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METABOLIC SYNDROME DEFINED BY NEW CRITERIA IN JAPANESE IS ASSOCIATED WITH INCREASED LIVER ENZYMES AND C-REACTIVE PROTEIN

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ABSTRACT

Metabolic syndrome (MetS) is characterized by the presence of atherogenic risk factors, and is associated with a marked increase in the risk of cardiovascular disease. Recently, the criteria of MetS were newly defined in Japan. We examined the relationship between MetS and the various metabolic parameters in Japanese subjects. This study included 458 Japanese subjects undergoing medical checkups at Nagoya University Hospital. New criteria developed by the joint committee of eight Japanese medical societies for the clinical recognition of MetS were adopted. We examined the association between MetS and various metabolic parameters, including liver enzymes (alanine aminotransferase, ALT; gamma glutamyltransferase, GGT) and highly sensitive C-reactive protein (hsCRP). The mean overall prevalence of MetS was 8.7% (male: 12.9%; female: 2.2%, p=0.0001). MetS was significantly associated with elevated ALT (>45 IU/L) (OR: 3.37, 95% CI: 1.19–9.52, $p<0.05$) and GGT (>64 IU/L in males, >45 IU/L in females) (OR: 4.96, 95% CI: 2.31–10.66, p=0.0001), respectively. MetS was also significantly associated with elevated hsCRP (≥ 0.1 ng/mL) (OR: 2.77, 95% CI: 1.20–6.41, $p<0.05$). Thus, MetS was associated with elevated liver enzymes (especially, GGT), and inflammation (hsCRP).

Key Words: Metabolic syndrome, Japanese, Liver enzymes, Inflammation

INTRODUCTION

Metabolic syndrome (MetS) is characterized by the presence of a cluster of atherogenic risk factors, and is associated with a marked increase in the risk of cardiovascular disease.[1, 2] In 1999, MetS was defined by the World Health Organization (WHO),[3] and in 2001 another definition was proposed by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and the Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III).[4] Further definitions have been proposed recently by various organizations or associations; for example, in Japan, the definition of MetS was determined in collaboration with eight Japanese medical societies in 2005.[5]

Several studies have demonstrated elevations of serum alanine aminotransferase (ALT) and

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gamma glutamyltransferase (GGT) in subjects with MetS. Such elevations of these serum liver enzymes are related to the presence of non-alcoholic fatty liver disease in these patients,[6,7] and are suggested to be simple markers of cardiovascular risk.[8,9] In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incidents of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death.[10,11] Thus, MetS using the criteria of WHO and NCEP-ATP III, has been investigated for its possible relation to serum liver enzymes and CRP. To our knowledge, however, the associations of MetS with liver enzymes and CRP have not been fully investigated in Japan using the new criteria. Therefore, in the present study, we used those new criteria to examine the relationship of MetS, and various metabolic parameters, including liver enzymes and CRP in Japanese subjects.

METHODS

Subjects

This study included 458 Japanese subjects undergoing medical checkups at Nagoya University Hospital. From a total of 564 examinees invited to participate in the present study, 458 (81.2%) agreed to provide their residual blood. Written informed consent was obtained from all subjects, and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

Definitions of metabolic syndrome

New criteria developed by the joint committee of eight Japanese medical societies for the clinical recognition of MetS were adopted. Participants who suffered from obesity (waist ≥ 85 cm in males, ≥ 90 cm in females) plus ≥ 2 of the following three components were defined as MetS: (1) HDL-C < 1.036 mmol/L or TG ≥ 1.695 mmol/L or medication for hyperlipidemia; (2) FBG ≥ 6.10 mmol/L or medication for diabetes; and (3) blood pressure ≥ 130/85 mm Hg or taking an antihypertensive.[5]

Smoking and drinking

Smoking status was expressed by the Brinkman index (duration of smoking × cigarette consumption level), and drinking status by the alcohol index (duration of drinking × ethanol consumption level).

Liver enzymes

The serum levels of aspartate aminotransferase (AST), ALT, and GGT were determined by standard laboratory methods of the Japan Society of Clinical Chemistry (JSCC). We defined elevated AST levels as > 41 IU/L, elevated ALT levels as > 45 IU/L and elevated GGT levels as > 64 IU/L (males) and >45 IU/L (females), according to the criteria of Nagoya University Hospital.

hsCRP

The highly sensitive CRP (hsCRP) level was measured by a high-sensitivity assay using a latex aggregation immunoassay (Nanopia CRP, Daiichi Pure Chemicals Co., Ltd.) with a Hitachi

7170 analyzer (Hitachi Instruments Engineering Co., Ltd). We defined the elevated hsCRP levels as ≥ 0.1 ng/mL, according to the criteria of the Nagoya University Hospital.

Statistical Analysis

Statistical analysis of data was performed using Stat View version 5.0 statistical software (SAS Corporation, Cary, NC, USA). All variables are expressed as mean±SD. Comparisons between more than three groups were performed using a Kruskal-Wallis or Dunnet test. A Mann-Whitney U test was used for comparisons between two groups. In a search for correlations between variables, Spearman's rank correlation test was used. A logistic regression model was used to estimate the odds ratio (OR, 95% CI) for MetS. We adjusted that ratio for age, gender, alcohol index and Brinkman index. Age, alcohol index and Brinkman index were then used as continuous variables. Gender (male and female) was used as a categorical variable. *p* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the clinical and biochemical characteristics of all the subjects and subjects with or without MetS as defined by the new Japanese criteria for its clinical recognition. The age of the subjects enrolled ranged from 18 to 89 years, with a mean age of 49.6±12.8 (males: 50.6±12.9 years; females: 47.9±12.7 years). The mean overall prevalence of MetS and the number of MetS risk factor components were 8.7% (males: 12.9%; females: 2.2%, p=0.0001), and 0.51±1.00 (males: 0.80±1.15; females: 0.07±0.46, p=0.0001), respectively. Using the NCEP ATP III criteria, the prevalence of MetS and the number of MetS risk factor components were 5.0% (males: 5.4%; females: 4.5%), and 0.79±0.91 (males: 0.89±0.88; females: 0.63±0.93), respectively. Under the new Japanese criteria, subjects with MetS compared to those without it had significantly greater levels of height, weight, waist, waist-to-height ratio, body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, triglyceride, LDL cholesterol, red blood cell counts, hemoglobin, white blood cell counts, albumin, creatinine, uric acid, AST, ALT, GGT, cholinesterase, alkaline phosphatase (ALP), hsCRP and bone mineral density, but lower levels of HDL cholesterol and amylase.

MetS, liver enzymes and hsCRP

Compared with the non-MetS group, the MetS group exhibited significant elevations of AST, ALT and GGT (Fig. 1), especially, in its showing of significantly increased GGT. In an unadjusted model, MetS showed a marked association with increased ALT and GGT with respective odds ratios of 4.10 (95% CI: 1.53–10.98, $p<0.01$) and 6.55 (95% CI: 3.17–13.53, p=0.0001) (Fig. 2-A). Obesity group (waist circumference: ≥85 cm in males, ≥90 cm in females) also showed a significant association with respective odds ratios of 7.43 (95% CI: 3.23-17.09, p=0.0001) and 3.17 (95% CI: 1.91-5.28, p=0.0001). In addition, after adjustment for age, gender, alcohol index and Brinkman index, MetS was also significantly associated with increased ALT and GGT with respective odds ratios of 3.37 (95% CI: 1.19–9.52, $p<0.05$) and 4.96 (95% CI: 2.31–10.66, p=0.0001) (Fig. 2-B). Waist circumference also exhibited a significant association with respective odds ratios of 4.83 (95% CI: 1.93-12.10, $p<0.001$) and 2.08 (95% CI: 1.17-3.68, $p<0.05$). In both unadjusted and adjusted models, MetS was significantly associated with increased hsCRP with respective odds ratios of 2.85 (95% CI: 1.31–6.21, $p<0.01$) and 2.77 (95% CI: 1.20–6.41, $p<0.05$) (Fig. 3-A, 3-B).

Table 1 Relationship between clinical characteristics and metabolic syndrome

Variables	Total	Metabolic syndrome		P value
		–	+	
Subjects (n)	458	423	35	–
Male/female (n/n)	279/179	247/176	32/3	< 0.0001
Age (y)	49.6±12.8	49.2±12.9	54.1±11.2	< 0.05
Height (cm)	164.6±8.7	164.3±8.7	167.8±7.6	< 0.05
Weight (kg)	61.9±11.5	61.0±11.3	73.0±7.9	< 0.0001
Waist (cm)	77.2±10.2	76.1±9.7	90.8±4.3	< 0.0001
Waist/height	0.47±0.05	0.46±0.05	0.54±0.03	< 0.0001
Body mass index (kg/m^2)	22.7±3.0	22.5±2.9	25.9±2.8	< 0.0001
Systolic blood pressure (mmHg)	123±17	121±17	140±13	< 0.0001
Diastolic blood pressure (mmHg)	78±12	77±11	90±9	< 0.0001
Glucose (mg/dL)	92±14	90±11	112±28	< 0.0001
Total cholesterol (mg/dL)	203±37	201±36	219±40	< 0.05
Triglyceride (mg/dL)	108±77	100±57	202±173	< 0.0001
HDL cholesterol (mg/dL)	56.2±14.2	56.9±14.0	47.6±14.5	< 0.0001
LDL cholesterol (mg/dL)	125±34	125±34	131±41	NS
Red blood cell counts (×10^4/μL)	456±45	453±45	488±31	< 0.0001
Hemoglobin (g/dL)	14.1±1.4	14.0±1.4	15.1±1.0	< 0.0001
White blood cell counts (/μL)	5143±1447	5107±1446	5577±1407	0.05
Platelet count (×10^4/μL)	23.3±5.3	23.2±5.3	23.8±4.8	NS
Total protein (g/dL)	7.3±0.4	7.3±0.4	7.4±0.4	NS
Albumin (g/dL)	4.4±0.2	4.4±0.2	4.5±0.2	< 0.05
Creatinine (mg/dL)	0.78±0.16	0.78±0.16	0.86±0.13	< 0.001
Creatinine clearance (mL/min)	95.7±25.2	95.1±24.8	103.1±28.5	NS
Uric acid (mg/dL)	5.6±1.4	5.54±1.36	6.49±1.32	< 0.0005
AST (GOT) (IU/L)	22.0±8.3	21.6±8.2	27.0±8.1	< 0.0001
ALT (GPT) (IU/L)	23.0±17.2	22.1±16.9	34.1±16.9	< 0.0001
GGT (γ-GTP) (IU/L)	41.3±44.1	37.3±38.0	89.5±75.0	< 0.0001
Cholinesterase (ΔpH)	1.03±0.23	1.03±0.23	1.14±0.19	< 0.005
Alkaline phosphatase (IU/L)	210±64	209±64	221±51	NS
hsCRP (mg/dL)	0.084±0.212	0.081±0.216	0.114±0.144	< 0.005
Bone mineral density (g/cm^2)	0.73±0.09	0.73±0.09	0.78±0.08	< 0.005

Values are expressed as mean±SD.
Abbreviation: HDL, high-density lipoprotein, LDL, low-density lipoprotein, AST (GOT), asparate aminotransferase, ALT (GPT), alanine aminotransferase, GGT, gamma-glutamyltransferase, hsCRP, highly sensitive C-reactive protein, NS, not significant

Table 2 Clinical characteristics of subjects stratified by number of risk factors of metabolic syndrome

Variables	Number of risk factors				P value
	0	1	2	≥ 3	
Subjects (n)	349	23	51	35	–
Male/female (n/n)	175/174	22/1	50/1	32/3	< 0.0001
Age (y)	49.0±13.1	48.0±13.4	51.2±11.2	54.1±11.2	0.08
Height (cm)	163±9	170±7	171±6	168±8	< 0.0001
Weight (kg)	57.9±9.3	75.9±8.3	75.3±8.2	73.0±7.9	< 0.0001
Waist (cm)	73.1±7.6	90.1±5.7	90.3±4.3	90.8±4.3	< 0.0001
Waist/height	0.45±0.04	0.53±0.04	0.53±0.03	0.54±0.03	< 0.0001
Body mass index (kg/m^2)	21.7±2.4	26.2±2.1	25.8±2.5	25.9±2.8	< 0.0001
Systolic blood pressure (mmHg)	120±17	118±7	128±15	140±13	< 0.0001
Diastolic blood pressure (mmHg)	76±11	75±5	84±12	90±9	< 0.0001
Glucose (mg/dL)	89±11	92±6	93±11	112±28	< 0.0001
Total cholesterol (mg/dL)	200±37	209±33	206±37	219±40	< 0.05
Triglyceride (mg/dL)	96±56	93±29	127±68	202±173	< 0.0001
HDL cholesterol (mg/dL)	58.4±13.9	51.1±6.4	49.7±13.9	47.6±14.5	< 0.0001
LDL cholesterol (mg/dL)	123±34	139±33	131±34	131±41	< 0.0001
Red blood cell counts ($\times 10^4/\mu L$)	451±38	472±28	462±80	488±31	< 0.0001
Hemoglobin (g/dL)	13.8±1.4	14.6±0.8	14.7±1.2	15.1±1.0	< 0.0001
White blood cell counts (/μL)	5000±1350	5100±1156	5856±1944	5577±1407	< 0.01
Platelet count ($\times 10^4/\mu L$)	23.3±5.2	22.7±3.6	23.3±6.9	23.8±4.8	NS
Total protein (g/dL)	7.3±0.4	7.2±0.4	7.3±0.4	7.4±0.4	NS
Albumin (g/dL)	4.4±0.2	4.4±0.2	4.4±0.2	4.5±0.2	NS
Creatinine (mg/dL)	0.76±0.16	0.85±0.10	0.84±0.11	0.86±0.13	< 0.0001
Creatinine clearance (mL/min)	91±22	115±23	114±30	103±28	< 0.0001
Uric acid (mg/dL)	5.3±1.3	5.9±1.1	6.6±1.5	6.5±1.3	< 0.0001
AST (GOT) (IU/L)	20.6±5.9	23.5±7.9	27.1±16.2	27.0±8.1	< 0.0001
ALT (GPT) (IU/L)	19.5±10.2	29.2±15.2	36.3±36.4	34.1±16.9	< 0.0001
GGT (γGTP) (IU/L)	34.9±39.5	49.5±33.3	47.7±24.8	89.5±75.0	< 0.0001
Cholinesterase (ΔpH)	1.01±0.24	1.08±0.18	1.10±0.19	1.14±0.19	< 0.0001
Alkaline phosphatase (IU/L)	209±63	194±45	221±81	221±51	NS
hsCRP (mg/dL)	0.068±0.164	0.085±0.134	0.173±0.435	0.114±0.144	< 0.0001
Bone mineral density (g/cm^2)	0.71±0.09	0.78±0.07	0.78±0.07	0.78±0.08	< 0.0001

Values are expressed as mean±SD.

Abbreviation: HDL, high-density lipoprotein, LDL, low-density lipoprotein, AST (GOT), asparate aminotransferase, ALT (GPT), alanine aminotransferase, GGT, gamma-glutamyltransferase, hsCRP, highly sensitive C-reactive protein, NS, not significant

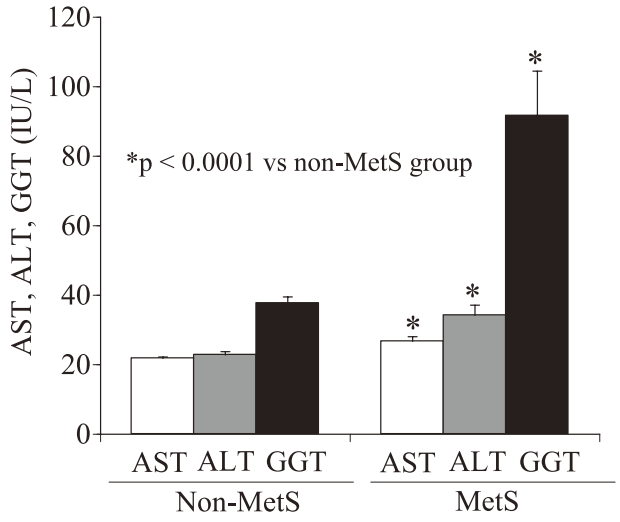

Fig. 1 AST, ALT and GGT in subjects with or without metabolic syndrome (MetS) defined by the new criteria in Japanese subjects. Data expressed as mean with SD. *P<0.0001 as compared with non-MetS.

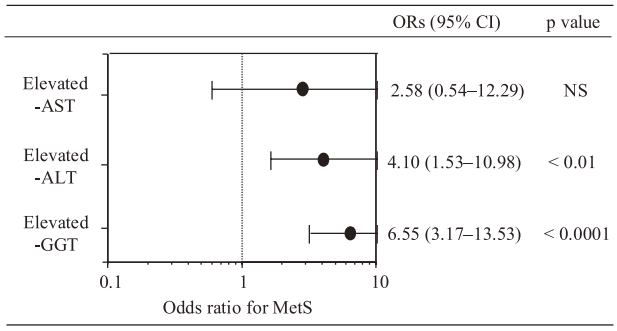

Fig. 2-A Odds ratios of elevated AST, elevated ALT and elevated GGT for metabolic syndrome (MetS) by unadjusted logistic regression analysis. NS: not significant.

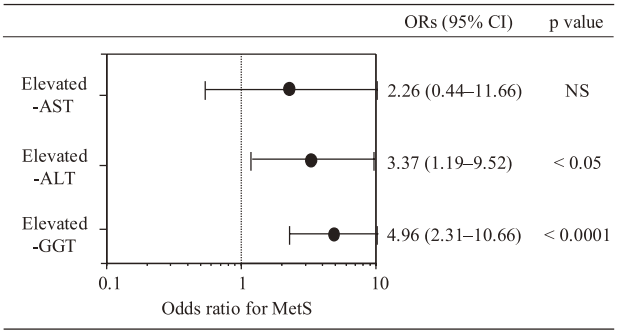

Fig. 2-B Odds ratios of elevated AST, elevated ALT and elevated GGT for metabolic syndrome (MetS) by adjusted logistic regression analysis. NS: not significant.

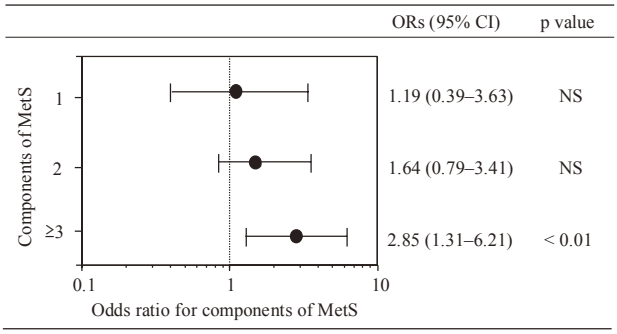

Fig. 3-A Odds ratios of elevated CRP for components of metabolic syndrome (MetS) by unadjusted logistic regression analysis. NS: not significant.

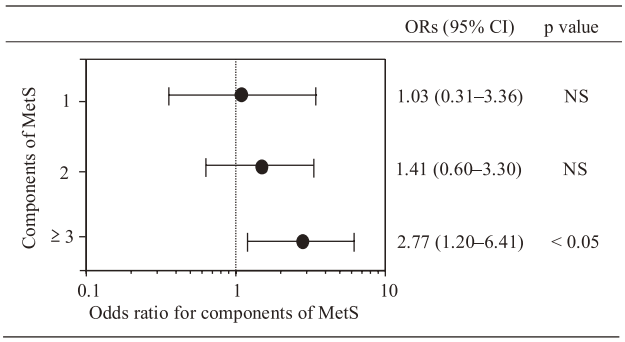

Fig. 3-B Odds ratios of elevated CRP for components of metabolic syndrome (MetS) by adjusted logistic regression analysis. NS: not significant.

DISCUSSION

In the present study, we demonstrated, when using the new criteria in Japanese subjects, that ALT, GGT and hsCRP were associated with the prevalence of MetS. Because our present effort is an association study, further research will be required to elucidate the mechanism of the association.

Several studies have suggested that abdominal obesity plays a key role in the elevated cardiovascular risk associated with MetS,[12] since the waist circumference is a robust marker of abdominal obesity.[1] Although the parameter for abdominal obesity adopted by the new criteria of MetS in Japan is not BMI but the waist, studies on the MetS-adopted waist as a parameter of obesity are very few.

The elevated serum ALT and/or GGT in subjects with MetS are related to the presence of non-alcoholic fatty liver disease.[6,7] Recent studies have suggested that elevations of these liver enzymes are simple markers of cardiovascular risk.[8,9] The present study showed that serum levels of AST, ALT and GGT in the MetS group were high compared with non-MetS subjects. GGT in particular was found to be remarkably high (more than two-fold) in subjects with MetS compared with non-MetS subjects. Elevated ALT and GGT were significantly associated with MetS not only by an unadjusted model, but also by a multivariate model after adjusting for age,

sex, drinking and smoking status. In addition, serum levels of GGT in the MetS group were higher than in the obesity group, although serum levels of ALT in the former group were low compared with those in the latter group. Thus, ALT, and especially GGT, showed a significant association with MetS. There was a remarkable impact of waist circumference on the ALT and GGT levels group, with the large waist group showing significantly higher ALT and GGT than a normal waist group (ALT: 19.6±10.2 IU/L for a normal group, 34.1±27.5 IU/L for a large group, GGT: 35.0±39.5 IU/L for normal, 61.5±51.5 IU/L for large).

Systemic inflammation is closely involved in the pathogenesis of MetS.[13-15] Several clinical studies have demonstrated that CRP was increased in subjects with MetS.[14,16] Kerner *et al.*[8] demonstrated, in a general population, an association between increased plasma levels of CRP and elevated serum ALT in subjects with one or more components of MetS, and they proposed that hepatic inflammation related to non-alcoholic fatty liver disease might be involved in the systemic inflammation associated with MetS. Atherosclerosis and insulin resistance were found to share a common inflammatory basis when it was shown that CRP exerts directly harmful effects on vessel walls.[17] Obesity-mediated cytokine production is presumed to be a central mechanism for systemic elevations of CRP. Cytokines produced by adipocytes, such as IL-1, IL-6, and TNF-α, stimulate the hepatic synthesis of CRP,[18] and modify the glucose and lipid metabolism.[19] Thus, the systemic acute-phase response may mediate systemic metabolic impairments. Interestingly, a recent report demonstrated that atorvastatin, a lipid-lowering agent, directly reduces CRP levels and consequently reduces the incidence of cardiovascular events.[20] In addition, it was suggested that CRP has proatherogenic and prothrombic properties.[21] A recent Japanese study found a geometric mean CRP of 1.0 mg/L for men (mean 69.0 years) and 0.8 mg/L for women (mean 67.6 years), with their CRP values associated with obesity.[22] In the present study, hsCRP was increased in the MetS as compared with the non-MetS group. Furthermore, a dose-effect relationship with the number of MetS risk factors was significantly associated with increased hsCRP, when the number of risk factors was more than three. Thus, hsCRP showed a significant association with MetS. In addition, hsCRP showed a significant correlation with AST, ALT and GGT (r=0.16, 0.16, and 0.24; p=0.0004, p=0.0007, and p=0.0001, respectively). Waist circumference was remarkably correlated with GGT and CRP (r=0.54, and 0.34; p=0.0001, and p=0.0001, respectively).

In conclusion, GGT, a liver enzyme, was strongly associated with MetS as compared with waist obesity. Moreover, CRP, an inflammation marker and a cardiovascular risk factor, was also associated with MetS. GGT and CRP can thus be simple, powerful markers of MetS.

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