Original Article

Analysis of the Factors Contributing to Serum Retinol Binding Protein and Transthyretin Levels in Japanese Adults

Akihiro Yoshida[1], Yasuko Matsutani[2], Yoshiko Fukuchi[2], Kensuke Saito[3], and Michitaka Naito[2]

[1]Department of Clinical Laboratory, Nakatsugawa Municipal Hospital, Nakatsugawa, Gifu, Japan.
[2]Division of Nutrition & Health, School and Graduate School of Life Studies, Sugiyama Jogakuen University, Nagoya, Japan.
[3]Marketing Division, Dade Behring, Tokyo, Japan.

***Objective*: We examined various factors possibly related to metabolic syndrome, particularly focusing on nutritional assessment proteins such as retinol binding protein (RBP) and transthyretin (TTR), and remnant lipoproteins.**
***Materials and Methods*: Fasting serum lipid was analyzed in 58 Japanese adult volunteers (33 men and 25 women, 42.5 ± 10.1 years old).**
***Results*: The lipid profiles of the subjects were classified by lipoprotein polyacrylamide gel electrophoretic patterns into Types S (n=10), A (n=37), and N (n=11), according to the method described in Internal Medicine 42: 244, 2003. RBP and TTR were significantly higher in Type N than in Types S and A. In multivariate analysis, RBP was accounted for by remnant-like particle-triglyceride (RLP-TG), interleukin 6, body mass index and low-density lipoprotein (LDL)-cholesterol (adjusted R^2=0.621). TTR was accounted for by lipoprotein(a), adiponectin and RLP-TG (adjusted R^2=0.415). Malondialdehyde-LDL was significantly accounted for by LDL-cholesterol and RLP-cholesterol (adjusted R^2=0.601). Lipoprotein(a) and LDL-cholesterol were independent variables for oxidized LDL antigen (adjusted R^2=0.620). High-sensitivity C-reactive protein was accounted for by interleukin 6, immunoreactive insulin and oxidized LDL antigen (adjusted R^2=0.361). Uric acid and body mass index were independent variables for adiponectin (adjusted R^2=0.429).**
***Conclusion*: RBP and TTR may be useful as convenient and simple clinical markers of overnutrition and possibly of metabolic syndrome.**

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Key words; Remnant lipoprotein, Retinol binding protein, Overnutrition, Metabolic syndrome

Introduction

Lowering low-density lipoprotein-cholesterol (LDL-C) levels is widely accepted as an effective tool in reducing and preventing coronary heart disease (CHD) progression and cardiac events in hypercholesterolemic and even normocholesterolemic subjects. However, triglyceride (TG) has also been shown as an independent risk factor for cardiovascular disease, even adjusted for high-density lipoprotein-cholesterol (HDL-C). Evidence is accumulating that the risk for CHD can be reduced still further through the combination of LDL-lowering therapy with the modification of other risk factors. One potential secondary target of therapy is metabolic syndrome (MS), which represents a constellation of lipid and nonlipid risk factors of metabolic origin.

The National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP-ATPⅢ) Guidelines published in 2001 define MS as a new secondary target for cardiovascular risk reduction therapy beyond LDL-C lowering[1-3]. One of this publication's major features is that it identifies persons with multiple metabolic risk factors as candidates for intensified therapeutic lifestyle changes. The atherogenic lipid profile

Address for correspondence: Michitaka Naito, Division of Nutrition & Health, Graduate School of Life Studies, Sugiyama Jogakuen University, 17-3, Hoshigaoka-motomachi, Chikusa-ku, Nagoya 464-8662, Japan.
E-mail: naito@sugiyama-u.ac.jp
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associated with MS consists of the following: increased apolipoprotein (Apo) B, plasma TG, and intermediate density lipoprotein levels; reduced HDL-C concentration; and smaller, dense, cholesteryl ester-depleted LDL particles.

In a previous study, we classified lipoprotein profiles by polyacrylamide gel electrophoresis (PAGE) and showed that this classification may offer a new clinical tool to make up for the weak points in WHO classification, particularly in relation to the presence of a mid-band[4]. We also proposed the usefulness of serum total cholesterol (TC)/TG and LDL-C/TG ratios for predicting the presence of small, dense LDL as a simple indicator[5].

In this study, we examined various factors possibly related to MS, particularly focusing on nutritional assessment proteins such as retinol binding protein (RBP), transthyretin (TTR) and remnant lipoproteins.

Materials and Methods

Subjects

Fifty-eight Japanese volunteers (33 men and 25 women, 42.5 ± 10.1 years old) who visited Nakatsugawa Municipal Hospital for an annual health checkup were enrolled in the study. None of the subjects had a history of cardiovascular disease, diabetes, liver, or renal disease. Blood was drawn from each subject after an overnight fast. All studies were approved by the institutional review board of the hospital, and written consent was obtained from all participants.

Lipoprotein Analysis

Serum TC and TG were determined using enzymatic assay kits (Kyowa Medex, Tokyo, Japan). Apo A-Ⅰ, A-Ⅱ, B, C-Ⅱ, C-Ⅲ, and E were measured with turbidimetric immunoassay kits (Daiichi Chemicals, Tokyo, Japan), and lipoprotein(a) (Lp(a)) with enzyme immunoassay kits (Daiichi Chemicals, Tokyo, Japan). Remnant-like particle-cholesterol (RLP-C) and triglyceride (RLP-TG) levels were determined by an immune-adherence method (Japan Immunoresearch Laboratories, Tokyo, Japan).

PAGE of lipoprotein fractions was performed using the LipoPhor system (Joko, Tokyo, Japan) as described previously[4]. The LDL-migration index (LDL-MI) was calculated as described by Mishima *et al.*[6] as the distance between the very low-density lipoprotein (VLDL) peak and the LDL peak divided by the distance between the VLDL peak and the HDL peak. Lipoprotein profiles were classified into four types (SAND) according to the method described previously[4]: Type S (symmetric), the LDL wave is sharp and is symmetrical to the perpendicular line from the LDL peak to the baseline; Type A (asymmetric), the LDL wave is asymmetric with a broad foot on the cathodic side; Type N (nodular), a nodule is observed on the shoulder of the LDL wave; and Type D (disrupted), continuous components are observed between LDL and VLDL waves with no clear LDL wave.

Retinol Binding Protein (RBP) and Transthyretin (TTR)

Levels of RBP, which has a half-life of about 12 hours, and TTR (also known as prealbumin), which has a half-life of 2 days, were determined by an immunonepherometric procedure (Dade Behring, Tokyo)[7].

Other Materials

Other materials used in this study were obtained as follows: fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) from Arkray (Kyoto); immunoreactive insulin (IRI) from Eiken Chemical (Tokyo); uric acid (UA) from Kyowa Medex (Tokyo); high-sensitivity C-reactive protein (HsCRP) from Dade Behring (Tokyo); interleukin 6 (IL6) from Fujirebio (Tokyo); leptin (Lep) from BioVendor Laboratory Medicine (Tokyo); adiponectin (AN) from Otsuka Pharmaceutical (Tokyo); anti-oxidized LDL antibody (OxLDLAb) and oLAB from Biomedica (Vienna); oxidized LDL antigen (OxLDLAg) and MX kit from Kyowa Medex (Tokyo); and malondialdehyde-modified LDL (MDA-LDL) and sandwich ELISA using a monoclonal anti-MDA-LDL antibody (ML25) from Daiichi Chemicals (Tokyo).

Insulin resistance was calculated using a homeostasis model assessment: insulin resistance (HOMA-IR)[8]. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). Pulse wave velocity (PWV) and ankle-brachial pressure index (ABI) were measured using Vasera VS-1000 (Fukuda Denshi, Tokyo). Systolic blood pressure (SBP), diastolic blood pressure (DBP), right (R-) and left (L-) ankle-brachial pressure index (ABI), and right (R-), left (L-) and brachial (B-) PWV were determined.

Statistical Analysis

Statistical analysis was performed with one-way ANOVA, using StatView, ver. 5.0 (SAS Institute, USA). The results are expressed as the means ± SD. A level of $p < 0.05$ was considered significant. Univariate regression analysis was performed using linear regression and Pearson's correlation coefficient, considering $R < -0.4$ or $R > 0.4$ to be of significance. Multivariate analysis was performed using stepwise regression analysis.

Table 1. Characteristics of study subjects

	Men	Women	Total
Number	33	25	58
Age	39.8 ± 8.5	46.1 ± 11.1	42.5 ± 10.1
TC (mg/dL)	205.9 ± 37.0	213.4 ± 36.4	209.2 ± 36.5
TG (mg/dL)	168.9 ± 151.8	127.2 ± 131.8	150.9 ± 143.8
HDL-C (mg/dL)	56.5 ± 15.7	65.0 ± 13.2*	60.1 ± 15.2
LDL-C (mg/dL)	123.2 ± 32.2	124.6 ± 31.4	123.8 ± 31.6
ApoA-Ⅰ (mg/dL)	136.8 ± 19.7	145.7 ± 15.2	140.7 ± 18.3
ApoA-Ⅱ (mg/dL)	30.6 ± 3.4	28.9 ± 4.5	29.8 ± 4.0
ApoB (mg/dL)	96.0 ± 24.6	97.4 ± 25.3	96.6 ± 24.7
ApoC-Ⅱ (mg/dL)	4.2 ± 2.6	3.7 ± 2.6	4.0 ± 2.6
ApoC-Ⅲ (mg/dL)	10.3 ± 3.9	9.8 ± 3.7	10.1 ± 3.8
ApoE (mg/dL)	4.7 ± 1.6	4.8 ± 1.5	4.8 ± 1.5
Lp(a) (mg/dL)	14.0 ± 20.0	15.0 ± 16.1	14.4 ± 18.3
RLP-C (mg/dL)	16.2 ± 12.8	13.1 ± 12.0	14.9 ± 12.4
RLP-TG (mg/dL)	66.8 ± 117.3	36.7 ± 76.3	53.8 ± 102.0
OxLDLAb (mU/mL)	1304.4 ± 4095.6	810.4 ± 2112.2	1091.5 ± 3369.9
OxLDLAg (U/mL)	9.2 ± 4.6	9.2 ± 4.9	9.2 ± 4.7
MDA-LDL (U/L)	110.9 ± 40.5	111.6 ± 42.9	111.2 ± 41.2
TC/TG	1.93 ± 1.09	2.41 ± 1.08	2.14 ± 1.10
LDL-C/ApoB	1.30 ± 0.19	1.29 ± 0.16	1.30 ± 0.18
LDL-MI	0.33 ± 0.04	0.34 ± 0.04	0.34 ± 0.04
FPG (mg/dL)	101.2 ± 23.4	97.6 ± 15.9	99.7 ± 20.4
HbA_{1c} (%)	5.2 ± 0.8	5.2 ± 0.7	5.2 ± 0.8
IRI (μU/mL)	9.90 ± 4.56	8.91 ± 4.60	9.48 ± 4.56
HOMA-IR	2.47 ± 1.17	2.25 ± 1.44	2.37 ± 1.29
UA (mg/dL)	5.7 ± 1.1	4.5 ± 1.1***	5.2 ± 1.3
HsCRP (mg/dL)	0.10 ± 0.11	0.28 ± 1.05	0.17 ± 0.69
RBP (mg/dL)	4.7 ± 2.4	3.4 ± 1.3*	4.1 ± 2.1
TTR (mg/dL)	32.2 ± 6.9	25.7 ± 6.6**	29.4 ± 7.5
IL-6 (pg/mL)	1.56 ± 1.08	1.68 ± 1.50	1.61 ± 1.27
Lep (ng/mL)	7.6 ± 12.8	14.1 ± 12.6	10.4 ± 13.0
AN (ng/mL)	0.84 ± 0.44	1.28 ± 0.70*	1.03 ± 0.60
BMI (kg/m^2)	23.8 ± 2.0	23.5 ± 4.1	23.7 ± 3.0
SBP (mmHg)	126.5 ± 11.4	127.2 ± 21.7	126.8 ± 16.5
DBP (mmHg)	81.9 ± 7.8	81.9 ± 14.0	81.9 ± 10.8
R-ABI	1.16 ± 0.06	1.14 ± 0.05	1.15 ± 0.06
L-ABI	1.16 ± 0.06	1.15 ± 0.06	1.16 ± 0.06
R-PWV (m/sec)	12.4 ± 1.4	12.6 ± 2.0	12.5 ± 1.7
L-PWV (m/sec)	12.5 ± 2.0	12.7 ± 2.0	12.6 ± 2.0
B-PWV (m/sec)	6.2 ± 0.9	6.1 ± 1.3	6.2 ± 1.1

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$, Men vs Women

Results

The lipid profiles of the subjects are summarized in **Table 1**. They were classified by the lipoprotein PAGE pattern into Types S (n=10), A (n=37), and N (n=11). No subjects showed the Type D pattern. The relationship between SAND classifications and lipid profiles is shown in **Table 2**. Serum TC was not different among the three types, but LDL-C was slightly higher in Type A than in Type S. HDL-C significantly decreased from Type S to Type N. Serum TG tended to increase from Type S to Type N. ApoB was higher in Type A and N compared with Type S. ApoC-Ⅱ, C-Ⅲ and E were higher in Type N than in Types S and A.

Table 2. Characteristics of study subjects according to the SAND classification

SAND Classification	S	A	N
Number	10	37	11
TC (mg/dL)	185.9 ± 32.6	214.4 ± 36.4	212.5 ± 35.5
TG (mg/dL)	58.1 ± 18.0	138.2 ± 122.6	278.2 ± 191.1$^{**, §§}$
HDL-C (mg/dL)	78.8 ± 15.0	58.4 ± 11.4***	49.0 ± 12.1$^{***, §§}$
LDL-C (mg/dL)	101.5 ± 30.6	132.3 ± 29.3**	115.7 ± 30.2
ApoA-Ⅰ (mg/dL)	150.8 ± 24.3	139.3 ± 16.2	135.9 ± 17.3
ApoA-Ⅱ (mg/dL)	30.3 ± 5.6	29.4 ± 2.9	30.8 ± 5.5
ApoB (mg/dL)	74.1 ± 20.7	100.6 ± 24.5**	103.5 ± 17.4**
ApoC-Ⅱ (mg/dL)	2.1 ± 1.4	3.7 ± 2.3*	6.6 ± 2.6$^{***, §§}$
ApoC-Ⅲ (mg/dL)	7.5 ± 2.2	9.3 ± 2.8	15.1 ± 3.8$^{***, §§§}$
ApoE (mg/dL)	4.5 ± 1.3	4.4 ± 1.3	6.2 ± 1.8$^{**, §§}$
Lp(a) (mg/dL)	23.7 ± 32.3	14.2 ± 6.6	14.2 ± 14.8
RLP-C (mg/dL)	8.7 ± 4.7	13.5 ± 10.9	24.9 ± 16.7$^{**, §§}$
RLP-TG (mg/dL)	13.9 ± 12.9	45.9 ± 98.6	116.8 ± 134.2$^{*, §}$
OxLDLAb (mU/mL)	1447.6 ± 3150.1	1207.9 ± 3906.8	376.0 ± 336.1
OxLDLAg (U/mL)	10.4 ± 0.6	9.5 ± 4.7	7.0 ± 1.8
MDA-LDL (U/L)	75.6 ± 25.9	111.6 ± 40.4**	142.3 ± 29.3$^{**, §}$
TC/TG	3.42 ± 0.95	2.12 ± 0.90***	1.07 ± 0.58$^{***, §§}$
LDL-C/ApoB	1.36 ± 0.07	1.33 ± 0.13	1.12 ± 0.28$^{**, §§}$
LDL-MI	0.31 ± 0.02	0.33 ± 0.03	0.39 ± 0.03$^{***, §§§}$
FPG (mg/dL)	93.8 ± 6.1	100.5 ± 24.4	102.3 ± 12.3
HbA_{1c} (%)	5.1 ± 0.7	5.2 ± 1.8	5.6 ± 0.6
IRI (μU/mL)	9.27 ± 3.70	9.02 ± 5.02	11.19 ± 3.42
HOMA-IR	2.17 ± 0.99	2.28 ± 1.41	2.86 ± 1.05
UA (mg/dL)	4.9 ± 1.1	5.1 ± 1.2	5.8 ± 1.5
HsCRP (mg/dL)	0.60 ± 1.65	0.08 ± 0.09	0.10 ± 0.14
RBP (mg/dL)	3.0 ± 0.9	3.9 ± 1.7	5.8 ± 3.0$^{**, §§}$
TTR (mg/dL)	25.0 ± 5.6	28.7 ± 6.0	35.8 ± 9.6$^{**, §§}$
IL-6 (pg/mL)	2.27 ± 2.22	1.56 ± 1.05	1.21 ± 0.37
Lep (ng/mL)	11.8 ± 17.3	10.2 ± 13.0	10.1 ± 9.3
AN (ng/mL)	1.15 ± 0.54	1.08 ± 0.61	0.76 ± 0.57
BMI (kg/m^2)	22.8 ± 3.8	23.8 ± 2.9	24.0 ± 2.8
SBP (mmHg)	122.9 ± 19.0	125.9 ± 13.8	133.4 ± 21.7
DBP (mmHg)	78.5 ± 11.8	81.7 ± 10.2	85.9 ± 11.5
R-ABI	1.17 ± 0.04	1.15 ± 0.06	1.15 ± 0.06
L-ABI	1.17 ± 0.06	1.15 ± 0.07	1.17 ± 0.04
R-PWV (m/sec)	12.1 ± 1.8	12.5 ± 1.7	12.9 ± 1.6
L-PWV (m/sec)	12.2 ± 1.8	12.5 ± 2.1	13.1 ± 1.9
B-PWV (m/sec)	5.4 ± 1.0	6.3 ± 0.9*	6.5 ± 1.3*

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.0001$ compared with Type S.
$^{§}p < 0.05$, $^{§§}p < 0.01$, $^{§§§}p < 0.0001$ compared with Type A.

The TC/TG ratio significantly decreased from Type S to Type N. LDL-MI was significantly higher, and LDL-C/ApoB was significantly lower, in Type N than in Types S and A. The tendencies in the lipid profiles observed in this study are consistent with the results we previously reported[4]. RBP and TTR were significantly higher in Type N than in Types S and A. MDA-LDL significantly increased from Type S to Type N.

In univariate analysis, a strong positive correlation was observed between RBP and logTG, ApoC-Ⅱ, C-Ⅲ, E, logRLP-C, and logRLP-TG (**Table 3**). There was a negative correlation between RBP and HDL-C. There was also a negative correlation between RBP and TC/TG and LDL-C/ApoB, and a positive correlation

Table 3. Correlation of RBP and TTR with other variables

		R	P
RBP	logTG	0.676	<0.0001
	HDL-C	−0.474	0.0001
	ApoC-II	0.600	<0.0001
	ApoC-III	0.640	<0.0001
	ApoE	0.626	<0.0001
	logRLP-C	0.657	<0.0001
	logRLP-TG	0.702	<0.0001
	TC/TG	−0.541	<0.0001
	LDL-C/ApoB	−0.593	<0.0001
	LDL-MI	0.560	<0.0001
	TTR	0.652	<0.0001
TTR	logTG	0.485	<0.0001
	ApoC-II	0.455	0.0003
	ApoC-III	0.540	<0.0001
	logRLP-C	0.452	0.0003
	logRLP-TG	0.496	<0.0001
	TC/TG	−0.473	0.0001
	LDL-MI	0.427	0.0007
BMI	TC	0.487	<0.0001
	LDL-C	0.450	0.0003
	ApoB	0.570	<0.0001
	MDA-LDL	0.402	0.0016
	IRI	0.543	<0.0001
	logHsCRP	0.405	0.0014
	logIL6	0.402	0.0016
	logLeptin	0.514	<0.0001
MDA-LDL	TC	0.720	<0.0001
	log TG	0.540	<0.0001
	LDL-C	0.670	<0.0001
	ApoB	0.822	<0.0001
	ApoC-II	0.486	<0.0001
	ApoC-III	0.494	<0.0001
	logRLP-C	0.550	<0.0001
	logRLP-TG	0.503	<0.0001
	TC/TG	−0.469	<0.0001
	LDL-MI	0.582	<0.0001
logOxLDLAg	log Lp(a)	0.767	<0.0001
AN	logRLP-TG	−0.405	0.0014
	TC/TG	0.428	0.0007
	UA	−0.570	<0.0001
	BMI	−0.395	0.0020
	HOMA-IR	−0.413	0.0011
	DBP	−0.452	0.0003

between RBP and LDL-MI. There was no significant correlation between RBP and BMI.

There was a positive correlation between TTR and logTG, ApoC-II, C-III, logRLP-C and logRLP-TG. There was also a negative correlation between TTR and TC/TG, and a positive correlation between TTR and LDL-MI. There was no significant correlation between TTR and BMI.

Multivariate analysis was performed by a forward stepwise regression procedure, using HDL-C, LDL-C, logLp(a), logRLP-C, logRLP-TG, MDA-LDL, logOxLDLAg, logFPG, HbA1c, IRI, UA, RBP, TTR, logHsCRP, logIL-6, logLep, BMI and AN as independent variables (**Table 4**).

RBP was accounted for by logRLP-TG (0.560), TTR (0.363), and LDL-C (−0.185) (adjusted R^2=0.646). TTR was accounted for by RBP (0.541), UA (0.247), and logLp(a) (−0.203) (adjusted R^2=0.527). Analysis was also performed by excluding RBP and TTR from the independent variables. In this case, RBP was accounted for by logRLP-TG (0.867), logIL-6 (0.288), BMI (−0.251), and LDL-C (−0.199) (adjusted R^2=0.621). TTR was accounted for by logLp(a) (−0.378), AN (−0.315), and logRLP-TG (0.309) (adjusted R^2=0.415)

MDA-LDL was accounted for by LDL-C (0.566) and logRLP-C (0.405) (R^2=0.717). logLp(a) (0.793) and LDL-C (0.183) were independent variables for logOxLDLAg (R^2=0.620). logHsCRP was accounted for by logIL-6 (0.354), IRI (0.253), and logOxLDLAg (0.254) (R^2=0.361). UA (−0.517) and BMI (−0.304) were independent variables for AN (R^2=0.429).

Discussion

RBP and TTR have been used clinically as rapid turnover proteins for assessing the short-term fluctuation of nutritional states. RBP is the only specific transport protein for retinol (vitamin A) in the circulation[9]. Although hepatocytes are regarded as the principal source of circulating RBP, adipocytes have the second-highest expression level, indicating that they may be involved in retinoid storage and metabolism[10]. RBP is easily filtered through the renal glomerular membrane and binds TTR to form a complex that prevents renal clearance[11]. The only known function of RBP has been to deliver retinol to tissues[9]; however, very recently, Yang *et al.*[12] reported that serum RBP levels were elevated in insulin-resistant mice and also in humans with obesity and type 2 diabetes. Serum RBP levels were increased in obese-nondiabetic and obese-diabetic subjects compared with lean controls; however, there was no difference in the magnitude of serum RBP elevation between the obese and obese-diabetic groups, suggesting that obesity and insulin resistance are associated with elevated RBP. These results suggest that RBP and TTR may be related to the pathophysi-

Table 4. Multivariate regression analysis

Dependent variables	Independent variables with statistical significance					Adjusted R^2
HDL-C	logRLP-TG (−0.564)					0.318
LDL-C	MDA-LDL (0.710)	logOxLDLAg (0.244)	RBP (−0.226)	logLp(a) (−0.127)		0.577
logLp(a)	logOxLDLAg (0.720)	TTR (−0.226)				0.637
logRLP-C	logRLP-TG (0.752)	MDA-LDL (0.172)				0.725
logRLP-TG	logRLP-C (0.502)	RBP (0.284)	logIL-6 (−0.220)	HDL-C (−0.178)	BMI (0.180)	0.812
MDA-LDL	LDL-C (0.566)	logRLP-C (0.405)				0.601
logOxLDLAg	logLp(a) (0.729)	LDL-C (0.183)				0.620
logFPG	HbA_{1c} (0.770)					0.593
HbA_{1c}	logFPG (0.770)	logLep (0.171)				0.623
IRI	BMI (0.543)					0.294
UA	AN (−0.570)					0.325
RBP	logRLP-TG (0.560)	TTR (0.363)	LDL-C (−0.185)			0.646
TTR	RBP (0.541)	UA (0.247)	logLp(a) (−0.203)			0.527
logHsCRP	logIL-6 (0.354)	IRI (0.253)	logOxLDLAg (0.244)			0.361
logIL-6	logHsCRP (0.486)					0.237
logLep	BMI (0.514)					0.265
BMI	logIL-6 (0.297)	logLep (0.299)	LDL-C (0.235)	IRI (0.234)	logRLP-TG (0.204)	0.577
AN	UA (−0.517)	BMI (−0.304)				0.429

ology of MS or remnant lipoprotein metabolism. Interestingly, there was no or only a weak correlation between RBP or TTR and BMI, suggesting that the increase of these proteins may not be a simple result of obesity. RLP-TG was shown to be an independent variable for RBP. By the SAND classification, RBP and TTR are significantly higher in Type N than in Types S and A, suggesting that these proteins are related to lipoproteins, particularly remnant lipoproteins. To our knowledge, the detailed relation between these proteins and MS has never been reported.

AN, an adipose-specific secretory protein, exhibits antidiabetic and antiatherogenic properties. Plasma AN concentrations have been reported to be significantly lower in men than in women, but were not different between pre- and postmenopausal women, suggesting that androgens decrease plasma AN and that androgen-induced hypoadiponectinemia may be related to a high risk of insulin resistance and atherosclerosis in men[13]. Plasma concentrations of AN have also been shown to be significantly lower in obese subjects than in non-obese subjects[14]. Interestingly, these results showed a significant negative correlation between AN and UA. The precise mechanism is not clear, but the increase of UA may be a response to oxidative stress. In the hypoadiponectinemic state, *in vivo* oxidative stress may be increased. Plasma AN concentrations have been reported to be correlated negatively with waist circumference, visceral fat area, serum TG concentration, FPG, fasting plasma insulin, SBP and DBP in both sexes[15]. Hypoadiponectinemia has been closely associated with the clinical phenotype of MS, using the criteria for Japanese people.

OxLDLAg, a marker of modified LDL, was mainly accounted for by Lp(a) and LDL-C, suggesting that the concentration of OxLDLAg may be mainly determined by Lp(a) and LDL-C; however, MDA-LDL, another marker of modified LDL, was significantly related with LDL-C and RLP-C. Further analysis will be needed to clarify the determinants of oxidative modification of LDL.

MS is quite common among the US population, and to a lesser extent, among the Japanese. The age-adjusted prevalence of MS among the US population as defined by NCEP-ATPⅢ was calculated as 23.7%[16]. Another study showed that 44% of the US population over 50 years of age meets the NCEP criteria[17]. MS is very common even in Japan, and affects 24.4% of the Japanese male population aged 60 ± 12 years[18], when using the criteria of an 85 cm abdominal circumference (instead of the 102 cm proposed by NCEP-ATPⅢ) recommended by the joint committee for the guideline of obesity and MS in Japan[19]. In addition to genetic predisposition, MS is clearly associated with overeating and lack of exercise. It is urgent to clarify the pathophysiology of MS in order to prevent early death and disability caused by MS-related outcomes such as myocardial infarction. In this study, we found that

RBP and TTR may be new markers of overnutrition, and possibly of MS. It is necessary to study the relationship between these proteins and MS in greater detail.

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