	6.1	1.3	<0.0001
white blood cell count /L ⁻⁶	6209	1529	5451	1444	<0.0001
heart rate /min	63.4	9.6	58.7	8.8	<0.0001
	n	%	n	%	
JMS	190	68.6	55	3.4	<0.0001
diabetes	48	17.3	62	3.9	<0.0001
current smoker	113	40.8	518	32.3	<0.01
antihypertensive medication	103	37.2	243	15.2	<0.0001
antidiabetic medication	31	11.2	39	2.4	<0.0001
antihyperlipidemic medication	38	13.7	127	7.9	<0.01
stroke	6	2.2	21	1.3	ns
ischemic heart disease	21	7.6	58	3.6	<0.01
chronic renal failure	2	0.7	1	0.1	<0.05

MS: metabolic syndrome defined by revised NCEP criteria for Japanese, HDL: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, GGT: gamma glutamyltransferase, ALT: alanine aminotransferase, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate ($194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ in men, and $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ in women), JMS: Japanese metabolic syndrome defined by the Examination Committee for Criteria of Metabolic Syndrome. Values in ( ) show medians.

the quartile of GGT. MS-related risk factors other than HDL cholesterol and LDL cholesterol in men were significantly different between the lowest quartile and the highest quartile of GGT. The prevalence of MS and JMS was significantly higher in the highest quartile than in the lowest quartile of GGT and the trend was linear through the quartiles of GGT as shown in Fig. 1A. The results were similar both in everyday drinkers and in subjects excluding everyday drinkers though the differences were not significant in female everyday drinkers due to the inadequate number of subjects (data not shown). Table 5 shows the prevalence of diabetes, MS, and JMS by the quartile of ALT. The prevalence of MS and JMS was significantly higher in the highest quartile than in the lowest quartile of ALT and the trend was linear through the quartiles of ALT as shown in Fig. 1B. The results were similar both in everyday drinkers and in subjects excluding everyday drinkers though the differences were not significant in female everyday drinkers due to the inadequate num-

ber of subjects (data not shown). AUC and optimal cut-off points of GGT and ALT as optional components of MS or JMS are shown in Table 6. The optimal cut-off point of GGT as an optional component of MS or JMS was 42 U/L or 41 U/L, respectively in men and 21 U/L or 23 U/L, respectively in women. The optimal cut-off point of ALT as an optional component of MS or JMS was both 25 U/L in men and 20 U/L or 25 U/L, respectively in women. Partial correlation coefficients between GGT or ALT and MS-related risk factors controlling for age and excluding subjects with antihypertensive, antidiabetic, or antihyperlipidemic medication are presented in Table 7. All MS-related risk factors other than HDL cholesterol and LDL cholesterol in men and HDL cholesterol and heart rate in women were significantly correlated with GGT. All MS-related risk factors were significantly correlated with ALT.

Table 2. Basal Data according to MS or Non-MS in Women

n	MS		non-MS		p
	76		1003		
	mean	SD	mean	SD	
age years	57.1	9.7	50.4	9.4	<0.0001
body mass index kg/m ²	25.7	3.3	21.3	2.8	<0.0001
body fat %	33.8	5.6	26.0	5.5	<0.0001
waist circumference cm	89.8	7.4	77.9	8.0	<0.0001
systolic blood pressure mmHg	130.2	19.8	110.1	15.6	<0.0001
diastolic blood pressure mmHg	80.5	11.7	68.9	9.6	<0.0001
fasting glucose mg/dL	104.5	21.3	88.0	8.4	<0.0001
triglycerides mg/dL	144.8 (125)	71.7	79.0 (70)	43.5	<0.0001
HDL cholesterol mg/dL	51.5	11.6	68.3	14.0	<0.0001
hs-CRP mg/L	0.77 (0.54)	0.83	0.41 (0.20)	0.68	<0.0001
GGT U/L	36.3 (26.5)	31.0	21.6 (17)	17.4	<0.0001
ALT U/L	26.2 (23)	14.9	16.7 (15)	8.3	<0.0001
LDL cholesterol mg/dL	140.2	27.5	119.3	28.3	<0.0001
uric acid mg/dL	5.3	1.1	4.4	0.9	<0.0001
white blood cell count /L ⁶	5418	1064	4788	1245	<0.0001
heart rate /min	63.8	9.9	60.4	8.0	<0.001
	n	%	n	%	
JMS	20	26.3	1	0.1	<0.0001
diabetes	11	14.5	6	0.6	<0.0001
current smoker	4	5.3	62	6.2	ns
antihypertensive medication	36	47.4	60	6.0	<0.0001
antidiabetic medication	9	11.8	4	0.4	<0.0001
antihyperlipidemic medication	18	23.7	89	8.9	<0.0001
stroke	1	1.3	14	1.4	ns
ischemic heart disease	3	3.9	13	1.3	ns
chronic renal failure	0	0.0	2	0.2	ns

Abbreviations and ( ) are the same as Table 1.

Table 3. Data by the Quartile of Gamma Glutamyltransferase (GGT) in Men

GGT range (U/L) n	Q1 7 - 24 (19.5) 455		Q2 25 - 35 (30) 455		Q3 36 - 58 (44) 455		Q4 59 - 802 (91) 455	
	mean	SD	mean	SD	mean	SD	mean	SD
age (years)	51.1	10.1	51.0	9.4	51.5	8.5	51.2	8.0
body mass index (kg/m ²)	21.9	2.4	22.9***	2.7	23.9****	3.2	24.1****	3.0
body fat (%)	19.2	4.1	21.6***	4.6	23.0****	4.9	24.3****†††	5.1
waist circumference (cm)	80.3	7.1	83.2***	7.7	86.3****	8.4	87.1****	7.8
systolic blood pressure (mmHg)	115.1	15.4	120.3***	16.5	125.3****	17.7	127.1****	16.6
diastolic blood pressure (mmHg)	73.1	9.3	76.4***	10.2	79.4****	10.8	81.3****†	10.1
fasting glucose (mg/dL)	91.8	11.6	94.5*	12.2	96.75***	14.4	100.6****	18.9
triglycerides (mg/dL)	89.4 (79)	51.4	109.7*** (96)	65.6	126.6**** (112)	72.0	157.0****††† (132)	104.3
HDL cholesterol (mg/dL)	59.0	14.3	57.3	13.3	57.0	14.9	57.5	14.9
hs-CRP (mg/L)	0.41 (0.22)	0.80	0.52 (0.28)	0.83	0.73*** (0.39)	1.12	0.84**** (0.43)	1.26
ALT (U/L)	18.3 (17)	6.7	22.4*** (20)	9.4	27.8**** (25)	13.5	38.7****††† (31)	24.0
LDL cholesterol (mg/dL)	115.7	26.4	119.7	27.3	124.6***	28.7	119.5	31.9
uric acid (mg/dL)	5.7	1.1	6.0**	1.1	6.2***	1.2	6.6****†††	1.3
white blood cell (/L ⁻⁶)	5253	1440	5439	1419	5716***	1498	5805****	1493
heart rate (/min)	57.4	9.0	58.7*	8.2	60.1***	9.0	61.4****	9.1
MS (%)	4.3		10.5*		18.4****		26.1****††	
JMS (%)	4.1		9.2		15.3***		24.0****†††	
diabetes (%)	4.1		5.5		6.1		7.8	

*, **, ***, indicate p < 0.05, < 0.01 and < 0.001 respectively comparing with Q1, ****, p < 0.05, < 0.01 and < 0.001 respectively comparing with Q2, †, ††, †††, p < 0.05, < 0.01 and < 0.001 respectively comparing with Q3. Abbreviations and ( ) are the same as Table 1.

Table 4. Data by the Quartile of Gamma Glutamyltransferase (GGT) in Women

GGT range (U/L) n	Q1		Q2		Q3		Q4	
	6 - 13 (12)		14 - 17 (15)		18 - 24 (20)		25 - 267 (35)	
	249		249		249		249	
	mean	SD	mean	SD	mean	SD	mean	SD
age (years)	47.4	9.8	50.7 ^{**}	9.4	52.5 ^{***}	9.6	53.2 ^{***†}	8.4
body mass index (kg/m ²)	20.7	2.3	21.3	2.9	21.8 ^{***}	3.2	22.6 ^{***##†}	3.3
body fat (%)	24.5	4.4	26.0 [*]	5.5	27.0 ^{***}	6.4	28.6 ^{***##††}	6.0
waist circumference (cm)	75.5	6.9	77.4	8.0	79.8 ^{***#}	9.0	81.9 ^{***##†}	8.8
systolic blood pressure (mmHg)	107.2	15.2	110.9	15.9	111.2 [*]	15.6	116.7 ^{***##††}	18.8
diastolic blood pressure (mmHg)	67.0	9.2	69.2	9.6	69.3	9.5	73.0 ^{***##†††}	11.3
fasting glucose (mg/dL)	85.6	6.9	88.9 ^{**}	8.6	89.0 ^{**}	10.1	93.0 ^{***##†††}	14.7
triglycerides (mg/dL)	69.8 (62)	31.2	75.0 (67)	32.1	83.0 ^{**} (74)	39.5	103.4 ^{***##†††(93)}	72.6
HDL cholesterol (mg/dL)	68.1	12.7	68.3	14.8	67.4	16.0	65.0 [#]	13.9
hs-CRP (mg/L)	0.26 (0.13)	0.49	0.38 (0.20)	0.59	0.46 ^{**} (0.23)	0.77	0.65 ^{***##††} (0.35)	0.84
ALT (U/L)	13.0 (13)	3.4	15.1 ^{**} (14)	4.8	17.1 ^{***} (16)	6.3	23.6 ^{***##†††(21)}	12.2
LDL cholesterol (mg/dL)	113.6	26.9	119.6	30.0	122.0 ^{**}	27.5	122.0 [*]	27.5
uric acid (mg/dL)	4.0	0.7	4.3 ^{**}	0.8	4.6 ^{***}	0.9	4.8 ^{***##}	0.98
white blood cell (/L ⁻⁶)	4621	1191	4752	1201	4904	1270	5009 ^{**}	1266
heart rate (/min)	59.7	7.4	60.3	7.9	60.7	8.4	61.7 [*]	8.6
MS (%)	0.4		4.4		6.0		16.4 ^{***##†††}	
JMS (%)	0.0		1.6		0.8		5.2 ^{***††}	
diabetes (%)	0.8		1.2		0.8		3.2	

^{*}, ^{**}, ^{***}, indicate p < 0.05, < 0.01 and < 0.001 respectively comparing with Q1, [#], ^{##}, ^{###}, p < 0.05, < 0.01 and < 0.001 respectively comparing with Q2, [†], ^{††}, ^{†††}, p < 0.05, < 0.01 and < 0.001 respectively comparing with Q3. Abbreviations and ( ) are the same as Table 1.

Figure 1. Prevalence of metabolic syndrome (MS) defined by revised NCEP criteria for Japanese and Japanese metabolic syndrome (JMS) defined by the examination committee for criteria of metabolic syndrome by the quartile of gamma glutamyltransferase (GGT) (A) and alanine aminotransferase (ALT) (B).**Table 5.** Frequency of MS, JMS, and Diabetes by the Quartile of Alanine Aminotransferase (ALT)

	men			
	Q1	Q2	Q3	Q4
ALT range (U/L)	6 - 16 (14)	17 - 21 (19)	22 - 29 (25)	30 - 325 (40)
n	427	476	488	489
MS (%)	4.2	9.2 ^{**}	14.5 [#]	29.4 [#]
JMS (%)	4.4	7.6	13.9 [#]	24.9 [#]
diabetes (%)	3.3	4.6	6.4 [*]	8.8 ^{***}
	women			
	Q1	Q2	Q3	Q4
ALT range (U/L)	5 - 12 (11)	13 - 15 (14)	16 - 19 (17)	20 - 138 (24)
n	282	276	253	268
MS (%)	1.8	3.3	5.9 [*]	17.5 [#]
JMS (%)	0.4	0.4	1.6	5.6 ^{***}
diabetes (%)	0.4	0.7	1.6	3.7 ^{**}

^{*}, ^{**}, ^{***}, and [#] indicate p < 0.05, < 0.01, < 0.001, and < 0.0001, respectively comparing with Q1. Abbreviations and ( ) are the same as Table 1.

Discussion

Ruttmann et al reported in a large prospective study that GGT is independently and dose-responsively associated with

cardiovascular mortality (7). Lee et al also reported that GGT predicts the onset of MS, incidence of cardiovascular disease, and mortality adjusting for established cardiovascular risk factors and CRP (8). GGT may play a role in the pathogenesis of atherosclerosis because it was detected in

Table 6. Optimal Cutoff Points of GGT and ALT as Optional Components of MS or JMS

			AUC	95% CI		cutoff point	sensitivity	specificity
men	GGT	MS	0.694	0.663	0.725	42 U/L	0.66	0.65
		JMS	0.695	0.662	0.728	41 U/L	0.67	0.63
	ALT	MS	0.719	0.687	0.752	25 U/L	0.68	0.78
		JMS	0.706	0.672	0.740	25 U/L	0.67	0.65
women	GGT	MS	0.743	0.688	0.797	21 U/L	0.67	0.70
		JMS	0.742	0.639	0.845	23 U/L	0.67	0.74
	ALT	MS	0.761	0.702	0.820	20 U/L	0.61	0.80
		JMS	0.825	0.731	0.919	25 U/L	0.67	0.90

AUC: area under receiver operating characteristic curve, CI: confidence interval.

Other abbreviations are the same as Table 1.

Table 7. Partial Correlation Coefficients between GGT or ALT and Metabolic Risk Factors Controlling for Age

n	GGT				ALT			
	men*		women*		men*		women*	
	1437		901		1437		901	
	r	p	r	p	r	p	r	p
body mass index	0.184	<0.001	0.12	<0.001	0.392	<0.001	0.168	<0.001
body fat %	0.244	<0.001	0.147	<0.001	0.421	<0.001	0.167	<0.001
waist circumference	0.231	<0.001	0.161	<0.001	0.38	<0.001	0.202	<0.001
systolic blood pressure	0.207	<0.001	0.093	0.005	0.172	<0.001	0.15	<0.001
diastolic blood pressure	0.218	<0.001	0.086	0.01	0.157	<0.001	0.113	0.001
fasting glucose	0.151	<0.001	0.105	0.002	0.138	<0.001	0.119	<0.001
triglycerides	0.322	<0.001	0.367	<0.001	0.284	<0.001	0.484	<0.001
HDL cholesterol	-0.034	ns	-0.053	ns	-0.202	<0.001	-0.152	<0.001
hs-CRP	0.093	<0.001	0.083	0.013	0.149	<0.001	0.072	0.03
GGT					0.554	<0.001	0.579	<0.001
ALT	0.554	<0.001	0.579	<0.001				
LDL cholesterol	0.024	ns	0.081	0.015	0.159	<0.001	0.083	0.013
uric acid	0.181	<0.001	0.161	<0.001	0.164	<0.001	0.231	<0.001
white blood cell count	0.118	<0.001	0.073	0.029	0.126	<0.001	0.075	0.025
heart rate	0.137	<0.001	0.041	ns	0.134	<0.001	0.088	0.008

*: excluding subjects with antihypertensive, antidiabetic, or antihyperlipidemic medication.

Abbreviations are the same as Table 1.

atheromatous plaques triggering pro-oxidant process (14). While, Kotronen and Yki-Jarvinen showed that liver fat storage is highly significantly and linearly correlated with all components of MS, independent of obesity and proposed fatty liver as a novel component of MS (1). Nakanishi et al reported that GGT may be an important predictor for developing MS and diabetes in middle-aged Japanese men (3). Devers et al proposed to include GGT in the criteria of MS because this inclusion could increase its predictive nature for cardiovascular disease (4). Goessling et al reported that ALT is an independent predictor of MS and diabetes (9) and Schindhelm et al reported that the predictive value of ALT for coronary events is significant and seems to be independent of traditional risk factors and the features of MS in a population-based cohort (10). However, there are few reports examining the association between GGT or ALT and MS or JMS in Japanese men and women.

In the present study, direct associations between GGT or

ALT and MS defined by revised NCEP criteria for Japanese and between GGT or ALT and JMS defined by the Examination Committee for Criteria of Metabolic Syndrome were examined using medical check-up data from 1,880 men and 1,079 women. The results showed that the prevalence of MS and JMS increased with the increase in blood levels of GGT or ALT even through the normal range in both men and women. The optimal cut-off points of GGT and ALT as optional components of MS or JMS were 42 U/L or 41 U/L and both 25 U/L, respectively in men and 21 U/L or 23 U/L and 20 U/L or 25 U/L, respectively in women.

MS (15) or insulin resistance syndrome (syndrome X) (16) is thought to be an important risk factor of diabetes and cardiovascular disease, but, there remain many unresolved problems regarding the definition of MS (17-22). MS may be a pre-disease state of diabetes, cardiovascular disease, fatty liver disease (1, 2), chronic kidney disease (CKD) (23), or chronic lung disease (24). The core mechanisms of MS

may be increased adiposity, insulin resistance (16), leptin resistance (25, 26), low-grade systemic inflammation (22, 27), endothelial dysfunction (28), and autonomic dysfunction (26). GGT or ALT (fatty liver) may be an important component of MS and we should not ignore increased levels of GGT or ALT as a risk factor of diabetes and cardiovascular disease even in its normal range.

Limitations

The present study was a cross-sectional study and the subjects were not the general population but visitors to our medical check-up center which is in a central city of a rural region in Japan. These conditions may influence the low prevalence of MS in our subjects. However, both the prevalence of MS in rural regions and the prevalence of obesity

are very low in Japan. Therefore, the present data may not merely represent a quite peculiar population and thus the conclusions may be relevant in other regions and populations in Japan. Longitudinal studies are required to establish GGT or ALT as a risk factor of diabetes and cardiovascular disease in the Japanese population.

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