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REVIEW

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RELATIONSHIP BETWEEN SERUM ADIPONECTIN LEVELS AND METABOLIC SYNDROME DIAGNOSED BY USING THE NEW CRITERIA FOR METABOLIC SYNDROME FOR JAPANESE: THE TANNO AND SOBETSU STUDY

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ABSTRACT. THE AIM OF THIS REVIEW STUDY is to determine the relationship between adiponectin level and metabolic syndrome (MS), based on a new clinical definition made for Japanese. A total of 1067 participants in mass-screening tests for residents of two rural communities in Japan in 2002 and 2003 were selected after exclusion of patients undergoing treatment for hypertension or diabetes. MS was defined on the basis of visceral fat accumulation, which is defined as waist circumference (WC) ≥85 cm for males and ≥90 cm for females, plus any two of the following three factors: 1. elevated triglyceride levels (≥150 mg/dL) or specific treatment for this lipid abnormality and/or reduced high-density lipoprotein (< 40 mg/dL) or specific treatment for this lipid abnormality; 2. elevated blood pressure (BP; systolic BP ≥130 and/or diastolic BP ≥85 mmHg); 3. elevated fasting plasma glucose (≥110 mg/dL). In multiple regression analysis with adiponectin as a dependent variable, the body mass index (BMI) and WC were selected as independent variables, and so as the sex differences, age, and fasting plasma insulin levels. Furthermore, adiponectin showed tighter, negative standardized regression coefficients with WC than with BMI (–0.268 versus –0.160). Adiponectin levels were significantly lower in subjects with MS than in subjects without MS in both males and females, and were still significantly lower after adjustment for age differences. Plasma levels of adiponectin, an adipocyte-derived antiatherogenic protein, were low in subjects with MS diagnosed by the new criteria for Japanese.

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1. INTRODUCTION

Multiple risk factor syndrome, in which there is clustering of high blood pressure, lipid abnormality and glucose intolerance, is one of the important risk factors of atherosclerotic disease. Multiple risk factor syndrome has also been called visceral fat syndrome, syndrome X, deadly quartet, syndrome of insulin resistance, and recently metabolic syndrome (MS) [1-5]. A new worldwide definition of MS, emphasizing the importance of central obesity with modifications according to ethnic group, was announced by the International Diabetes Federation in 2005 [6]. In the same year, the Committee on Criteria for Metabolic Syndrome in Japan provided a definition of MS for Japanese [7] (TABLE 1).

Adiponectin is a plasma protein (composed of 244 amino acid residues), and was identified from a gene, apM1, that is specifically expressed in fat tissue [8]. Adiponectin has been shown to circulate as a trimer, hexamer, or higher-molecular-weight form in the blood of healthy subjects and to be present at a high level of 5–10 μg/mL [9-13]. It has been shown that the ratios among these forms determine their activity [14-16]. There are also significant sex differences in the circulating concentrations of adiponectin and in the ratios of their subunits [14,17]. It has been reported that adiponectin is closely associated with visceral fat accumulation [10] and insulin resistance [18-22] and that low levels of adiponectin are linked to components of MS. Adiponectin level is low in subjects carrying excessive organ fat and it increases with a reduction in body weight [10]. It has also been shown to be correlated negatively with blood pressure, triglyceride level, fasting plasma glucose level, plasma glucose level 2 h after a meal and fasting insulin concentration and to be correlated positively with high-density lipoprotein level [23-27].

We have shown that adiponectin is low in subjects having MS diagnosed by modified NCEP-ATP III criteria for Japanese [28]. In this review study, we examined the association between MS and adiponectin level by using a new definition of MS for Japanese in participants in mass-screening tests for residents in a region of Hokkaido, Japan.

2. SUBJECTS AND METHODS

Of 1,555 participants in mass-screening tests for the residents of Tanno Town and Sobetsu Town in Hokkaido, Japan in 2002 and 2003, 1,067 males and females with an average age of 59.9 ± 12.3 years (364 males with an average age of 62.9 ± 12.3 years and 703 females with an average age of 58.4 ± 12.0 years) were selected after exclusion of patients undergoing treatment for hypertension or diabetes.

The mass-screening tests were carried out between 0600 h and 0800 h in the morning. Height and body weight were measured before blood pressure measurement, and blood was collected from the subjects under fasting conditions before breakfast. Blood pressure was measured more than once from the right arm after resting for several minutes in a sitting position, and average blood pressure was calculated. Blood was collected from the median cubital vein in a sitting position with a vacuum tube. The items measured were systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), waist circumference (WC), and concentrations of fasting plasma glucose (FPG), fasting plasma insulin (F-IRI), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) and serum adiponectin. Biochemical data were assayed as follows: FPG, the glucose-oxidase electrode method; F-IRI, enzyme immunoassay (ST AIA-PACK IRI, TOSOH, Tokyo, Japan); TC, the cholesterol oxidase enzymatic assay method; TG, the enzymatic colorimetric method; HDL, the direct liquid-stable assay; adiponectin, the sandwich enzyme-linked immunosorbent assay method (human adiponectin ELISA kit, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). The insulin resistance index determined by homeostasis model assessment (HOMA-IR) was calculated by the formula HOMA-IR = FPG (mg/dL) × F-IRI (μU/mL)/405.

According to the new definition for Japanese in 2005 [7] (TABLE 1), MS was diagnosed as visceral fat accumulation (defined as WC ≥85 cm for males and ≥90 cm for females) plus any two of the following three factors: (1) raised TG level (≥150 mg/dL) or specific treatment for this lipid abnormality and/or reduced HDL (<40 mg/dL) or spe

TABLE 1. DEFINITION OF METABOLIC SYNDROME ACCORDING TO A JAPANESE CRITERIA PUBLISHED IN 2005.

According to the Japanese definition, for a person to be defined as having metabolic syndrome, one must have visceral fat accumulation (defined as waist circumference ≥ 85 cm for men and ≥ 90 cm for women), plus any two of the following three factors:
• raised TG level (≥ 150 mg/dL) or specific treatment for this lipid abnormality, and/or, reduced HDL (< 40 mg/dL) or specific treatment for this lipid abnormality both in males and females.
• raised BP: systolic BP ≥ 130 and / or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension.
• raised FPG ≥ 110 mg/dL, or treatment of previously diagnosed type 2 diabetes.
NOTE: Subjects receiving specific treatment for type 2 diabetes or for hypertension were excluded in this study. TG, triglyceride; HDL, high-density lipoprotein; BP, blood pressure; FPG, fasting plasma glucose. Converting factors: TG, mM = mg/dL × 0.01129; HDL, mM = mg/dL × 0.02586; FPG, mM = mg/dL × 0.05551.

TABLE 2. BASELINE CHARACTERISTICS (MEAN VALUES AND CORRELATIONS TO LNADIPONECTIN).

	Males	*r*	*P* value	Females	*r*	*P* value
	N = 364			N = 703		
Age (years)	62.9 ± 12.3†	0.353	<0.001	58.4 ± 12.0	0.123	0.001
BMI (kg/m^2)	23.8 ± 3.3†	–0.311	<0.001	23.1 ± 3.2	–0.181	<0.001
WC (cm)	84.8 ± 9.3†	–0.342	<0.001	79.8 ± 10.3	–0.239	<0.001
SBP (mmHg)	133.3 ± 21.0†	0.010	0.842	129.2 ± 21.2	0.005	0.890
DBP (mmHg)	75.8 ± 11.8†	–0.135	0.010	73.3 ± 11.9	–0.051	0.176
FPG (mg/dL)	97.0 ± 16.1†	–0.115	0.028	91.2 ± 11.2	–0.106	0.005
F-IRI (μU/mL)	4.6 ± 4.7	–0.286	<0.001	4.6 ± 2.8	–0.251	<0.001
HOMA-IR	1.1 ± 1.4	–0.262	<0.001	1.1 ± 0.8	–0.213	<0.001
TC (mg/dL)	193.2 ± 33.1†	–0.153	0.003	207.5 ± 33.8	–0.039	0.297
TG (mg/dL)	115.1 ± 74.6†	–0.333	<0.001	89.1 ± 42.0	–0.237	<0.001
HDL (mg/dL)	51.3 ± 11.6†	0.281	<0.001	54.3 ± 12.1	0.260	<0.001
Adipo (μg/mL)	6.0 ± 3.3†			7.2 ± 4.2		

Values are means ± standard deviations.
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure.
FPG, fasting plasma glucose; F-IRI, fasting plasma insulin.
HOMA-IR, homeostasis model assessment.
TC, total cholesterol, TG, triglyceride; HDL, high-density lipoprotein; Adipo, adiponectin.
r, versus LnAdiponectin, Peason's correlation coefficient; † $P < 0.05$, versus females, unpaired *t*-test.
Conversion factors: FPG, mM = mg/dL × 0.05551; F-IRI, pM = μU/mL × 6.0; TC, mM = mg/dL × 0.02586; TG, mg/dL × 0.01129; HDL, mM = mg/dL × 0.02586.
Data are from ref. [28] and amended in part.

TABLE 3. MULTIPLE REGRESSION ANALYSIS RELATED TO LNADIPONECTIN.

	β	*t* value	*P* value		β	*t* value	*P* value
Sex	0.117	3.922	<0.001	Sex	0.079	2.652	0.008
Age	0.181	6.071	<0.001	Age	0.226	7.546	<0.001
BMI	–0.160	–4.937	<0.001	WC	–0.268	–8.138	<0.001
F-IRI	–0.167	–5.183	<0.001	F-IRI	–0.125	–3.950	<0.001

β, standardized regression coefficients.
Sex, male = 0, female =1; BMI, body mass index; WC, waist circumference; F-IRI, fasting plasma insulin.

TABLE 4. RATIO OF FACTORS COMPRISING METABOLIC SYNDROME, AND ADIPONECTIN LEVELS IN SUBJECTS POSITIVE FOR VISCERAL FAT ACCUMULATION (VFA), LIPID ABNORMALITY (LA), HIGH LEVEL OF BLOOD PRESSURE (H-BP) OR HIGH LEVEL OF FASTING PLASMA GLUCOSE (H-FPG) AND IN SUBJECTS NEGATIVE FOR VFA, LA, H-BP OR H-FPG IN MALES AND FEMALES.

	Males (N = 364)			Females (N = 703)		
	%	Adiponectin (μg/mL)		%	Adiponectin (μg/mL)	
		+	–		+	–
VFA	53.8	5.0 ± 2.6†	7.2 ± 3.7	18.1	6.0 ± 3.7†	7.4 ± 4.2
LA	25.8	4.6 ± 2.3†	6.5 ± 3.5	19.6	5.8 ± 3.5†	7.5 ± 4.2
H-BP	53.6	6.0 ± 3.3	6.1 ± 3.4	44.5	7.1 ± 4.1	7.2 ± 4.2
H-FPG	9.6	5.0 ± 2.8	6.1 ± 3.4	4.6	6.6 ± 4.7	7.2 ± 4.1

Values are means ± standard deviations.
%, ratio of factors comprising metabolic syndrome.
+, subjects positive for visceral fat accumulation or lipid abnormality or high level of blood pressure or high level of fasting plasma glucose criteria.
–, subjects negative for visceral fat accumulation or lipid abnormality or high level of blood pressure or high level of fasting plasma glucose criteria.
VFA, visceral fat accumulation: waist circumference ≥85 cm for males or ≥90 cm for females.
LA, lipid abnormality: hypertriglyceridemia: triglyceride ≥150 mg/dL and/or low level of high-density lipoprotein: high-density lipoprotein <40 mg/dL and/or specific treatment for these lipid abnormality.
H-BP, high level of blood pressure: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.
H-FPG, high level of fasting plasma glucose: fasting plasma glucose ≥110 mg/dL.
† $P < 0.05$ versus subjects in the "–" group, unpaired *t*-test.
Conversion factors: triglyceride, mM = mg/dL × 0.01129.
high-density lipoprotein, mM = mg/dL × 0.02586.
fasting plasma glucose, mM = mg/dL × 0.05551.
Data are from ref. [28] and amended in part.

cific treatment for this lipid abnormality; (2) raised blood pressure (BP; systolic BP ≥130 and/or diastolic BP ≥85 mmHg); (3) raised FPG (≥110 mg/dL).

Multiple regression analysis was performed using adiponectin as a dependent variable and using sex differences, age, BMI, WC and F-IRI as dependent variables. The ratio of factors comprising MS was calculated, and adiponectin levels were compared among these factors. Since the female subjects diagnosed as having MS were significantly older than those not diagnosed as having MS (non-MS), adiponectin levels adjusted for each average age (males, 63 years of age; females, 58 years of age) were compared between MS and non-MS groups in males and females.

The present study was carried out in accordance with the Declaration of Helsinki (1981) of the World Medical Association, and the study protocol was approved by the Research Committee of Sapporo Medical University, Sapporo. Written informed consent was obtained from each subject after a full explanation of the purpose, nature, and risk of all procedures used.

Statistical analysis was performed with Windows SPSS version 12.0 in Japanese (SPSS Japan Inc.). Since adiponectin showed an F-distribution, natural logarithmic-transformed values (LnAdipo) were used, and each value is presented as mean ± standard deviation (SD). The unpaired *t*-test was used to compare data between two groups. A *P* value less than 0.05 was considered statistically significant.

3. RESULTS

Clinical characteristics of the study subjects are shown in TABLE 2. Adiponectin concentrations

TABLE 5. UNPAIRED *T*-TESTS BETWEEN METABOLIC SYNDROME AND NON-METABOLIC SYNDROME IN MALES AND FEMALES (MEAN VALUES).

	Males		Females	
	MS	Non-MS	MS	Non-MS
	N = 47	N = 317	N = 40	N = 663
Age (years)	63.7 ± 11.3	62.8 ± 12.5	64.3 ± 10.0†	58.0 ± 12.0
BMI (kg/m^2)	26.2 ± 3.5†	23.4 ± 3.1	27.1 ± 3.2†	22.9 ± 3.0
WC (cm)	91.2 ± 6.4†	83.8 ± 9.3	95.5 ± 4.9†	78.9 ± 9.7
SBP (mmHg)	147.6 ± 21.0†	131.1 ± 20.1	143.4 ± 12.5†	128.3 ± 21.4
DBP (mmHg)	82.0 ± 11.9†	74.9 ± 11.5	79.8 ± 11.2†	72.9 ± 11.8
FPG (mg/dL)	109.9 ± 31.0†	95.1 ± 11.4	100.3 ± 13.5†	90.6 ± 10.8
TC (mg/dL)	198.9 ± 37.3	192.4 ± 32.5	212.3 ± 39.9	207.2 ± 33.4
TG (mg/dL)	190.1 ± 115.8†	104.0 ± 59.0	131.9 ± 48.0†	86.5 ± 40.2
HDL (mg/dL)	44.5 ± 10.0†	52.3 ± 11.5	42.1 ± 9.5†	55.0 ± 11.9
Adipo (μg/mL)	4.4 ± 2.3†	6.3 ± 3.4	5.4 ± 3.4†	7.3 ± 4.2

Values are means ± standard deviations.
MS, subjects diagnosed as having metabolic syndrome.
Non-MS, subjects not diagnosed as having metabolic syndrome.
BMI, body mass index.
WC, waist circumference.
SBP, systolic blood pressure.
DBP, diastolic blood pressure.
FPG, fasting plasma glucose.
TC, total cholesterol.
TG, triglyceride.
HDL, high-density lipoprotein.
Adipo, adiponectin.
†$P < 0.05$ versus Non-MS group, unpaired *t*-test.
Conversion factors: FPG, mM = mg/dL × 0.05551.
TC, mM = mg/dL × 0.02586.
TG, mM = mg/dL × 0.01129.
HDL, mM = mg/dL × 0.02586.
Data are from ref. [28] and amended in part.

were 6.0 ± 3.3 μg/mL in males and 7.2 ± 4.2 μg/mL in females, the concentration being significantly higher in females than in males. LnAdipo correlated positively with age and HDL and negatively with BMI, WC, DBP, FPG, F-IRI, HOMA-IR, TC and TG in males and correlated positively with age and HDL and negatively with BMI, WC, FPG F-IRI, HOMA-IR and TG in females. Age, BMI, WC, SBP, DBP, FPG and TG were significantly higher in males than in females, and TC and HDL were significantly lower in males than in females (TABLE 2).

In multiple regression analysis of sex differences, age, BMI, WC and F-IRI with LnAdipo as a dependent variable, BMI and WC were selected as significant independent variables as well as sex differences, age and F-IRI (TABLE 3). Furthermore, adiponectin showed tighter, negative standardized regression coefficients with WC than with BMI (–0.268 versus –0.160).

The ratio of factors comprising MS and the adiponectin level in each factor are shown in TABLE 4. Ratios of subjects positive for visceral fat accumulation (VFA) were 53.8% in males and 18.1% in females. Ratios of subjects positive for lipid abnormality (LA) were 25.8% in males and

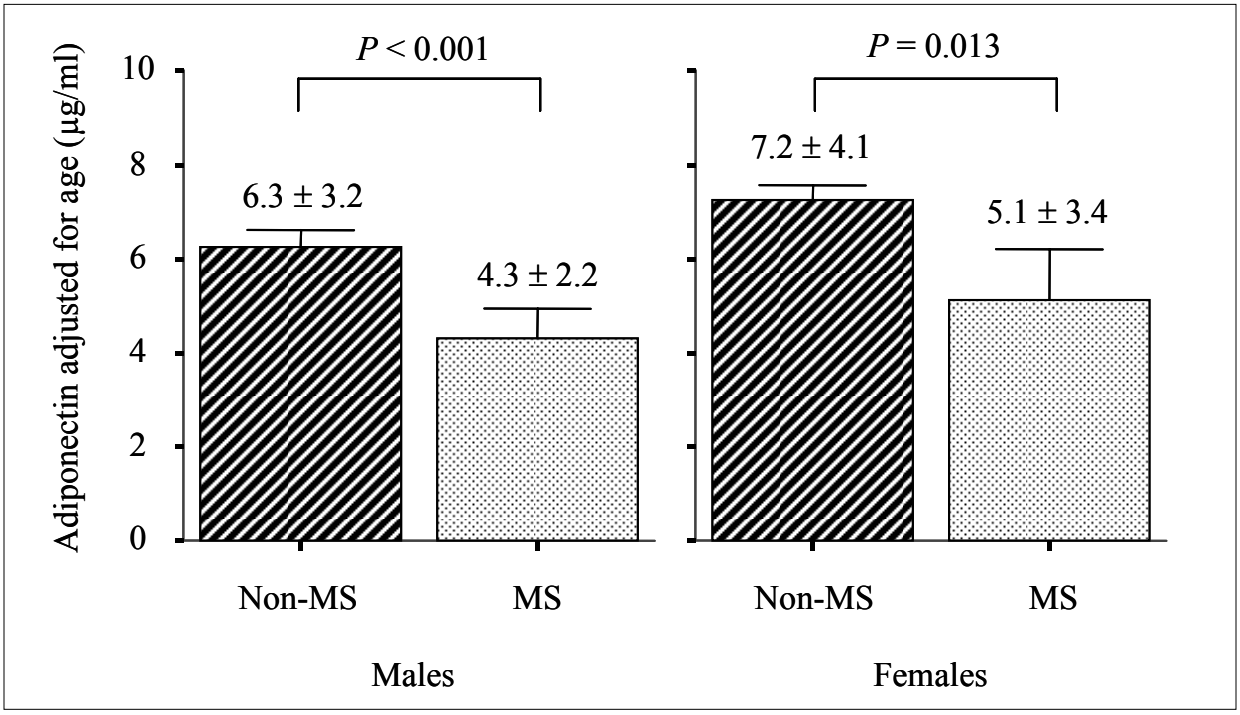

FIGURE 1. AGE-ADJUSTED PLASMA ADIPONECTIN LEVELS IN MALE AND FEMALE SUBJECTS WITH AND WITHOUT METABOLIC SYNDROME. Adiponectin level was adjusted for 63 years of age in males and was adjusted for 58 years of age in females. Non-MS, subjects not diagnosed as having metabolic syndrome; MS, subjects diagnosed as having metabolic syndrome. Values are means ± SDs. Data are from ref. [28] and amended in part.

19.6% in females. Ratios of subjects positive for high levels of blood pressure (H-BP) were 53.6% in males and 44.5% in females. Ratios of subjects positive for high levels of fasting plasma glucose (H-FPG) were 9.6% in males and 4.6% in females. Adiponectin concentrations were statistically lower in subjects positive for VFA or for LA than in subjects negative for VFA or for LA both in males and females.

The results of unpaired *t*-tests between the MS and non-MS groups are shown in TABLE 5. Adiponectin concentrations were significantly lower in the MS group than in the non-MS group both in males and females. Though there was no statistically significant difference in ages of males, females in the MS group were significantly older than females in the non-MS group. Adiponectin levels after adjustment for age were still significantly lower in the MS group than in the non-MS group both in males and females (FIG. 1).

4. DISCUSSION

In this study, adiponectin showed positive correlations with age and HDL and showed negative correlations with BMI, WC, FPG, F-IRI, HOMA-IR and TG both in males and females. In multiple regression analysis related to LnAdipo, BMI and WC were selected as significant predictor variables as well as sex differences, age and F-IRI. Furthermore, WC showed tighter, inverse standardized regression coefficients with adiponectin than BMI did. Adiponectin was also significantly lower in the MS group than in the non-MS group both in males and females and was still significantly lower after adjustment for age. These results suggest that WC

might be a more suitable parameter than BMI with regard to visceral fat accumulation and atherosclerosis and that adiponectin, an anti-atherogenic protein, might be an important predictor for MS.

Previous studies showed that adiponectin was closely associated with visceral fat accumulation and insulin resistance and that low levels of adiponectin were linked to components of MS [10,18-27]. Adiponectin has been shown to have potential inhibitory activities of the following three atherogenic cellular phenomena: (1) monocyte adhesion to endothelial cells by the expression of adhesion molecules; (2) oxidized LDL uptake of macrophages through scavenger receptors; and (3) proliferation of migrating smooth muscle cells by the action of platelet-derived growth factors or heparin-binding endothelial growth factor-like growth factor [29]. These anti-atherosclerotic and anti-inflammatory functions of adiponectin are thought to be associated with atherosclerosis [30-32] and to play a key role in the prevention of MS [29]. Other previous studies showed that lower adiponectin levels are associated with MS, diagnosed on the basis of modified NCEP-ATP III guidelines [5], in an urban area in Southern India [33] and that adiponectin level might be useful for diagnosis of MS in obese Japanese children [34].

The ratios of subjects with MS in this study were 12.9% in males and 5.7% in females. We have reported that the ratio of Japanese male subjects with MS in the early 1990s, diagnosed on the basis of modified NCEP-ATP III guidelines, was about 25% [35,36]. Since subjects undergoing treatment for hypertension or diabetes were excluded in this study, it is thought that the ratio of subjects with MS in this study is lower than the actual ratio. In all subjects, including subjects undergoing treatment for hypertension or diabetes, the ratios of subjects with MS were 24.4% in males and 8.9% in females in this study. In 2005, the International Diabetes Federation announced a new worldwide definition of MS, emphasizing the importance of central obesity with modifications according to ethnic group [6]. Further investigation using the new criteria for Japanese MS is needed to clarify the proportion of Japanese with MS.

Adiponectin concentrations in subjects positive for VFA or for LA were lower than those in subjects negative for VFA or for LA in both males and females. On the other hand, there were no significant differences between adiponectin concentrations in subjects positive for H-BP and those negative for H-BP and between adiponectin concentrations in subjects positive for H-FPG and those negative for H-FPG both in males and females. In a previous study, adiponectin concentration in subjects with essential hypertension was lower than that in normotensive healthy subjects [26]. It has also been reported that adiponectin level increases with aging [37-39]. Since blood pressure is known to increase with aging, this increase in adiponectin level with aging is thought to offset the difference between adiponectin concentrations in subjects positive for H-BP and those negative for H-BP. In the present study, adiponectin level had a tendency to decrease in both male and female subjects positive for H-FPG, and there was almost statistical significance between the difference in adiponectin levels in male subjects positive for H-FPG and those negative for H-FPG ($P = 0.051$). Since the number of excluded subjects undergoing treatment for diabetes was large, only 9.6% of the males and 4.6% of the females had H-FPG. This large number of excluded subjects might be the reason why there was no significant difference between adiponectin concentrations in subjects positive for H-FPG and those negative for H-FPG.

In previous studies, thiazolidinediones [40,41], temocapril and candesartan [42], which are used for treating diabetes and hypertension, were found to increase the serum level of adiponectin. Therefore, subjects undergoing treatment for diabetes or hypertension were excluded in this study. Although it is not clear whether lipid lowering-properties would influence serum adiponectin concentration, subjects undergoing treatment for hyperlipidemia, which was present only in females, were not excluded in this study. After exclusion of the female subjects receiving antilipotropic drugs, 15.5% of the female subjects were positive for LA, and results of analysis excluding female subjects receiving antilipotropic drugs were similar to the results

presented in this report.

One limitation of this study is that it was a cross-sectional study. More prospective studies may be needed to clarify the relationship between adiponectin concentration and prevention of MS.

In conclusion, the results of this study suggest that the plasma level of adiponectin, an adipocyte-derived anti-atherogenic protein, is low in subjects with MS diagnosed by the new criteria for Japanese and might be an important predictor for MS.

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