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High molecular weight multimer form of adiponectin as a useful marker to evaluate insulin resistance and metabolic syndrome in Japanese men

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Abstract

Adiponectin is an adipocyte-specific secretory protein that possesses antidiabetic and antiatherosclerotic properties. Recent studies have demonstrated that the high molecular weight (HMW) multimer form is the active form of this protein. In patients with type 2 diabetes mellitus, HMW-total adiponectin ratio was reported to be a more useful marker than total adiponectin in the prediction of insulin resistance and metabolic syndrome. In the present study of healthy Japanese male subjects without any medication, we investigated the hypothesis that measuring only HMW adiponectin may be as effective as HMW-total ratio to predict insulin resistance and/or metabolic syndrome. This was a working community–based cross-sectional study of 637 male subjects aged 30 to 65 years. Total and HMW adiponectin concentrations in serum were measured by enzyme-linked immunosorbent assay using commercially available kits. Serum HMW adiponectin level was inversely correlated with homeostasis model assessment of insulin resistance (HOMA-IR) ($r = -0.375$, $P < .0001$) even after adjustment for age and body mass index ($r' = -0.245$, $P < .0001$). When we divided the study subjects into quartile groups with equal numbers of subjects, HOMA-IR in the 4 groups based on serum HMW adiponectin level was significantly different ($P < .01$). Metabolic syndrome score in the 4 groups based on serum HMW adiponectin level was also significantly different ($P < .01$). Area under the curve of receiver operator characteristic curves of HMW adiponectin (0.73) to evaluate the presence of insulin resistance (HOMA-IR >2.5) was larger than that of total adiponectin (0.68) or HMW-total ratio (0.70). Area under the curve of receiver operator characteristic curves of HMW adiponectin (0.70) to evaluate the presence of metabolic syndrome (body mass index–based modified criteria) was also larger than that of total adiponectin (0.65), but equal to that of HMW-total ratio (0.70). These results suggest that simply measuring HMW adiponectin may be as effective as HMW-total ratio to evaluate the presence of insulin resistance and metabolic syndrome, at least in nondiabetic subjects who are not receiving any medication.

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

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endothelial cell apoptosis, whereas neither the middle nor the low molecular weight form had this effect. It was also reported that the ratio of HMW to total adiponectin, but not the absolute amount (total) of adiponectin, determines insulin sensitivity in humans and rodents [26]. Despite having similar total adiponectin levels to their wild-type littermates, *db*/*db* diabetic mice have a much lower percentage of the HMW form in circulation.

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] 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].

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 the HMW-total 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 ratio had better predictive power for the prediction of insulin resistance and metabolic syndrome than plasma total adiponectin level; and Aso et al [27] also reported that the HMW-total ratio was more useful to evaluate CAD in patients with type 2 diabetes mellitus than simply measuring serum total adiponectin. However, no studies have compared the HMW adiponectin level with the HMW-total ratio to predict insulin resistance and/or metabolic syndrome in healthy subjects.

In the present study of healthy Japanese male subjects without any medication, we investigated the hypothesis that measuring HMW adiponectin may be as effective as HMW-total ratio to predict insulin resistance and/or metabolic syndrome.

2. Subjects and Methods

2.1. Subjects

This study included 637 Japanese male teachers and workers at Keio University aged 30 to 65 years who underwent an annual health checkup. Subjects with endocrine disease or significant renal or hepatic disease and those receiving medication for diabetes mellitus, hypertension, or hyperlipidemia were excluded. 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 and diastolic blood pressure was measured twice in the sitting position after resting for at least 3 minutes. Height, weight, fasting plasma glucose, serum insulin, adiponectin, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured at around 9 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 [28,29]. 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 [29]. The insulin resistance index was assessed by homeostasis model assessment of insulin resistance (HOMA-IR).

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 coefficient of variation <10%. The HMW 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.

2.3. Definition of HOMA-IR

The HOMA-IR was calculated as fasting serum insulin (in microunits per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5. We defined subjects with HOMA-IR >2.5 as having insulin resistance because this cutoff point has been adopted in the Japanese guidelines for the treatment of diabetes [11].

2.4. Definition of metabolic syndrome

Because the measurement of waist circumference was not collected in this study, we defined metabolic syndrome based on a modification of the Japanese diagnostic criteria [30]. In addition to BMI ≥25 kg/m^2 (instead of waist circumference ≥85 cm in men), the presence of at least 2 of the following 3 abnormalities indicated metabolic syndrome:

(1) Dyslipidemia: triglycerides ≥150 mg/dL and/or HDL cholesterol <40 mg/dl.
(2) High blood pressure: systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg.
(3) Hyperglycemia: fasting plasma glucose ≥110 mg/dL.

In the present study, we also defined metabolic syndrome score (MS score) as 0 to 3, representing the number of risk factors listed in (1) to (3).

2.5. Statistical analysis

Statistical analyses were performed using the StatView program for Windows (version 5.0-J; SAS Institute, Cary, NC). Student *t* test was used to compare various parameters between the metabolic syndrome group and the nonmetabolic syndrome group. Because HOMA-IR, serum triglycerides, total adiponectin, and HMW adiponectin levels were normally distributed after logarithmic transformation, we used logarithms of these data for the analyses. Pearson correlation coefficient was used to evaluate the association of HMW, total, and the ratio of adiponectin with various parameters. *P* values < .05 were considered to denote statistical significance.

We divided the study subjects into quartile groups with equal numbers of subjects: T1 to T4 based on serum total adiponectin level, A1 to A4 based on serum HMW adiponectin level, and A/T1 to A/T4 based on HMW-total ratio. Comparisons of both HOMA-IR and the MS score in the 4 groups, based on total and HMW adiponectin and HMW-total ratio, were analyzed by Kruskal-Wallis test followed by Scheffé multiple comparison tests.

The receiver operator characteristic (ROC) curves for HOMA-IR and metabolic syndrome were plotted using JMP for Windows (version 6.0; SAS Institute). Area under the curve (AUC) of the ROC curve has diagnostic ability as described by Hara et al [11]. The ROC analyses were performed using the Statistical Package for the Social Sciences (version 12.0J; SPSS, Chicago, IL).

Table 1
Clinical and laboratory characteristics of 637 healthy male subjects

	Metabolic syndrome	Nonmetabolic syndrome	P[a]
No. of subjects	55	582	
Age (y)	49.1 ± 10.3	47.2 ± 11.1	.25
Height (cm)	169.3 ± 6.0	170.2 ± 6.0	.31
Body weight (kg)	79.4 ± 8.8	67.4 ± 9.5	<.0001
BMI (kg/m^2)	27.7 ± 2.3	23.2 ± 2.8	<.0001
Systolic blood pressure (mm Hg)	135.1 ± 12.2	119.4 ± 14.5	<.0001
Diastolic blood pressure (mm Hg)	86.2 ± 9.3	74.2 ± 10.4	<.0001
Glucose (mg/dL)	110.2 ± 27.2	94.4 ± 13.6	<.0001
Insulin (μU/mL)	8.82 ± 8.80	5.18 ± 3.83	<.0001
HOMA-IR	2.44 ± 1.58	1.23 ± 0.97	<.0001
Total cholesterol (mg/dL)	229 ± 34	211 ± 33	.0001
Triglycerides (mg/dL)	213 ± 98	117 ± 95	<.0001
HDL cholesterol (mg/dL)	48.3 ± 9.6	59.0 ± 14.6	<.0001
LDL cholesterol (mg/dL)	142 ± 32	127 ± 29	.0003
HMW adiponectin (μg/mL)	2.8 ± 1.6	4.4 ± 2.6	<.0001
Total adiponectin (μg/mL)	5.7 ± 3.1	7.1 ± 3.9	.009
HMW-total ratio	0.49 ± 0.15	0.61 ± 0.19	<.0001

Values are mean ± SD.

[a] Student *t* test. Logarithmic transformation of HOMA-IR, serum insulin, triglycerides, HMW adiponectin, and total adiponectin levels was performed as needed to improve normality.

Table 2
Correlation coefficients of HMW, total, and ratio of adiponectin with various parameters in 637 healthy male subjects

	vs log(HMW)		vs log(total)		vs HMW-total ratio	
	r[a]	P	r[a]	P	r[a]	P
Age	0.009	.815	−0.004	.928	0.036	.360
BMI	−0.370	<.0001	−0.318	<.0001	−0.248	<.0001
Systolic blood pressure	−0.177	<.0001	−0.141	<.001	−0.121	.002
Diastolic blood pressure	−0.177	<.0001	−0.136	<.001	−0.127	.001
log(HOMA-IR)	−0.375	<.0001	−0.323	<.0001	−0.256	<.0001
Total cholesterol	−0.151	<.001	−0.151	<.001	−0.083	.037
LDL cholesterol	−0.238	<.0001	−0.219	<.0001	−0.142	<.001
HDL cholesterol	0.352	<.0001	0.307	<.0001	0.226	<.0001
log(triglycerides)	−0.351	<.0001	−0.335	<.0001	−0.195	<.0001
Glucose	−0.142	<.001	−0.135	<.001	−0.075	.057
Score of metabolic syndrome	−0.259	<.0001	−0.194	<.0001	−0.210	<.0001

[a] Pearson correlation coefficient. Logarithmic transformation of HOMA-IR, serum triglycerides, total adiponectin, and HMW adiponectin levels was performed as needed to improve normality.

3. Results

The clinical and laboratory characteristics of 637 healthy male subjects are shown in Table 1. All metabolic parameters listed, excluding age and height, were significantly different between the metabolic syndrome group and the nonmetabolic syndrome group.

Table 2 shows the correlation coefficients of HMW, total, and the ratio of adiponectin with various parameters in

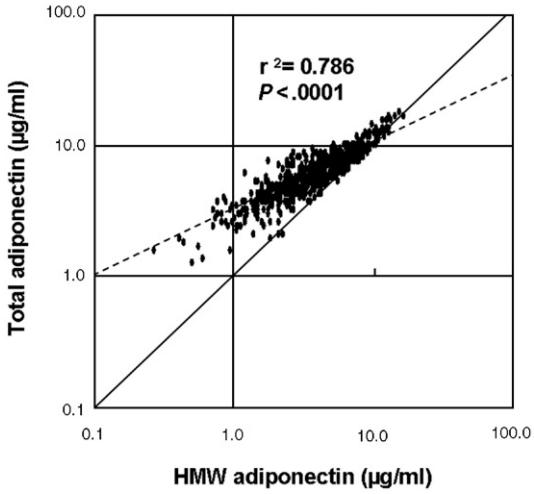

Fig. 1. Scattered plot graph of serum HMW adiponectin levels (x-axis) and total adiponectin levels (y-axis) in 637 Japanese male subjects.

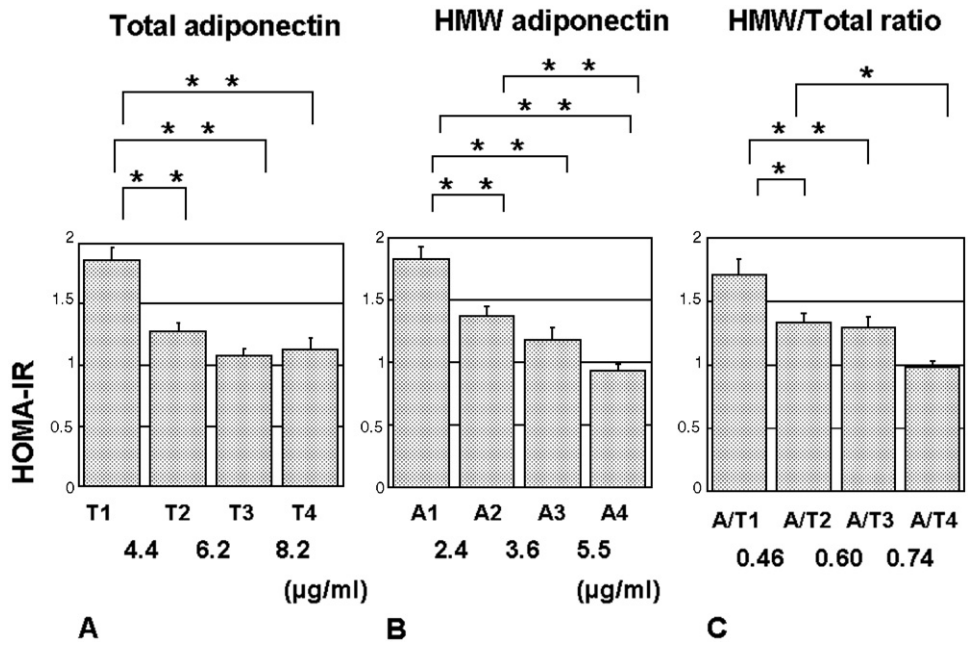

Fig. 2. The HOMA-IR in each quartile based on serum levels of total adiponectin (A), HMW adiponectin (B), and HMW-total ratio (C). Data are mean ± SEM. *$P < .05$ and **$P < .01$ by Scheffé multiple comparison tests after Kruskal-Wallis test. The presence of insulin resistance was defined as HOMA-IR >2.5.

637 healthy male subjects. There were no correlations of age with HMW, total, or the ratio of adiponectin. There were strong inverse correlations of HMW adiponectin with HOMA-IR ($r = -0.375$, $P < .0001$) and BMI ($r = -0.370$, $P < .0001$). Correlations of HMW adiponectin level with HOMA-IR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose were significant even after adjustment for BMI.

Fig. 1 shows the scatter plot graph of serum HMW adiponectin and total adiponectin. In the range of total adiponectin concentration less than approximately 10 μg/mL, HMW adiponectin level was much lower than that of total adiponectin.

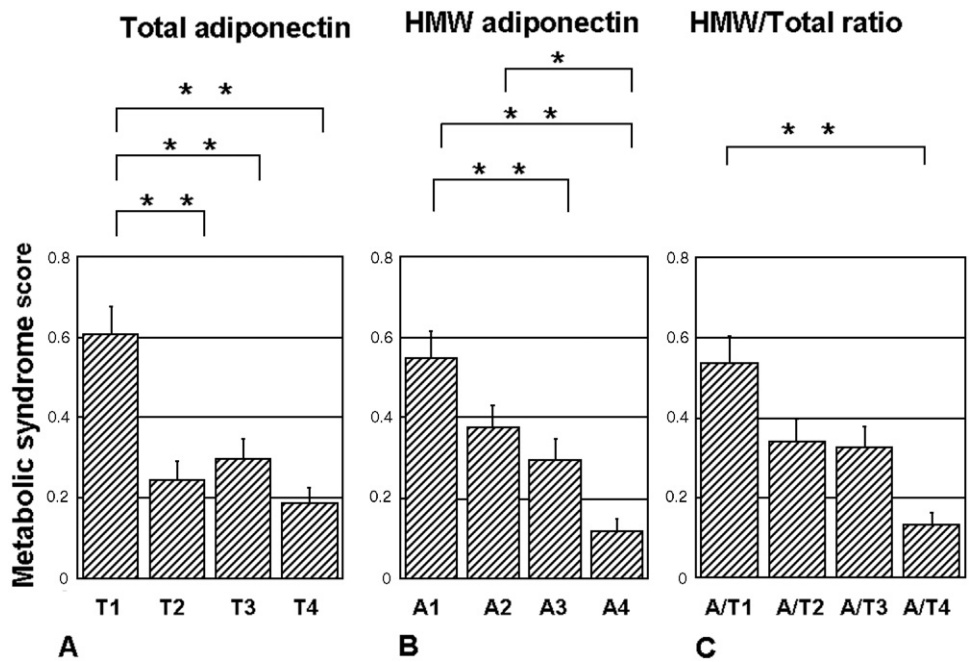

Fig. 3. Metabolic syndrome score in each quartile based on serum levels of total adiponectin (A), HMW adiponectin (B), and HMW-total ratio (C). Data are mean ± SEM. *$P < .05$ and **$P < .01$ by Scheffé multiple comparison tests after Kruskal-Wallis test. Diagnosis of metabolic syndrome was based on a modification of the Japanese diagnostic criteria [30].

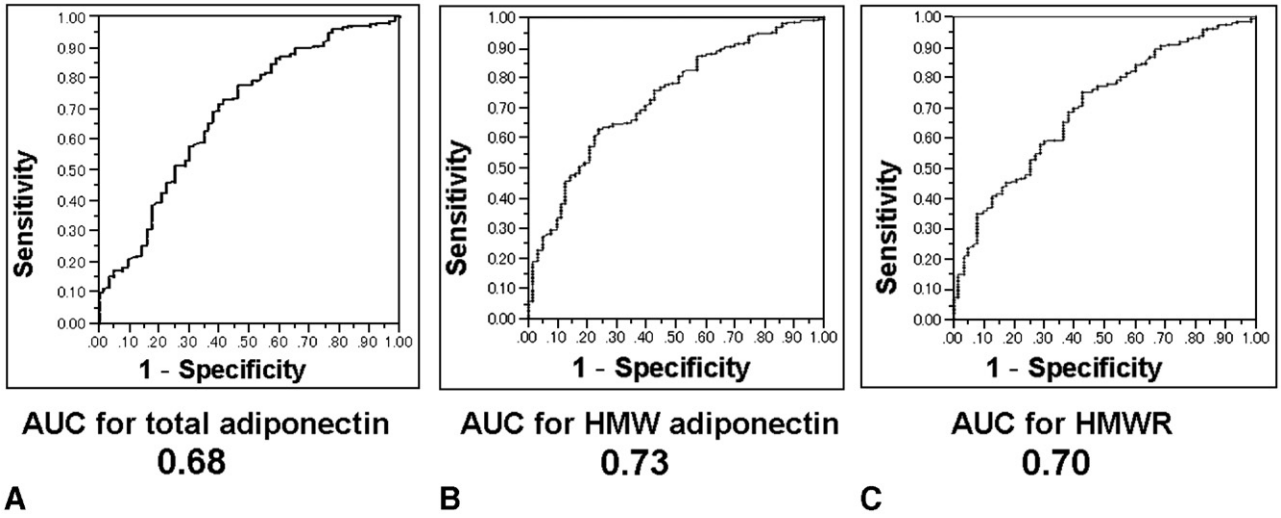

Fig. 4. The ROC curves of serum levels of total adiponectin (A), HMW adiponectin (B), and HMW-total ratio (C) for evaluation of insulin resistance in 637 Japanese male subjects. The presence of insulin resistance was defined as HOMA-IR >2.5. The AUC of serum HMW adiponectin level (B, 0.73) was larger than that of total adiponectin level (A, 0.68) and of HMW-total ratio (C, 0.70).

3.1. HOMA-IR and MS score

As shown in Fig. 2, the interquartile ranges based on HMW adiponectin level were 0 to 2.4, 2.4 to 3.6, 3.6 to 5.5, and >5.5 μg/mL (number of subjects: 160, 159, 159, and 159, respectively).

Based on our criteria used in this study, 9.7% of men were diagnosed as having insulin resistance. As shown in Fig. 2A, HOMA-IR in T1 was significantly higher than that in T2, T3, and T4 ($P < .01$ for all). HOMA-IR in A1 was significantly higher than that in A2, A3, and A4 ($P < .01$ for all). HOMA-IR in A2 was also significantly higher than that in A4 ($P < .01$, Fig. 2B). HOMA-IR in A/T1 was significantly higher than that in A/T2 and A/T3 ($P < .05$ and $P < .01$, respectively). HOMA-IR in A/T2 was also significantly higher than that in A/T4 ($P < .05$, Fig. 2C). Overall, HOMA-IR in each quartile based on serum HMW adiponectin level was significantly different among the 4 groups.

Based on our criteria used in this study, 8.7% of men were diagnosed as having metabolic syndrome. MS score of T1 was significantly higher than that of T2, T3, and T4 ($P < .01$ for all, Fig. 3A). MS score of A1 was significantly higher than that of A3 and A4 ($P < .01$ for both). MS score of A2 was also significantly higher than that of A4 ($P < .05$, Fig. 3B). MS score of A/T1 was significantly higher than that of A/T4 ($P < .01$, Fig. 3C). Overall, MS score in each quartile

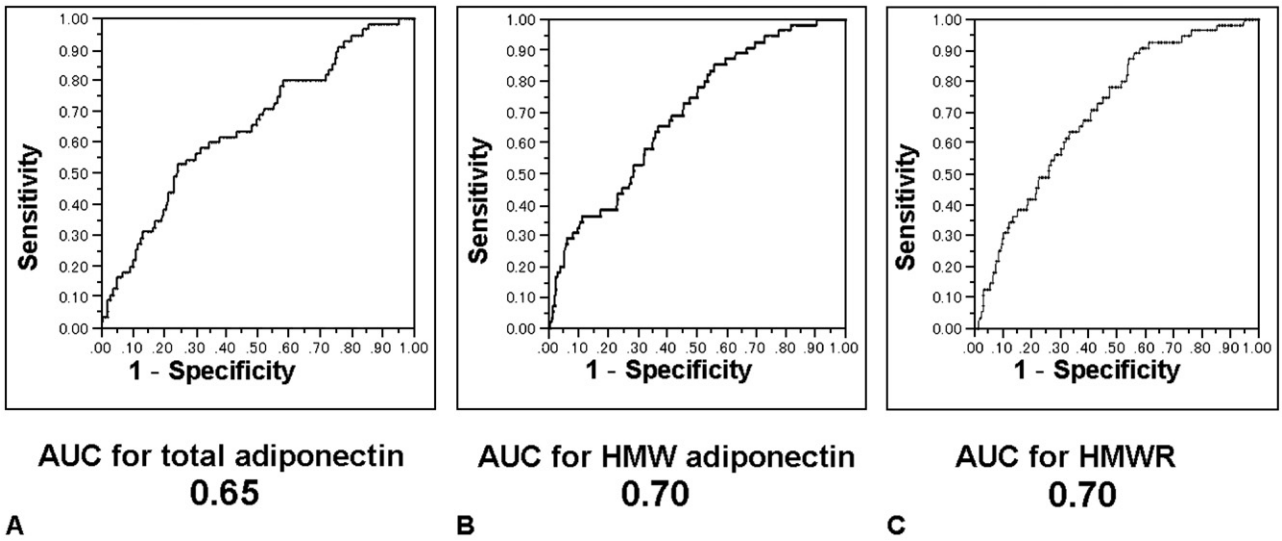

Fig. 5. The ROC curves of serum levels of total adiponectin (A), HMW adiponectin (B), and HMW-total ratio (C) for evaluation of metabolic syndrome in 637 Japanese male subjects. The AUC of serum HMW adiponectin level (B, 0.70) was larger than that of total adiponectin level (A, 0.65) and was equal to that of HMW-total ratio (C, 0.70).

based on serum HMW adiponectin concentration was significantly different among the 4 groups.

3.2. ROC curves for models to evaluate presence of insulin resistance

The ROC curves of total, HMW, and HMW-total ratio of adiponectin were plotted to evaluate insulin resistance, defined as HOMA-IR index >2.5 (n = 637). The AUC of serum HMW adiponectin level was larger than that of total adiponectin (0.73 [95% confidence interval {CI} 0.670-0.795] vs 0.68 [95% CI 0.612-0.758], Fig. 4B vs A). The AUC of HMW adiponectin was also larger than that of HMW-total ratio (0.73 [95% CI 0.670-0.795] vs 0.70 [95% CI 0.637-0.767], Fig. 4B vs C).

3.3. ROC curves for models to evaluate presence of metabolic syndrome

The ROC curves of total, HMW, and HMW-total ratio of adiponectin were plotted to evaluate metabolic syndrome (n = 637). The AUC of serum HMW adiponectin level was larger than that of total adiponectin (0.70 [95% CI 0.628-0.765] vs 0.65 [95% CI 0.576-0.727], Fig. 5B vs A). However, the AUC of HMW adiponectin was equal to that of HMW-total ratio (0.70 [95% CI 0.628-0.765] vs 0.70 [95% CI 0.640-0.771], Fig. 5B vs C).

4. Discussion

There have been many reports that the ratio of HMW to total adiponectin, but not the absolute amount of adiponectin, determines insulin sensitivity in diabetic rodents [5,26]. Clinical data have also confirmed that patients with type 2 diabetes mellitus and CAD had a selective reduction in HMW adiponectin [25-27]. Furthermore, weight reduction [25] or treatment of type 2 diabetes mellitus patients with the insulin-sensitizing agent rosiglitazone [26] preferentially increased the HMW form of adiponectin, but not the other 2 oligomeric complexes. In subjects with type 2 diabetes mellitus, it has also been reported that HMW-total ratio was more useful to predict insulin resistance and metabolic syndrome than total adiponectin level [11]. Moreover, HMW-total ratio was more useful for evaluating CAD in patients with type 2 diabetes mellitus than total adiponectin level in serum [27].

Fisher et al [31] reported that the HMW-total ratio was more important as a determinant of glucose intolerance than total adiponectin in 34 Indo-Asian male subjects, none of whom had been previously diagnosed as having type 2 diabetes mellitus. They demonstrated the HMW-total ratio to be more significantly (inversely) correlated with 2-hour glucose level in the oral glucose tolerance test than total adiponectin level [31]. However, they did not compare data with those of HMW adiponectin. In another report [32], serum adiponectin level was associated with increased insulin sensitivity, reduced abdominal fat, and high basal lipid oxidation. However, it was HMW quantity that was primarily responsible for these relationships in 68 subjects with and without type 2 diabetes mellitus (medication was withdrawn in all patients with type 2 diabetes mellitus for at least 3 weeks, and they were followed on an outpatient basis). From the viewpoint of these previous reports, it seems evident that HMW-total ratio is a better marker than total adiponectin to predict insulin resistance. Moreover, HMW-total ratio might be more significant than serum HMW adiponectin level in patients with type 2 diabetes mellitus receiving medication including peroxisome proliferator–activated receptor γ agonists.

The implication of measuring adiponectin in the clinical setting has been vigorously investigated not only in insulin resistance and/or metabolic syndrome but also in the progression to type 2 diabetes mellitus [13,14,33] and cardiovascular disease [34]. We have previously reported a 2-year follow-up study in healthy Japanese population suggesting that serum HMW adiponectin concentration predicts subsequent change in HOMA-IR, but not in lipid profile or body weight [29].

The limitations of this study were the cross-sectional study design in male subjects only. Furthermore, waist circumference was not collected in this study. We used BMI instead as a modified criterion of metabolic syndrome [30]. However, waist circumference and BMI were well correlated in our other cohort (r = 0.870, P < .0001, in 465 male subjects, unpublished data). Although we had to use BMI instead of waist circumference in this study, we consider that the modified criteria adequately characterized the metabolic syndrome status. Further studies of different races including female subjects and also longitudinal studies are needed and would facilitate understanding of the importance of total, HMW, and HMW-total ratio of adiponectin.

In conclusion, it is suggested that HMW adiponectin may be as effective as HMW-total ratio to evaluate the presence of insulin resistance and metabolic syndrome, at least in nondiabetic subjects who are not receiving any medication.

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