Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 355–360
Metabolism
Clinical and Experimental
www.metabolismjournal.com

High-molecular-weight adiponectin is a predictor of progression to metabolic syndrome: a population-based 6-year follow-up study in Japanese men

Yoshie Seino[a], Hiroshi Hirose[a,b,*], Ikuo Saito[a,b], Hiroshi Itoh[a]

[a]*Department of Internal Medicine, School of Medicine, Keio University, Tokyo 160-8582, Japan*
[b]*Health Center, School of Medicine, Keio University, Tokyo 160-8582, Japan*

Received 4 April 2008; accepted 21 October 2008

Abstract

Adiponectin is an adipocyte-specific secretory protein, which possesses antidiabetic and antiatherosclerotic properties. Adiponectin exists as multimers in serum, and high-molecular-weight (HMW) adiponectin is particularly considered to be the active form of the protein. The objective of the present study was to examine whether decreased HMW adiponectin is a predictor of progression to metabolic syndrome during a 6-year follow-up period in Japanese men. The study subjects were 416 Japanese men without metabolic syndrome, aged 30 to 59 years at baseline, who had participated in annual health checkups in both 2000 and 2006. Low concentration of HMW adiponectin (≤2.65 μg/mL) was associated with substantially higher hazard ratio of the progression to metabolic syndrome after adjustment for age and body mass index (hazard ratio, 1.561; 95% confidence interval, 1.051-2.292; $P = .028$). The number of subjects with the progression to metabolic syndrome in each tertile based on baseline HMW adiponectin concentration was significantly different among the 3 groups (HMW adiponectin: $\chi^2 = 7.473$, $P = .0238$; total adiponectin: $\chi^2 = 4.477$, $P = .1066$; HMW-total adiponectin ratio: $\chi^2 = 1.676$, $P = .4325$). It was suggested that decreased HMW adiponectin is a predictor of the progression to metabolic syndrome in a 6-year follow-up study of Japanese men. Furthermore, it was suggested longitudinally that measuring HMW adiponectin is efficient to predict the progression to metabolic syndrome compared with measuring total adiponectin or HMW-total adiponectin ratio.

1. Introduction

Adiponectin (also named *Acrp30* [1], *AdipoQ* [2], *GBP28* [3], and *apM1* [4]) is an adipocyte-specific secretory protein that circulates in serum in at least 3 forms: low-molecular-weight, middle-molecular-weight, and high-molecular-weight (HMW) form multimer including 12mer and 18mer [5-7]. Serum adiponectin level is reported to correlate well with insulin sensitivity and lipid metabolism [8,9]. There have been many reports that adiponectin is related to metabolic syndrome [10,11], type 2 diabetes mellitus [12-14], obesity [15], and arteriosclerosis [16,17]. Its level is reported to be decreased in patients and animal models of obesity, diabetes, and coronary artery disease (CAD) [15,18-20]; and weight reduction increased the adiponectin level in obese patients [19]. Moreover, adiponectin is reported to have protective activities on the vasculature [16,17,21-23].

Recent studies have demonstrated that the HMW multimer form of adiponectin is the active form of this protein [6,24,25]: For example, it was reported that the HMW form of adiponectin stimulated the phosphorylation of 5′-adenosine monophosphate–activated protein kinase [6,24]; the HMW form was the most active form in suppressing hepatic glucose production [6]; and Kobayashi et al [25] reported that only HMW adiponectin selectively suppressed endothelial cell apoptosis, whereas neither the low- nor the middle-molecular-weight form had this effect.

Clinical data also confirmed that type 2 diabetes mellitus patients with CAD have a selective reduction in HMW adiponectin [25-27]. Furthermore, weight reduction [25]

Disclosure statement: Fujirebio, Tokyo, Japan (formerly Chugai Diagnostic Science, Tokyo), and Dr Hirose have a partial patent concerning HMW adiponectin measurement.

* Corresponding author. Department of Internal Medicine and Health Center, School of Medicine, Keio University, Tokyo 160-8582, Japan. Tel.: +81 3 3353 1211x62383; fax: +81 3 5363 3635.
E-mail address: hhirose@hc.cc.keio.ac.jp (H. Hirose).

0026-0495/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.10.008

preferentially increased the HMW form of adiponectin but not the other 2 oligomeric complexes. Waki et al [6] revealed that human adiponectin with rare missense mutations (G84R and G90S) did not form HMW multimers. These mutations were associated with insulin resistance and type 2 diabetes mellitus. They concluded that the proportion of each adiponectin oligomeric complex is important for the antidiabetic and antiatherogenic activities of this protein [6].

Several reports have shown that HMW adiponectin is more useful than total adiponectin. Especially in patients with type 2 diabetes mellitus receiving medication including thiazolidinediones, HMW-total adiponectin ratio was reported to be more useful than simply measuring serum total adiponectin level: for example, Pajvani et al [26] reported that HMW-total adiponectin ratio was significantly more useful to monitor the improvement of insulin sensitivity in response to thiazolidinediones in type 2 diabetes mellitus; Hara et al [11] reported that the HMW-total adiponectin ratio had better predictive power for the prediction of insulin resistance and metabolic syndrome than plasma total adiponectin level; and Aso et al [27] reported that HMW-total adiponectin ratio was more useful to evaluate CAD in type 2 diabetes mellitus patients than simply measuring serum total adiponectin. We have reported a cross-sectional study in healthy Japanese male subjects without any medication that showed that measuring HMW adiponectin was as effective as HMW-total adiponectin ratio to predict insulin resistance and/or metabolic syndrome [28].

Recently, longitudinal data concerning HMW adiponectin have been reported. For example, decreased HMW adiponectin was an independent risk factor for the progression to type 2 diabetes mellitus in Japanese Americans during a 5.4-year follow-up study [29]; and Inoue et al [30] reported that serum HMW adiponectin level was a predictor of future cardiovascular events in patients with CAD during 7 years of follow-up.

The aim of this study was to investigate longitudinally whether measuring serum HMW adiponectin might be useful to predict the progression to metabolic syndrome compared with total adiponectin or HMW-total ratio in nondiabetic Japanese subjects.

2. Subjects and methods

2.1. Subjects

This study included 416 Japanese male teachers and workers at Keio University, aged 30 to 59 years at baseline, who underwent annual health checkups in both 2000 and 2006. Subjects with metabolic syndrome, endocrine disease, or significant renal or hepatic disease, and those receiving medication for diabetes mellitus at baseline were excluded. Twenty-six subjects were receiving hydroxymethylglutaryl–coenzyme A inhibitor, but none was receiving niacin in this study. The present study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject after full explanation of the purpose, nature, and risk of all procedures used. The protocol was approved by the ethical review committees of the Health Center and the Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.

2.2. Measurements

Systolic blood pressure, diastolic blood pressure, and heart rate were measured twice by well-trained staff at around 9:00 AM using an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Aichi-Prefecture, Japan) with the subject seated after resting for at least 5 minutes, as described previously [28,31,32]. Height, weight, fasting plasma glucose, serum insulin, total adiponectin, HMW adiponectin, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured at around 9:00 AM after an overnight fast. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Plasma glucose and serum lipids were assayed by routine automated laboratory methods, as described previously [28,31,32]. Serum insulin concentration was measured by an enzyme immunoassay using a commercially available kit (Tosoh, Tokyo, Japan) with intra- and interassay coefficients of 2.9% to 4.6% and 4.5% to 7.0%, respectively [28,31]. The insulin resistance index was assessed by homeostasis model assessment (HOMA-R).

Total adiponectin concentration in serum was measured by enzyme-linked immunosorbent assay (ELISA) (Adiponectin ELISA Kit; Otsuka Pharmaceutical, Tokyo, Japan) [15] with intra- and interassay coefficients of variation of less than 10%. High-molecular-weight adiponectin was measured using a commercially available kit (HMW Adiponectin ELISA Kit; Fujirebio, Tokyo, Japan). This ELISA system does not need a denaturing step, and the monoclonal antibody (IH7) is reported to react specifically with the HMW form of adiponectin [7]. The dilution curve was parallel to the standard curve. Intra- and interassay coefficients were 2.4% to 3.0% and 4.2% to 5.1%, respectively. The HMW-total adiponectin ratio was calculated as HMW adiponectin divided by total adiponectin.

2.3. Statistical analysis

Statistical analyses were performed using the StatView program for Windows (version 5.0-J; SAS Institute, Cary, NC). P values less than .05 were considered to denote statistical significance. We divided the study subjects into 5 groups with equal numbers of subjects based on serum HMW adiponectin level, and the 20th percentile of HMW adiponectin concentration was 2.65 μg/mL. Unpaired Student t test was used to compare various parameters between subjects who developed metabolic syndrome and those who did not, and between subjects with HMW adiponectin concentration of 2.65 μg/mL or less and those with HMW adiponectin concentration greater than 2.65 μg/mL. Because

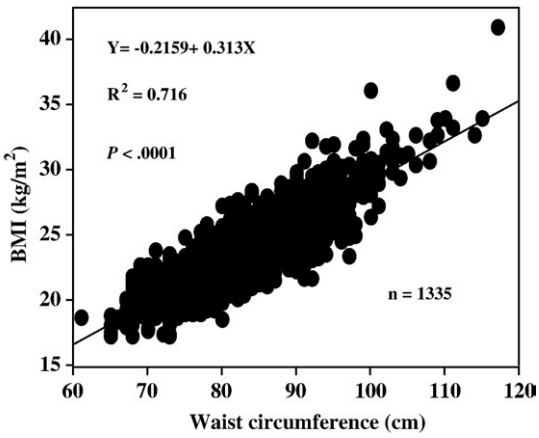

Fig. 1. Scatter plot of waist circumference (x) and BMI (y) in 1335 Japanese male subjects.

HOMA-R, serum triglycerides, total adiponectin, and HMW adiponectin levels were normally distributed after logarithmic transformation, we used logarithms of these data for the analyses.

The correlation between waist circumference and BMI in 1335 Japanese male teachers and workers at Keio University, aged 30 to 65 years, who underwent an annual health checkup in 2006 was determined by simple regression analysis.

Furthermore, we divided the study subjects into tertile groups with equal numbers of subjects: H1 to H3 based on serum baseline HMW adiponectin level, T1 to T3 based on serum baseline total adiponectin level, and R1 to R3 based on baseline HMW-total ratio. Tertile values of HMW adiponectin were as follows: H1, 0.25 to 3.16 μg/mL; H2, 3.17 to 5.06 μg/mL; and H3, 5.07 to 26.02 μg/mL. The number of subjects was 138, 139, and 139, respectively. Tertile values of total adiponectin were as follows: T1, 0.63 to 4.65 μg/mL; T2, 4.66 to 7.43 μg/mL; and T3, 7.44 to 37.10 μg/mL (number of subjects was 139, 138, and 139). Tertile values of HMW-total ratio were as follows: R1, 0.40 to 0.612; R2, 0.613 to 0.824; and R3, 0.825 to 1.0 (number of subjects was 138, 139, and 139). Comparisons of the number of subjects who developed metabolic syndrome in the 3 groups, based on total and HMW adiponectin and HMW-total ratio at baseline, were performed by χ^2 test.

A Cox proportional hazard model was used to test the significance of baseline HMW adiponectin levels in predicting the incidence of metabolic syndrome as a dependent variable using JMP for Windows (version 6.0, SAS Institute, Cary, NC). Hazards ratios were estimated through a Cox proportional hazard model. When we divided the study subjects into 5 groups based on serum HMW adiponectin level, the 20th percentile of HMW adiponectin concentration was 2.65 μg/mL.

2.4. Definition of metabolic syndrome

Because measurement of waist circumference was not performed in the baseline data of 2000, we defined

Table 1
Baseline clinical characteristics of subjects who developed or did not develop metabolic syndrome during the 6-year follow-up period

	MS	Non-MS	P*
n	27	389	
Age (y)	46.6 ± 9.2	44.1 ± 8.3	NS
Height (cm)	171.1 ± 6.4	169.8 ± 5.8	NS
Body weight (kg)	73.8 ± 9.9	65.2 ± 7.8	<.0001
BMI (kg/m^2)	25.1 ± 2.2	22.6 ± 2.3	<.0001
Systolic blood pressure (mm Hg)	133.9 ± 12.4	118.5 ± 13.8	<.0001
Diastolic blood pressure (mm Hg)	86.1 ± 9.1	74.7 ± 10.4	<.0001
Total cholesterol (mg/dL)	203.7 ± 30.5	196.3 ± 27.2	NS
Triglycerides (mg/dL)	179.5 ± 85.8	105.3 ± 59.7	<.0001
HDL cholesterol (mg/dL)	44.5 ± 7.3	55.9 ± 12.6	<.0001
LDL cholesterol (mg/dL)	130.8 ± 30.0	123.3 ± 26.0	NS
Glucose (mg/dL)	97.1 ± 7.9	91.9 ± 8.4	.0017
Glycated albumin (%)	16.3 ± 2.0	16.4 ± 2.0	NS
HOMA-R	1.68 ± 0.73	1.12 ± 0.65	<.0001
Total adiponectin (μg/mL)	5.3 ± 3.0	6.8 ± 3.9	.0274
HMW adiponectin (μg/mL)	3.5 ± 1.6	4.8 ± 2.9	.0143
HMW-total ratio	0.72 ±0.21	0.74 ± 0.21	NS

Values are mean ± SD. MS indicates metabolic syndrome; NS, not significant.

* $P > .1$, by unpaired t test (NS). Logarithmic transformation of HOMA-R, serum triglycerides, HMW adiponectin, and total adiponectin levels was performed as needed to improve normality.

Table 2
Baseline clinical characteristics of subjects with HMW adiponectin concentration less than or equal to 2.65 and greater than 2.65 μg/mL during 6-year follow-up period

	HMW adiponectin ≤2.65	HMW adiponectin >2.65	P*
n	84	332	
Age (y)	44.3 ± 8.1	44.3 ± 8.5	NS
Height (cm)	170.7 ± 5.8	169.8 ± 5.8	NS
Body weight (kg)	68.1 ± 7.9	65.1 ± 8.2	.0027
BMI (kg/m^2)	23.3 ± 2.2	22.6 ± 2.4	.0071
Systolic blood pressure (mm Hg)	122.2 ± 14.3	118.7 ± 14.1	.0396
Diastolic blood pressure (mm Hg)	77.5 ± 11.3	74.8 ± 10.4	.0399
Total cholesterol (mg/dL)	201.2 ± 29.0	195.5 ± 27.4	.0932
Triglycerides (mg/dL)	134.5 ± 71.5	103.9 ± 60.7	<.0001
HDL cholesterol (mg/dL)	49.5 ± 8.1	56.7 ± 13.2	<.0001
LDL cholesterol (mg/dL)	130.8 ± 28.1	121.7 ± 25.8	.0049
Glucose (mg/dL)	92.7 ± 7.1	92.0 ± 8.8	NS
Glycated albumin (%)	16.0 ± 1.6	16.5 ± 2.1	.0601
HOMA-R	1.38 ± 0.81	1.07 ± 0.64	.0003
Total adiponectin (μg/mL)	3.1 ± 1.2	7.6 ± 3.7	<.0001
HMW adiponectin (μg/mL)	2.0 ± 0.5	5.4 ± 2.8	<.0001
HMW-total ratio	0.72 ± 0.22	0.74 ± 0.20	NS

Values are mean ± SD.

* $P > .1$, by unpaired t test (NS). Logarithmic transformation of HOMA-R, serum triglycerides, HMW adiponectin, and total adiponectin levels was performed as needed to improve normality.

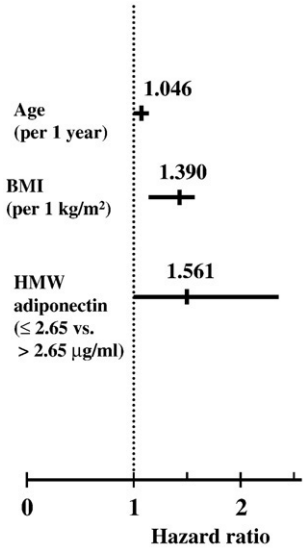

Fig. 2. Risk factors for the progression to metabolic syndrome in 6-year follow-up period. Results from the Cox proportional hazard model are shown. Hazard ratios are shown above the vertical bars. Horizontal bars are 95% confidence intervals.

metabolic syndrome based on a modification of the Japanese diagnostic criteria [33]: In addition to BMI of at least 24.32 kg/m^2 (instead of waist circumference ≥85 cm in men), the presence of at least 2 of the following 3 abnormalities was required:

1. Dyslipidemia: triglycerides of at least 150 mg/dL and/or HDL cholesterol less than 40 mg/dL or, alternatively, treatment with one or more antidyslipidemic agents.
2. High blood pressure: systolic blood pressure of at least 130 mm Hg and/or diastolic blood pressure of at least 85 mm Hg or, alternatively, treatment with one or more antihypertensive agents.
3. Hyperglycemia: fasting plasma glucose of at least 110 mg/dL.

Fig. 1 shows a scatter plot of waist circumference (x) and BMI (y) (R^2 = 0.716, P < .0001, n = 1335). Waist circumference of 85 cm corresponded to BMI of 24.32 kg/m^2.

3. Results

Of 416 men, 27 developed metabolic syndrome during the follow-up period of 6 years. Baseline characteristics of subjects who did and did not develop metabolic syndrome are shown in Table 1. At baseline, HMW adiponectin concentration was significantly lower in subjects who developed metabolic syndrome than in those who did not (P = .0143).

Baseline characteristics of subjects with HMW adiponectin concentration less than or equal to 2.65 μg/mL and those with HMW adiponectin concentration greater than 2.65 μg/mL are shown in Table 2.

3.1. Hazard ratio of the progression to metabolic syndrome

A Cox proportional hazard model was used to examine the association of serum level of HMW adiponectin with the progression to metabolic syndrome. Low concentrations of HMW adiponectin (≤2.65 μg/mL) were associated with substantially increased hazard ratio of the progression to metabolic syndrome after adjustment for age and BMI (hazard ratio, 1.561; 95% confidence interval, 1.051-2.292; P = .028) (Fig. 2).

3.2. Incidence of metabolic syndrome (HMW adiponectin vs total adiponectin or HMW-total ratio)

The association of adiponectin level with the progression to metabolic syndrome was analyzed in another way. We divided the study subjects into tertile groups with equal numbers of subjects: H1 to H3 based on baseline HMW adiponectin level, T1 to T3 based on baseline total adiponectin level, and R1 to R3 based on baseline HMW-

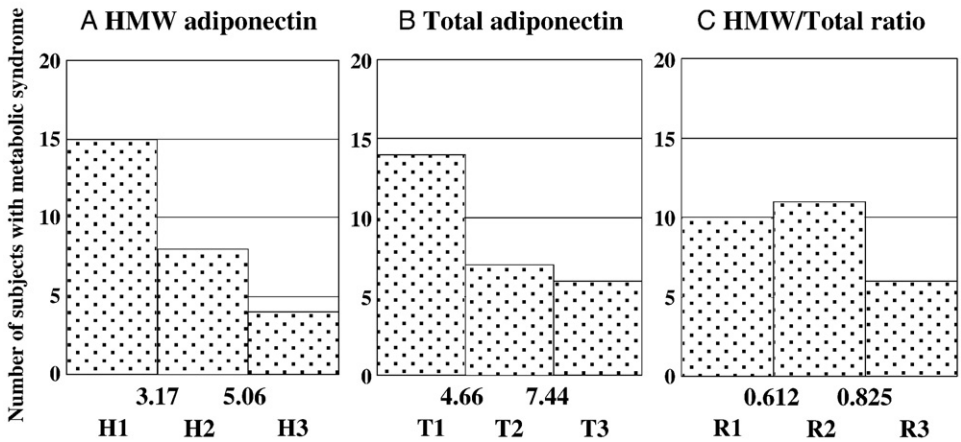

Fig. 3. Number of subjects who developed metabolic syndrome during 6-year follow-up period in each tertile based on serum levels of HMW adiponectin (A), total adiponectin (B), and HMW-total ratio at baseline (C).

total ratio. Overall, the number of subjects with metabolic syndrome in each tertile based on serum HMW adiponectin concentration was significantly different among the 3 groups (HMW adiponectin: $\chi^2 = 7.473$, $P = .0238$; total adiponectin: $\chi^2 = 4.477$, $P = .1066$; HMW-total ratio: $\chi^2 = 1.676$, $P = .4325$) (Fig. 3).

4. Discussion

Recently, longitudinal studies showing the clinical usefulness of HMW adiponectin level in circulation have been reported: for example, it was reported that decreased HMW adiponectin was an independent risk factor for the progression to type 2 diabetes mellitus in Japanese Americans during a 5.4-year follow-up study [29]. Inoue et al [30] also reported that serum HMW adiponectin level may serve as a predictor of future cardiovascular events in patients with CAD.

The present longitudinal study showed significant relevance of decreased HMW adiponectin level in development of metabolic syndrome. Furthermore, HMW adiponectin seemed to be a more useful predictor than total adiponectin or HMW-total ratio for assessing the risk of developing metabolic syndrome. It is reported that male patients with hypoadiponectinemia (<4.0 μg/mL) had a significant 2-fold increase in CAD prevalence, independent of well-known CAD risk factors [20]. In our previous cross-sectional study [28], the scatter plot showed that total adiponectin concentration (4.0 μg/mL) was roughly equal to HMW adiponectin (2.5 μg/mL). Because no definite cutoff value of HMW adiponectin has been established so far, we speculated that the value would be around 2.5 μg/mL from the reported cutoff value of total adiponectin (4.0 μg/mL). For this reason, we used HMW adiponectin cutoff value of the lowest quintile (2.65 μg/mL) for the Cox proportional hazard model analysis.

The limitations of this study were the study design with male subjects only and that waist circumference was not collected at baseline. We used BMI instead as a modified criterion of metabolic syndrome [33]. However, waist circumference and BMI were well correlated in our data ($R^2 = 0.716$ and $P < .0001$ in 1335 Japanese male subjects) (Fig. 1). Although we had to use BMI instead of waist circumference as the baseline of this study, we consider that the modified criteria adequately characterized the metabolic syndrome status. Further studies in different races including female subjects are needed and would facilitate understanding the importance of measuring HMW adiponectin.

In conclusion, it was suggested that decreased HMW adiponectin is a predictor of the progression to metabolic syndrome in a 6-year follow-up study of Japanese men. Furthermore, it was suggested longitudinally that measuring HMW adiponectin is efficient to predict progression to metabolic syndrome compared with measuring total adiponectin and HMW-total ratio.

Acknowledgment

This study was supported in part by a Grant-in Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (to HH), and by research grants (to HH) from Keio University, Tokyo.

References

[1] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-9.
[2] Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697-703.
[3] Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem (Tokyo) 1996;120:803-12.
[4] Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996;221:286-9.
[5] Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin: implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073-85.
[6] Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, et al. Impaired multimerization of human adiponectin mutants associated with diabetes: molecular structure and multimer formation of adiponectin. J Biol Chem 2003;278:40352-63.
[7] Nakano Y, Tajima S, Yoshimi A, Akiyama H, Tsushima M, Tanioka T, et al. A novel enzyme-linked immunosorbent assay specific for high-molecular-weight adiponectin. J Lipid Res 2006;47:1572-82.
[8] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947-53.
[9] Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.
[10] Miwa R, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. Circ J 2004;68:975-81.
[11] Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, et al. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care 2006;29:1357-62.
[12] Weyer C, Funahashi T, Tanaka S, Hotta K, Mtsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
[13] Spranger J, Kroke A, Möhlig M, Bergmann MM, Ristow M, Boeing H, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8.
[14] Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H, et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population: the Funagata study. Diabetes Care 2003;26:2015-20.
[15] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
[16] Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001;103:1057-63.

[17] Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, et al. Role of adiponectin in preventing vascular stenosis: the missing link of adipo-vascular axis. J Biol Chem 2002;277:37487-91.
[18] Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
[19] Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
[20] Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
[21] Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. Circulation 2000;102:1296-301.
[22] Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB–binding protein and regulates growth factor–induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002;105:2893-8.
[23] Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, et al. Adiponectin reduces atherosclerosis in apolipoprotein E–deficient mice. Circulation 2002;106:2767-70.
[24] Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, et al. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. J Biol Chem 2004;279:1304-9.
[25] Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 2004;94:e27-31.
[26] Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem 2004;279:12152-62.
[27] Aso Y, Yamamoto R, Wakabayashi S, Uchida T, Takayanagi K, Takebayashi K, et al. Comparison of serum high-molecular-weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. Diabetes 2006;55:1954-60.
[28] Seino Y, Hirose H, Saito I, Itoh H. High molecular weight multimer form adiponectin as a useful marker to evaluate insulin resistance and metabolic syndrome in Japanese men. Metabolism 2007;56:1493-9.
[29] Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. J Clin Endocrinol Metab 2006;91:3873-7.
[30] Inoue T, Kotooka N, Morooka T, Komoda H, Uchida T, Aso Y, et al. High molecular weight adiponectin as a predictor of long-term clinical outcome in patients with coronary artery disease. Am J Cardiol 2007; 100:569-74.
[31] Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, et al. Correlation of adipocyte-derived protein, adiponectin with insulin resistance index and serum HDL-cholesterol, independent of body mass index in the Japanese population. Clin Sci 2002;103:137-42.
[32] Hirose H, Saito I, Kawabe H, Saruta T. Insulin resistance index, HOMA-IR, and hypertension: seven-year follow-up study in middle-aged Japanese men (the KEIO study). Hypertens Res 2003;26: 795-800.
[33] Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome. J Jpn Soc Int Med 2005;94:188-203.