Determinants of Serum High Molecular Weight (HMW) Adiponectin Levels in Patients with Coronary Artery Disease: Associations with Cardio-renal-anemia Syndrome

Kenji Hara¹, Toshihiko Uchida², Kohzo Takebayashi¹, Yoshihiko Sakai², Teruo Inoue³,
Toshiko Inukai¹, Kan Takayanagi² and Yoshimasa Aso¹

Abstract

Objective A low serum adiponectin level is associated with a high incidence of coronary artery disease (CAD) in the healthy population. Paradoxically, serum adiponectin is elevated in patients with severe CAD or chronic heart failure. We investigated the determinants of serum high molecular weight (HMW) adiponectin in patients with CAD.

Patients and Methods We studied 228 consecutive patients with CAD confirmed by angiography. Anemia was defined as a hemoglobin of <13.0 g/dL in men and <12.0 g/dL in women. A high plasma B-type natriuretic-peptide (BNP) was defined as >100 pg/mL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min for more than 3 months. The patients with CAD were divided into eight groups according to the presence or absence of anemia, high BNP, and/or CKD.

Results In all 228 patients with CAD, serum HMW adiponectin correlated positively with age, high-density-lipoprotein cholesterol (HDL-C), and BNP, while this parameter showed negative correlations with body mass index, insulin resistance, triglycerides, eGFR, and hemoglobin. Multivariate analysis showed that HDL-C, BNP, gender, and age were independently associated with the HMW adiponectin. Serum HMW adiponectin was lower in CAD patients with than without metabolic syndrome. Serum HMW adiponectin and the HMW/total adiponectin ratio were highest in CAD patients who had anemia, high BNP, and CKD among the groups.

Conclusion In patients with CAD, metabolic syndrome is associated with a lower serum HMW adiponectin, while the presence of anemia, high BNP, and CKD is associated with elevation of the serum HMW adiponectin.

Key words: adiponectin, B-type natriuretic peptide, chronic kidney disease, metabolic syndrome, coronary artery disease

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Introduction

Adiponectin is an adipocyte-specific hormone that enhances insulin sensitivity, promotes lipid metabolism, and has an anti-inflammatory or anti-atherogenic effect (1-4). Adiponectin circulates in the plasma in three forms, which are a low molecular weight (LMW) trimer, a hexamer

(trimer-dimer) of medium molecular weight (MMW), and a larger multimeric high molecular weight (HMW) form (5, 6). HMW adiponectin may be the active form of this protein, since changes of the serum HMW adiponectin were associated with improvement of hepatic insulin sensitivity after treatment with thiazolidinediones (7).

The serum total adiponectin level is reduced in subjects with metabolic syndrome and patients with type 2 diabetes

¹Department of Internal Medicine, Koshigaya Hospital, Dokkyo Medical University, Japan, ²Department of Cardiology, Koshigaya Hospital, Dokkyo Medical University, Japan and ³Department of Cardiology, Dokkyo Medical University, Japan

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Correspondence to Dr. Yoshimasa Aso, yaso@dokkyomed.ac.jp

or coronary artery disease (CAD) (8-10). Several prospective studies have demonstrated that a low total adiponectin level is associated with an increased risk of developing type 2 diabetes (11) or acute myocardial infarction in the general population (12). A previous study also demonstrated that a low serum HMW adiponectin was a predictor of cardiovascular events in patients with CAD (13). However, recent prospective studies have indicated that low serum total or HMW adiponectin levels are not associated independently with the future occurrence of cardiovascular disease (CVD) in high-risk subjects (14, 15) or patients with type 2 diabetes (16). Several studies have shown that the serum level of adiponectin is paradoxically elevated in both non-diabetic and diabetic patients with renal failure or heart failure (17, 18). Zoccali et al demonstrated that a higher serum level of adiponectin is associated with a lower risk of CVD in patients with end-stage renal disease, suggesting that a high serum adiponectin acts as a protective factor for cardiovascular system (17). In contrast, some studies have shown that a high serum level of total or HMW adiponectin is associated with an increase of CVD events or high mortality in patients with congestive heart failure (18), overt CAD (19-21), or type 2 diabetes (22). Thus, the significance of total or HMW adiponectin as an indicator of prognosis seems to be still controversial. The mechanisms responsible for these apparently contradictory findings remain unclear.

Chronic kidney disease (CKD) is associated with an increased risk of an adverse outcome and a poor prognosis after acute coronary syndromes (23, 24). Anemia also is strongly associated with an adverse outcome and increased mortality rate in patients with acute coronary syndromes undergoing primary percutaneous coronary intervention (25, 26). A prospective study has demonstrated that anemia and CKD are independent and additive predictors of adverse cardiovascular events in patients with overt CAD (27, 28). The plasma level of B-type natriuretic peptide (BNP), a cardiac neurohormone synthesized by ventricles, is associated with left ventricular function, and is also a good marker of the long-term prognosis in patients with CAD (29) as well as indicating the severity of CAD (30). Several studies have demonstrated that serum total or HMW adiponectin levels are negatively correlated with the estimated glomerular filtration rate (eGFR) in non-diabetic and diabetic patients (10, 17), and are positively with plasma BNP level in patients with chronic heart failure (18). However, no reports have investigated simultaneously the relationship between serum HMW adiponectin and the presence of anemia, high BNP, and CKD in patients with CAD.

We therefore investigated the determinants of serum HMW adiponectin level in patients with CAD confirmed by angiography. We also characterized the CAD patients with a marked elevation of the serum HMW adiponectin level.

Materials and Methods

We studied 290 consecutive patients with CAD between

October 2005 and June 2007. All patients underwent coronary angiography for chest pain or other symptoms. Significant atherosclerotic CAD was confirmed with >75% luminal obstruction of at least one of the three major coronary arteries (left anterior descending, left circumflex, or right coronary artery) or with >50% luminal obstruction of the left main trunk. Two experienced invasive cardiologists evaluated the angiography. None of the patients had overt symptoms of heart failure. Patients with congenital heart disease or primary valvular disease were excluded from the study. We also excluded patients with renal dysfunction (serum creatinine concentration >1.3 mg/dL) or liver dysfunction. Patients receiving treatment with peroxisome proliferator-activated receptor (PPAR)- γ agonists, which increase the serum HMW adiponectin level, were also excluded (31).

Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mm Hg, or alternatively as treatment with antihypertensive agents. The diagnosis of metabolic syndrome was based on the criteria in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria (32). Hypercholesterolemia was defined as serum LDL (low density lipoprotein)-cholesterol level >140 mg/dL (3.6 mmol/L) or alternatively as treatment with a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin).

Anemia was defined as an Hb of <13.0 g/dL in men and <12.0 g/dL in women according to the guidelines of the World Health Organization (WHO). A high BNP level (cardiac dysfunction) was defined as plasma BNP level >100 pg/mL (33). CKD was defined as an eGFR of <60 mL/min/1.73 m² for more than 3 months.

All of the subjects gave informed consent to this study and it was approved by the Dokkyo Medical University Institutional Review Board.

Laboratory measurements

Venous blood was obtained between 6 and 8 AM on the day of coronary angiography after an overnight fast. Serum and plasma were separated after centrifugation at 2,500 rpm for 15 minutes and the supernatant was stored at -70°C until use. The total adiponectin level was measured with a sandwich ELISA (enzyme-linked immunosorbent assay) (Otsuka Pharmaceuticals, Tokyo, Japan). In brief, after boiling serum samples in SDS buffer for 5 minutes to convert all adiponectin to a monomeric form, the ELISA system was used to determine serum total adiponectin.

The serum HMW adiponectin level was measured by using our novel sandwich ELISA based on a monoclonal antibody for human HMW adiponectin (Fujirebio Inc., Tokyo, Japan), as described previously (10, 34). The intra- and inter-assay CV were 2.4% to 3.0% and 4.2% to 5.1%, respectively.

The plasma level of B-type natriuretic peptide (BNP) was measured with a chemiluminescent enzyme immunoas-

Table 1. Demographic, Clinical, and Laboratory Data for the 228 Patients with Coronary Artery Disease (CAD)

Age (years)	65.7±9.4
Men, n (%)	178 (78.1%)
Body mass index	24.8±3.5
Angiographic findings, n (%)	
1 vessel disease	97 (42.5%)
2 vessel disease	62 (27.2%)
3 vessel disease	69 (30.3%)
Classical risk factors	
Diabetes, n (%)	115 (50.4%)
Hypertension, n (%)	129 (56.6%)
Hypercholesterolemia, n (%)	129 (56.6%)
Family history of CAD, n (%)	34 (14.9%)
Current smoker, n (%)	146 (64.0%)
Metabolic syndrome, n (%)	102 (44.7%)
Chronic kidney disease, n (%)	65 (28.5%)
LDL cholesterol (mg/dL)	116.5±32.5
Triglyceride (mg/dL)	131.0 (94.0, 185.0)
HDL cholesterol (mg/dL)	46.1±11.1
HbA1c (%)	6.2±1.5
eGFR (mL/min/1.73m ²)	76.5±28.2
Hematocrit (%)	41.4±4.7
Hemoglobin (g/dL)	13.7±1.8
B type natriuretic peptide (pg/mL)	44.0 (24.0, 121.2)
Left ventricular ejection fraction (%)	62.5±13.0
Total adiponectin (μg/mL)	7.8 (5.7, 11.4)
HMW adiponectin (μg/mL)	4.0 (2.3, 6.6)
HMW/Total adiponectin ratio	0.53±0.15
High sensitivity C-reactive protein (mg/L)	0.08 (0.04, 0.16)
Medication	
Statin, n (%)	98 (43.0%)
β blocker, n (%)	65 (28.5%)
ACEI&ARB, n (%)	108 (47.4%)

Data are the mean±SD or the median and inter-quartile ranges. LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; GFR, glomerular filtration rate; HMW, high molecular weight; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

say in EDTA-anticoagulated blood samples (Kyowa Medics, Tokyo, Japan). The serum level of high-sensitivity C-reactive protein (hs-CRP) was determined by an immunonephelometric assay (N-High-sensitivity CRP, Dade Behring, Marburg, Germany). The eGFR was calculated with the formula of the Modification of Diet in Renal Disease (MDRD) by using Japanese coefficient (35). Insulin resistance was evaluated by homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated as fasting plasma insulin (μU/mL) × fasting plasma glucose (mg/dL)/405.

Statistical analysis

Data are presented as the mean ± SD or the median and interquartile range. Logarithmic transformation of the data for total and HMW adiponectin, hs-CRP, and BNP was used to render the distribution normal and allow the use of parametric tests. Correlations were determined by simple linear regression analysis or multivariate analysis. Between-group differences of normally distributed variables were assessed by one-way analysis of variance (ANOVA).

Results

A total of 228 patients were enrolled in the study (178 men and 50 women). Their characteristics and laboratory findings are shown in Table 1. The mean age was 65.7±9.4 years and 78.1% of the subjects were men.

As shown in Table 2 and Fig. 1A-C, linear regression analysis revealed that the serum HMW adiponectin levels were positively correlated with the age, HDL (high density lipoprotein)-cholesterol, and plasma BNP, while being negatively correlated with BMI, HOMA-IR, triglycerides, eGFR, hemoglobin (Hb), hematocrit, and hs-CRP. The HMW/total adiponectin ratio was positively correlated with the age and BNP, while it was negatively correlated with HOMA-IR, triglyceride, Hb, and hematocrit (Table 2). To identify independent determinants of HMW adiponectin level in patients with CAD, we performed stepwise regression analysis with forward selection of variables, including BMI, HDL cholesterol, eGFR, Hb, BNP, age, and gender. In a model that explained 54.8% of the variation of serum HMW adiponectin, HDL cholesterol ($\beta=0.330$, $p<0.001$), BNP ($\beta=0.278$, $p<0.001$), gender ($\beta=-0.177$, $p=0.011$), and age ($\beta=0.147$, $p=0.035$) were independent determinants of serum HMW adi-

Table 2. Linear Regression Analysis in the 228 Patients with Coronary Artery Disease

variables	Total adiponectin (ln $\mu\text{g/mL}$)		HMW adiponectin (ln $\mu\text{g/mL}$)		HMW/total adiponectin ratio	
	r	p value	r	p value	r	p value
Age (years)	0.3139	<0.0001	0.3138	<0.0001	0.1724	0.0093
BMI	-0.2847	0.0005	-0.2580	<0.0001	-0.1204	0.0702
HbA1c (%)	-0.0840	0.2233	-0.0783	0.2565	-0.0448	0.5161
HOMA-IR, (n=155)	-0.3282	<0.0001	-0.3165	<0.0001	-0.2162	0.0088
LDL cholesterol (mg/dL)	0.0372	0.5783	0.0444	0.5071	0.0364	0.5861
Triglyceride (mg/dL)	-0.3022	<0.0001	-0.3097	<0.0001	-0.2243	0.0007
HDL cholesterol (mg/dL)	0.3212	<0.0001	0.2757	<0.0001	0.0888	0.1830
eGFR (mL/min/1.73m ²)	-0.3477	<0.0001	-0.3096	<0.0001	-0.1244	0.0656
Hemoglobin (g/dL)	-0.2796	<0.0001	-0.3012	<0.0001	-0.2257	0.0006
Hematocrit (%)	-0.2492	0.0002	-0.2798	<0.0001	-0.2391	0.0003
BNP (log ₁₀ pg/mL)	0.2774	<0.0001	0.3199	<0.0001	0.2840	<0.0001
hs-CRP (log ₁₀ ng/mL)	-0.2662	0.0004	-0.2126	0.0060	-0.030	0.6731

BMI, body mass index; HbA1c, hemoglobin A1c; HOMA-IR, ; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; hs-CRP, high sensitivity C reactive protein.

Figure 1. Correlation between serum high molecular weight (HMW) adiponectin and hemoglobin (A), plasma B type natriuretic peptide (BNP) (B), or estimated glomerular filtration rate (eGFR) (C) in 228 patients with coronary artery disease.

ponectin level in patients with CAD (Table 3).

As shown in Fig. 2A-C, serum HMW adiponectin levels were lower in the CAD patients with metabolic syndrome than in those without it (5.9 [4.4, 8.2] vs. 9.1 [7.3, 13.6] $\mu\text{g/mL}$, $p < 0.0001$; 3.0 [1.8, 4.1] vs. 5.5 [3.6, 8.5] $\mu\text{g/mL}$, $p < 0.0001$). The HMW/total adiponectin ratio was also significantly lower in the patients with metabolic syndrome (0.485 ± 0.148 vs. 0.562 ± 0.153 , $p = 0.0003$).

To further investigate the determinants of serum HMW adiponectin in patients with CAD, we divided subjects into eight groups (described in Subjects and Methods) on the basis of the presence or absence of anemia, high BNP, or CKD. As shown in Table 3, the serum HMW adiponectin levels increased in parallel with the increase in the number of these three factors ($p < 0.0001$, respectively). The HMW adiponectin levels were the highest in CAD patients with all three factors (21.9 ± 14.6 and 14.6 ± 10.8 $\mu\text{g/mL}$, respectively; Table 4). In addition, the HMW/total adiponectin ratio was the highest in those patients with all three factors (Table 4).

Discussion

The present study showed that serum HMW adiponectin level was significantly lower in CAD patients with metabolic syndrome than in those without it. Multivariate analysis showed the presence of metabolic syndrome to be an independent determinant of serum HMW adiponectin (data now shown). Furthermore, we found that the HMW/total adiponectin ratio was significantly lower in the patients with than without metabolic syndrome. This suggests that a predominant decrease in the serum HMW adiponectin level may contribute to the decrease in the serum total adiponectin level in patients with metabolic syndrome. Recent studies have also demonstrated that the HMW/total adiponectin ratio is more closely associated with metabolic syndrome than the plasma total adiponectin level in the general population and in subjects with high risk (36, 37). Thus, the serum HMW adiponectin level is more useful clinically for evaluating the diagnosis of metabolic syndrome in patients with CAD than simply measuring the total

Table 3. Multiple Logistic Regression Analysis of Serum High Molecular Weight (HMW) Adiponectin in Patients with Coronary Artery Disease

Variable	β	p value
BMI	-0.086	0.220
HDL-C (mg/dL)	0.330	<0.001
Hb (g/dL)	-0.085	0.224
BNP (pg/mL)	0.278	<0.001
eGFR (mL/min/1.73m ²)	-0.035	0.608
Age (years)	0.147	0.035
Gender (m/f)	-0.177	0.011
R(R ²)	0.576 (0.333)	

The partial coefficient is indicated as β . BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Hb, hemoglobin; BNP, B type natriuretic peptide; eGFR, estimated glomerular filtration rate.

Figure 2. Serum total adiponectin (A), high molecular weight (HMW) adiponectin (B), or the HMW/total adiponectin ratio (C) in patients with coronary artery disease with and without metabolic syndrome. A, B: Boundaries of boxes, 25th percentile and 75th percentile; horizontal lines through boxes, median; filled circles, 5th and 95th percentiles.

serum adiponectin level.

The serum total adiponectin level is reduced in subjects with metabolic syndrome and in patients with type 2 diabetes or CAD (8-10). In clinically healthy subjects, a high adiponectin level appears to be protective against atherosclerotic cardiovascular disease (12). A low serum HMW adiponectin is also a predictor of cardiovascular events in patients with CAD (12). However, several studies have shown that the serum level of adiponectin is paradoxically elevated in both non-diabetic and diabetic patients with renal failure or heart failure (17, 18). Zoccali et al demonstrated that a higher serum level of adiponectin is associated with a lower risk of CVD in patients with end-stage renal disease, suggesting that a high serum adiponectin level acts as a protective factor for the cardiovascular system (17). In contrast, several recent prospective studies have demonstrated that a high total adiponectin level is a predictor of a poor outcome or mortality in patients with overt CAD, which is independent of known risk factors (19-21). Thus, the significance of HMW adiponectin as an indicator of prognosis still seems to be controversial in patients with CAD. The mechanisms responsible for these apparently contradictory findings remain unclear.

The present study demonstrated that serum HMW adiponectin level is closely associated with anemia, cardiac dysfunction (estimated by the plasma BNP level), and CKD in patients with overt CAD. In addition, multivariate analysis demonstrated that HDL-C, BNP, gender, and age were independent determinants of serum HMW adiponectin.

Although the present study showed that Hb was not an independent determinant of HMW adiponectin in patients with CAD, in a recent study, we found a strong negative correlation between HMW adiponectin and hemoglobin in patients with type 2 diabetes (38). Anemia is independently associated with an elevated serum level of HMW adiponectin in patients with type 2 diabetes (38). Anemia is independently associated with an increased risk of CAD or with a worse outcome in patients with symptomatic CAD (25, 26). Thus, anemia may be the link between a high HMW adiponectin level and a poor outcome in patients with CAD.

Table 4. Serum Total and High Molecular Weight (HMW) Adiponectin in Subgroups of Coronary Artery Disease (CAD) Patients Categorized according to the Presence or Absence of Anemia, High B-type Natriuretic Peptide (BNP) Level and Chronic Kidney Disease (CKD)

	Total adiponectin (μg/mL)	HMW adiponectin (μg/mL)	HMW/total adiponectin ratio
No anemia, high BNP or CKD: n(M/F)= 102(84/18)	7.9±3.9	4.2±2.9	0.50±0.16
Anemia only: n(M/F)= 18(13/5)	8.3±4.1	4.7±2.6	0.56±0.14
High BNP only: n(M/F)= 33(30/3)	8.5±5.3	5.0±3.9	0.55±0.16
CKD only: n(M/F)=32(24/8)	9.0±4.6	4.4±2.9	0.47±0.12
Anemia and high BNP: n(M/F)= 10(6/4)	12.6±6.0	8.2±4.0	0.62±0.11
High BNP and CKD: n(M/F)=10(7/3)	11.5±6.9	7.5±5.3	0.60±0.17
CKD and anemia: n(M/F)=10(7/3)	12.8±7.6	7.0±4.9	0.52±0.14
Anemia, high BNP and CKD: n(M/F)=13(5/8)	21.9±14.6	14.6±10.8	0.64±0.15
ANOVA	p<0.0001	p<0.0001	p=0.0012

The present study also showed a significant negative correlation between HMW adiponectin and eGFR, which is in agreement with several previous reports (10, 17, 38). Serum adiponectin levels are markedly elevated in CKD patients with stage 3 to 5 (17, 39). CKD is not only a major risk factor for CVD but it is also associated with an increased risk of an adverse outcomes and poor prognosis after acute coronary syndrome (23, 24), suggesting that CKD may also link high HMW adiponectin levels with a poor outcome in patients with CAD.

The present study also showed a positive correlation between serum HMW adiponectin and plasma BNP, a sensitive marker of cardiac function, in patients with CAD. Kistorp et al reported a high serum adiponectin level in patients with chronic heart failure (18). They also showed a positive correlation between the plasma level of the N-terminal Pro-B-type natriuretic peptide, an inactive form of BNP, and plasma total adiponectin in these patients (18). In a recent study, Tsutamoto et al demonstrated that plasma HMW adiponectin increases along with the New York Heart Association functional class (40). Serum total adiponectin was previously reported to be associated with plasma BNP in CAD patients (41), in agreement with our finding. Furthermore, a recent study demonstrated that BNP directly enhances the production of adiponectin by human adipocytes (42). Thus, in CAD patients with cardiac dysfunction, there may be a counter-regulatory or a compensatory increase of HMW adiponectin via defensive mechanism in the advanced stage of CAD.

The present study showed for the first time that the serum HMW adiponectin levels increased in parallel with the increase in the number of three factors (anemia, high BNP, and CKD) in patients with CAD. Serum HMW adiponectin was highest in patients with all three conditions, as was the HMW/total adiponectin ratio. Furthermore, the HMW/total adiponectin ratio increased as the number of these factors increased. Such findings suggest that HMW adiponectin, rather than LMW or MMW adiponectin, predominantly increases in CAD patients with the combination of anemia, high BNP, and CKD. The combination of anemia, cardiac dysfunction, and CKD has been termed the “cardio-renal-anemia syndrome” (43, 44). These three conditions create a

vicious circle, which can cause or can be caused by each other (43, 44). Therefore, the interaction between these three factors may cause the deterioration of cardiac and renal function as well as exacerbating anemia. Cardio-renal-anemia syndrome is poorly understood, but refers to the simultaneous presence of heart failure, CKD, and anemia in patients with CAD that may be associated with the worst prognosis and highest mortality. The present study demonstrated that serum HMW adiponectin was the highest in CAD patients with the triad of anemia, high BNP, and CKD. A prospective study demonstrated that renal insufficiency and anemia are significant, independent and additive of short-term and long-term predictors of adverse events in patients undergoing percutaneous coronary intervention (27, 28). Thus, a markedly elevated HMW adiponectin level may be associated with the presence of cardio-renal-anemia syndrome in patients with CAD. In other words, marked elevated HMW adiponectin may be an indicator of serious CAD, which is why high (rather than low) HMW adiponectin levels are associated with increased mortality of patients with CAD in some studies.

The present study had several limitations, including its cross-sectional design. As a causal relationship cannot be proven by cross-sectional data, a prospective study should be undertaken to confirm the relation between a high serum HMW adiponectin level and a poor prognosis or mortality in CAD patients who have anemia, high BNP, and CKD. Another limitation is the relatively small number of each subgroup stratified according to the presence or absence of anemia, cardiac dysfunction, and CKD, leading to a type II error. The third limitation is the difference in the proportion of male to female patients of each subgroup, because serum adiponectin, especially HMW adiponectin, is much higher in females than in males (10). The gender difference may modify the results of HMW adiponectin in each subgroup. We cannot conclude that only anemia, BNP, and GFR additively increase HMW adiponectin levels.

In conclusion, metabolic syndrome is associated with a decrease of serum HMW adiponectin or HMW/total adiponectin ratio in patients with CAD. In contrast, the presence of anemia, high BNP, and CKD is associated with marked elevation of the serum HMW adiponectin level in

patients with CAD. Thus, a marked elevation of HMW adiponectin level may indicate the clustering of factors associated with more severe CAD.

The authors state that they have no Conflict of Interest (COI).

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