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Potential impact of renin-angiotensin system inhibitors and calcium channel blockers on plasma high-molecular-weight adiponectin levels in hemodialysis patients

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Running title: HMW Adiponectin in Hemodialysis Patients

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Abstract

While metabolic syndrome confers an increased risk of cardiovascular disease in the general population, little is known about the alteration of abdominal adiposity and its association with adipocytokines in hemodialysis patients. We investigated the plasma high-molecular-weight (HMW) adiponectin level and its relationship to visceral fat area (VFA) and various markers of atherosclerosis in hemodialysis patients. In a cross-sectional study, conventional cardiovascular risk factors, plasma total and HMW adiponectin, the number of components of the metabolic syndrome, and, using computed tomography, the distribution of abdominal adiposity were assessed in 144 hemodialysis patients (90 men and 54 women; mean age, 60.7 years) and 30 age- and sex-matched patients with chronic kidney disease (CKD). Plasma HMW adiponectin levels in hemodialysis patients were significantly higher than those in patients with CKD, negatively associated with VFA and serum triglycerides and positively associated with plasma total adiponectin as well as the HMW-to-total adiponectin ratio in men and women (all $P<0.05$) in a simple regression analysis. In a multiple regression analysis, VFA was a significant determinant of HMW adiponectin in hemodialysis patients. Furthermore, after adjustment for classical risk factors, HMW adiponectin levels were significantly higher in patients undergoing treatment with renin-angiotensin system inhibitors or calcium channel blockers compared with patients not undergoing such treatment. This study shows that plasma HMW adiponectin levels

were negatively associated with VFA and positively associated with treatment with blockade of the renin-angiotensin system and of the calcium channel. Therefore, these drugs might be effective for improving adipocytokine-related metabolic abnormalities in hemodialysis patients.

Key words: high-molecular-weight adiponectin, visceral obesity, renin-angiotensin system inhibitors, calcium channel blockers, hemodialysis patients.

Introduction

It is well known that metabolic disturbances in chronic kidney disease (CKD), such as insulin resistance, inflammation and lipid abnormalities, are causally associated with atherosclerosis and cardiovascular death in hemodialysis patients [1]. In such patients, the risk of cardiovascular death is more than ten times higher than in subjects with normal kidney function [2].

Adipose tissue is currently considered to be not only a reservoir for storage of energy but also an active endocrine organ producing several adipocytokines [3]. Adiponectin, a 30-kDa collagen-like protein synthesized by adipocytes, is a multifunctional adipocytokine with favorable effects on glucose and lipid metabolism, insulin resistance and inflammation, and it has been shown to play a protective role in experimental models of vascular injury. Clinically, serum or plasma adiponectin is decreased in pathological states, including obesity, diabetes mellitus, and ischemic heart disease [4, 5]. Hypoadiponectinemia increases the prevalence of ischemic heart disease two-fold [4, 5] and has been shown to be a risk factor for ischemic heart disease in the general population. In hemodialysis patients with cardiovascular events, serum adiponectin levels are lower than in patients without cardiovascular events [6]. Therefore, the circulating adiponectin level is regarded as an inverse predictor of cardiovascular outcome in hemodialysis patients as in the general population. Adiponectin exists in several isoforms in the human blood, including low-,

middle-, and high-molecular-weight (HMW) isoforms [7]. The HMW form is most active and confers a protective effect on blood vessels. However, the prevalence of visceral fat obesity and the alteration of adipocytokines, such as plasma total and HMW adiponectin, tumor necrosis factor (TNF)-α, and inflammatory markers in hemodialysis patients, have not been fully elucidated. In the present study, we investigated plasma HMW adiponectin levels and its relationship to various markers of atherosclerosis including visceral fat obesity, which was determined by abdominal computed tomography (CT) in Japanese hemodialysis patients. Furthermore, we investigated the effect of anti-atherosclerotic treatment on HMW adiponectin and the HMW-to-total adiponectin ratio.

Methods

Subjects

A total of 218 maintenance hemodialysis patients with standard bicarbonate dialysate, age ≥20 years and a hemodialysis duration of ≥90 days were enrolled. The hemodialysis dose was checked using the following formula: $Kt/V = -\ln(R - 0.03) + [(4 - 3.5R) \times (UF/W)]$, where Kt/V is a single-pool Kt/V, R is the ratio of post-dialysis to pre-dialysis serum urea nitrogen, t is the duration of dialysis in hours, UF is the ultrafiltration volume in liters and W is the post-dialysis body weight in kilograms [8]. Age, gender, lipid parameters, and conventional cardiovascular risk factors were also recorded. Information regarding anti-hypertensive regimens, treatment with renin-angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), β-blockers, statins, and anti-diabetic regimens, or insulin was collected. The exclusion criteria were a weekly dialysis time of <12 h, urea Kt/V of <1.2, the use of a temporary hemodialysis catheter and comorbidity with malignancy, inflammation, infectious diseases or polycystic kidney disease. After removing these patients, we recruited 144 maintenance hemodialysis patients (90 men and 54 women; age, 60.7±11.8 years; duration of hemodialysis, 150.4±108.7 months) and 30 age- and sex-matched patients with CKD (18 men and 12 women; age, 61.9± 12.7 years).

This study was approved by the ethics committee of Asahikawa Medical College.

Informed consent was obtained from each patient before entry into the study.

Data collection

Blood samples were taken immediately before the first dialysis session of the week in a supine position and collected in vacuum plastic tubes. The samples were centrifuged at 3,000 rpm for 15 min at 4°C. The supernatant was decanted and frozen at -80°C until assayed. Plasma levels of total and HMW adiponectin and of TNF-α were measured using commercially available ELISA kits (Sekisui Medical, Tokyo, Japan and R&D Systems, Abingdon, UK, respectively), and the HMW-to-total adiponectin ratio was calculated. Among volunteers (20 females and 27 males), the means of the total and HMW adiponectin levels were significantly higher in females than in males (6.62±3.04 vs. 4.30±1.76 μg/ml, 3.24±2.13 vs. 1.62±1.02 μg/ml, respectively; $P<0.005$, by Student's *t*-test) as described previously [9]. Other parameters were measured by standard laboratory methods.

Waist circumference (WC) (in cm) at the umbilical level was measured in a standing position at the start of dialysis. Body weight denotes dry weight, and body mass index (BMI) was calculated by dividing dry weight (kg) by squared height (m^2). Smoking was defined as current smoking or a history of habitual smoking. Hypertension was defined as either systolic pressure $\geq$140 and/or diastolic pressure $\geq$90 mmHg or current use of anti-hypertensive medications. Diabetes was defined as one of the following: fasting blood

sugar ≥126 mg/dl; non-fasting blood sugar ≥200 mg/dl or HbA1c ≥6.0%; or current use of insulin or an oral hypoglycemic agent. Dyslipidemia was defined as: total cholesterol ≥220 mg/dl; high-density lipoprotein (HDL) cholesterol <40 mg/dl for men, <50 mg/dl for women, or triglyceride ≥150 mg/dl; or current use of an anti-hyperlipidemic medication. Metabolic syndrome (MS) criteria were determined using a modified version of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure (Adult Treatment Panel III) [10] as follows: (1) medication for hypertension or systolic blood pressure ≥130 and/or diastolic pressure ≥85 mmHg; (2) triglycerides≥150 mg/dl; (3) HDL cholesterol <40 mg/dl for men and <50 mg/dl for women; (4) medication for diabetes or HbA1c ≥6.0%; (5) WC ≥ 85 cm for men and ≥90 cm for women, which is the definition of metabolic syndrome in Japan [11]. Because data on fasting glucose was only available in a subsample of fasting subjects, we assessed HbA_{1c} instead.

Abdominal fat distribution was determined using an abdominal CT at the level of the umbilicus. Subcutaneous fat tissue was defined as the extra peritoneal fat between the skin and muscle. The intra-abdominal tissue with the same density as the subcutaneous fat tissue was defined as visceral fat tissue. The subcutaneous fat area (SFA) and visceral fat area (VFA) were also measured at the level of the umbilicus. We investigated the prevalence of visceral fat obesity defined as VFA>100 cm^2, which is a risk factor for metabolic syndrome in Japan and is a visceral fat mass that is approximated by a waist circumference of 85 cm in

men and 90 cm in women [11].

Statistical analysis

The results were expressed as the mean ± SD or SEM. Univariate and multivariate linear regression was used for continuous variables. The means of HMW adiponectin and VFA were compared to the different metabolic factors with a one-way analysis of variance (ANOVA) followed by multiple comparisons using Turkey's Studentized Range Test. The adjusted mean of HMW adiponectin was compared among the different medications with analysis covariance (ANCOVA) for age, sex, systolic BP, BMI, hemoglobin, albumin, prior CVD, smoking, medication for hypertension, medication for diabetes, and medication for dyslipidemia. *P* values <0.05 were considered statistically significant. All statistical analyses were performed with the SPSS software package Version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Relationship between HMW adiponectin and VFA

The baseline characteristics of the subjects are outlined in Table 1. The prevalence of hypertension, diabetes mellitus, and dyslipidemia was 81%, 31% and 63%, respectively, in hemodialysis patients. Table 2 shows the body composition, fat distribution and adipocytokines according to sex. Although mean BMI, WC and VFA were greater in men, no significant difference was found in SFA between the sexes in patients with CKD and on hemodialysis. The prevalence of VFA>100 cm^2 was 31.2% in men and 15.5% in women. There were no significant differences in age, WC, VFA or SFA between patients with CKD and those on hemodialysis within the same gender groups. Despite the higher body weight and BMI in female patients with CKD than those with hemodialysis, the HMW adiponectin levels were significantly higher in hemodialysis patients compared with patients with CKD in both men and women. Furthermore, HMW adiponectin levels of patients with CKD and hemodialysis were higher than those of healthy volunteers, as previously reported [9], although we did not have data from age- and sex-matched healthy volunteers.

As shown in Figure 1, a similar negative relationship between total or HMW adiponectin and VFA was observed in both men and women who were hemodialysis patients. Table 3 lists univariate correlations between HMW adiponectin and various parameters among hemodialysis patients. HMW adiponectin correlated significantly and positively

with total adiponectin, HMW-to-total adiponectin ratio and HDL-C and negatively with VFA, dyslipidemia, and triglycerides in both men and women who were hemodialysis patients. HMW adiponectin correlated significantly and negatively with BMI and WC in men, but not in women, suggesting that VFA is a more sensitive determinant for reduced plasma HMW adiponectin than BMI and WC in hemodialysis patients. To determine factors contributing to HMW adiponectin, we performed a multiple regression analysis for HMW adiponectin and demonstrated that VFA was a significant determinant for HMW adiponectin (r=-0.367, p<0.0001) in hemodialysis patients (Table 4).

Relationship between MS components and HMW adiponectin or VFA in hemodialysis patients

Figure 2 shows the relationship between the number of components of MS and HMW adiponectin or VFA. There was a stepwise decrease in HMW adiponectin levels corresponding to the accumulation of components of MS (p<0.0001 for trend) (Figure 2A). HMW adiponectin levels of subjects with three or more components of MS were significantly lower than those with none or only one component in men, but not in women because of the lower levels of HMW adiponectin in men than women with the same number of components of MS. In contrast, there was a stepwise increase in VFA corresponding to the accumulation of the components of MS (p<0.0001 for trend) (Figure 2B). The VFA of

the subjects with three or more components of MS was significantly greater than those with none or only one component in both men and women. Furthermore, a significant difference in VFA between subjects with two and four more components were also found in both men and women, suggesting that abdominal visceral fat obesity is associated with the accumulation of MS components in hemodialysis patients as it is in non-hemodialysis patients.

Impact of RAS inhibitors and CCBs on HMW adiponectin

Finally, we investigated the relationship between HMW adiponectin or HMW-to-total adiponectin ratio and anti-atherosclerotic treatments in hemodialysis patients. Figure 3 shows the differences in the HMW adiponectin and HMW-to-total adiponectin ratio according to medical treatment after adjustment for age, sex, systolic BP, BMI, hemoglobin, albumin, prior CVD, smoking, duration of hemodialysis, medication for hypertension, medication for diabetes, and medication for dyslipidemia. We found significant differences in the HMW adiponectin levels and HMW-to-total adiponectin ratio: compared with patients not taking any medications, the values were greater in patients using RAS inhibitors, CCBs and a combination of RAS inhibitors and CCBs, but not in patients using β-blockers and statins. There were no significant differences in age, sex, VFA, BMI and systolic BP in patients treated with or without the use of RAS inhibitors/CCBs (Table 5), suggesting that

the type of medication rather than blood pressure level affected adiponectin levels.

Discussion

In the present study, we observed two specific new findings. First, we found an association between plasma HMW adiponectin levels and the visceral fat obesity determined by direct measurement of VFA using abdominal CT in hemodialysis patients. Second, we found an association of plasma HMW adiponectin levels and HMW-to-total adiponectin ratio with the use of RAS inhibitors and CCBs in hemodialysis patients.

Several investigators have reported that total adiponectin levels are higher in patients on hemodialysis compared with healthy volunteers [6, 12-14] and those with pre-hemodialysis CKD [15]. In the present study, HMW adiponectin levels were significantly higher in hemodialysis patients compared with patients with CKD in both men and women. HMW adiponectin levels of patients with CKD and hemodialysis were higher than those of healthy volunteers as previously reported [9], suggesting that impaired renal function may affect the elimination of total and HMW adiponectin. Zoccali et al. [6] suggested that the down-regulation of adiponectin receptors may reset serum adiponectin concentrations to a higher level. Recently, Shen et al. [12] reported that both AdipoR1 and R2 upregulated peripheral blood mononuclear cells of hemodialysis patients in a manner unrelated to insulin resistance, suggesting that adiponectin signaling is an adaptive, protective mechanism in uremia rather than a cause of dysmetabolism. However, it is clear that hemodialysis patients have a high risk of atherosclerotic disease, despite hyperadiponectinemia. As for the reason for this

discrepancy, renal impairment might contribute to the decreasing HMW-to-total adiponectin ratio through decreasing HMW adiponectin. Odamaki et al. [16] reported that VFA is a major determinant of plasma total adiponectin in hemodialysis patients; however, none of the studies have investigated HMW adiponectin levels and directly measured VFA. Thus, we evaluated the correlation between HMW adiponectin and VFA in hemodialysis patients.

We found that plasma HMW adiponectin was negatively associated with VFA in both men and women, but there was no association with BMI and WC in women, suggesting that VFA is a more sensitive determinant of metabolic abnormality than BMI and WC. Women had significantly greater levels of HMW adiponectin than men, which is similar to what has been reported in the general population [4, 5, 17]. Thus, to minimize the influence of age and gender, we performed a multivariate analysis adjusted for age, gender, duration of dialysis, and other conventional risk factors and showed that the independent contribution of VFA to decreased plasma HMW adiponectin remained significant in hemodialysis patients. Furthermore, we demonstrated that the distribution of abdominal adiposity and the prevalence of VFA>100 cm^2 was 31.2% in men and 15.5% in women and that the accumulation of MS components was significant and correlated positively with VFA and negatively with HMW adiponectin, suggesting that reduced VFA might be important for the prevention of CVD not only in the general population but also in hemodialysis patients.

In contrast to the relationships found in the general population, numerous studies have

found that adiposity has a neutral or even protective association with mortality in hemodialysis patients, possibly due to so-called reverse epidemiology [19-21]. However, there is the possibility that the protective link observed between obesity and mortality may not actually exist. Most studies have not completely accounted for known mortality risk factors such as smoking, blood pressure, and medication. The incidence of cardiovascular disease is high even in non-obese individuals with a BMI within the normal range who have an accumulation of visceral fat [22]. Recently, VFA has been significantly associated with insulin resistance [23] and with the prevalence of CVD in participants from the Framingham Heart Study [24]; thus, the accurate assessment of both body fat distribution and VFA is critical for assessing the risk of arteriosclerotic disease. Ohkawa et al. [25] reported that VFA in hemodialysis patients increased irrespective of BMI, and a positive relationship existed between VFA and atherosclerosis. Thus, visceral fat obesity is not rare in Japanese hemodialysis patients, and this shift of abdominal adiposity might be associated with increased risks of CVD in hemodialysis patients.

Finally, we demonstrated here for the first time that levels of HMW adiponectin and HMW-to-total adiponectin ratio in patients taking RAS inhibitors, CCBs, and a combination of RAS inhibitors and CCBs were significantly higher than in patients not on these treatments after adjustment for age, sex, BMI and other cardiovascular risk factors. It has been reported that RAS inhibitors [26, 27] and CCBs [28] increase adiponectin levels in

non-hemodialysis patients. Previous studies have shown that ARB inhibits obesity-induced hypoadiponectinemia through the inhibition of reactive oxygen species generation in mice [29] and that some ARBs have peroxisome proliferator-activated receptor γ-activating properties [30], thereby stimulating adiponectin production. Some CCBs have also been reported to have the ability to increase adiponectin levels through the inhibition of reactive oxygen species generation [31] and of monocyte and platelet activation [28]. Based on these reports, we speculated that the blockade of RAS and of the calcium channel may be a powerful tool not only in patients with hypertension and pre-hemodialysis CKD but also in hemodialysis patients for improving metabolic disturbance. In contrast, some studies have reported that statins increased circulating levels of adiponectin [32, 33]. In the present study, we found no significant differences between patients treated with or without statins.

The limitations of the study were, first, that the definition of metabolic syndrome is still under debate. In Japan, a WC of 85 cm for men and 90 cm for women has been adopted as the definition of metabolic syndrome, which approximates a VFA of 100 cm^2 at the level of the umbilicus and is indicative of the risk of metabolic syndrome [11]. Thus, we used VFA>100 cm^2 as the cut-off value for visceral fat obesity. Second, we used nonfasting data, in particular, nonfasting high serum triglycerides and low HDL cholesterol, as a component of metabolic syndrome. Although justification by the same cut-off point during fasting is still under debate, the data of nonfasting triglycerides can be used because it is a significant

predictor for ischemic heart disease [34]. Therefore, we assessed HbA_{1c} instead of fasting glucose, nonfasting triglycerides and HDL cholesterol and used a "modified" metabolic syndrome definition rather than the standard definition. Third, we could not compare the adiponectin levels before and after medication in the present cross-sectional, observational study of chronic hemodialysis patients. However, there were no significant differences in WC, VFA, and SFA among patient groups treated with or without RAS inhibitors/CCBs, suggesting that types of medications rather than abdominal obesity affected the adiponectin levels. The effect of RAS inhibitors and CCBs on adiponectin levels is still under debate. Huang et al. [21] also investigated the effect of the RAS blockade and did not find any effect on adiponectin levels. However, several investigators reported that ACEI, ARB [25, 26], and CCB [27] increase adiponectin levels in non-hemodialysis patients. Thus, we speculated that these drugs might also increase adiponectin levels in hemodialysis patients. Fourth, the Japanese hemodialysis population is clearly different from others, such as that of the United States, which has a higher proportion of diabetic patients and African Americans [35]. There are several other differences in terms of patient age and sex distribution; therefore, the results may not be directly applicable to Westerners or individuals of certain ethnic groups. Thus, we must consider the potential associations between clinical practice and outcomes, adjusted for patient characteristics, which may affect clinical care. Furthermore, the relations to cardiovascular end-points must be examined in a future large prospective study.

In conclusion, we demonstrated that plasma HMW adiponectin levels were associated negatively with VFA and that the blockade of RAS as well as of the calcium channel might be effective for improving adipocytokine-related metabolic abnormalities in hemodialysis patients. These results highlight the importance of modern therapeutic efforts aimed at ameliorating metabolic disturbance in hemodialysis patients.

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None.

Disclosures

None.

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Figure legends

Fig 1. The relationship between the visceral fat area and plasma total adiponectin (A) or HMW adiponectin (B) in 90 male (filled circle; solid lines) and 54 female (open circle; dotted lines) hemodialysis patients.

Fig 2. The mean values of HMW adiponectin (A) and visceral fat area (B) according to the number of metabolic syndrome components in male (filled bars) and female (open bars) hemodialysis patients. The data were analyzed using one-way ANOVA; post hoc comparisons were made using Tukey's honest significance difference test. The bar graphs represent mean ± SEM (*P<0.05 vs. 0/1 component and †P<0.05 vs. 2 components). There was a stepwise decrease in HMW adiponectin levels and increase in VFA corresponding to the accumulation of components of MS (p<0.0001 for trend).

Fig 3. The adjusted mean values of HMW adiponectin (A) and HMW-to-total adiponectin (B) according to treatment in hemodialysis patients. Adjusted for age, sex, systolic BP, BMI, hemoglobin, albumin, prior CVD, smoking, medication for hypertension, medication for diabetes, and medication for dyslipidemia. The bar graphs represent mean ± SEM (*P<0.05). RASI, renin-angiotensin system inhibitors; CCB, calcium

channel blockers; β-b, β-blockers

Table 1. Baseline Characteristics

	CKD		HD	
	Men	Women	Men	Women
Number	16	12	90	54
Age, y	62.7±15.4	61.8±8.6	61.3±10.9	59.7±13.0
Duration of dialysis, m	-	-	133.8±107.5	178.6±105.8
Hypertension	13 (81%)	10 (83%)	74 (82%)	42 (78%)
Diabetes	5 (31%)	6 (50%)	32 (36%)	12 (22%)
Dyslipidemia	7 (44%)	9 (75%)	51 (57%)	40 (74%)
Smoking	8 (50%)	3 (25%)	40 (44%)	12 (22%)
Prior CVD	6 (38%)	3 (25%)	25 (28%)	12 (22%)
Systolic BP, mmHg	140±19	138±20	148±23	145±19
Diastolic BP, mmHg	78±15	77±14	84±16	82±13
Hemoglobin, g/dL	12.3±2.0	10.6±1.5	10.9±1.3	10.4±1.0
Hematocrit, %	36.1±4.9	32.2±3.6	32.0±3.7	30.8±2.8
Serum total cholesterol, mg/dL	174±38	178±41	134±26	160±35
Serum triglycerides, mg/dL	152±84	156±50	107±64	105±52
Serum HDL-cholesterol, mg/dL	46±10	48±18	41±11	47±9.2
Serum LDL-cholesterol, mg/dL	110±26	108±33	72±23	92±27
Serum uric acid, mg/dL	7.4±1.3	6.9±1.9	6.9±1.3	7.4±1.4
Serum potassium, mEq/L	4.2±0.4	4.4±0.3	4.9±0.7	4.9±0.6
Serum calcium, mg/dL	9.1±0.4	8.8±0.6	8.9±0.9	9.2±0.8
Serum phosphate, mg/dL	3.3±0.6	4.1±0.9	6.1±1.6	5.9±1.9
Serum intact PTH, pg/mL	50.3±31.3	78.5±49.3	148.6±143.4	136.0±148.1
Serum albumin, g/dL	4.0±0.5	3.7±0.4	3.9±0.3	3.9±0.3
Serum urea, mg/dL	28.6±12.9	37.6±19.6	64.4±16.0	61.8±17.3
Serum creatinine, mg/dL	1.6±0.8	2.5±1.7	12.1±3.0	10.2±2.2
Hemoglobin A1c, %	5.6±1.1	5.9±1.2	5.4±0.6	5.6±1.0
Kt/V urea	-	-	1.33±0.21	1.55±0.20

Variables are presented as mean±SD, or number (percentage). Kt/V denotes fractional urea clearance. CKD, chronic kidney disease; HD, hemodialysis; CVD, cardiovascular disease; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone.

Table 2. Body composition, fat accumulation and adipocytokines according to sex

	CKD		HD	
	Men	Women	Men	Women
Number	18	12	90	54
Body weight/Dry weight, kg	61.4±10.2	57.3±9.6	60.5±8.3	47.5±7.1 *†
Body mass index, kg/m^2	22.7±2.9	24.1±3.6	22.4±2.6	20.8±3.2 *†
Waist circumference, cm	83.3±6.7	86.3±11.2	85.4±8.7	80.5±9.6*
Subcutaneous fat area, cm^2	90.1±33.7	127.9±56.5 *	90.3±47.9	96.4±49.0
Visceral fat area, cm^2	80.9±42.4	62.3±22.9	82.8±48.8	57.5±36.1*
Visceral fat area $\geq$ 100cm^2, %	31.3	0.0	31.2	15.5*
Plasma total adiponectin, μg/ml	6.4±3.5	9.0±6.1	9.5±4.5 †	10.9±5.1
Plasma HMW adiponectin, μg/ml	2.3±2.0	3.9±3.0	4.1±2.7 †	5.3±3.4 *†
Plasma TNF-α, pg/mL	1.8±1.5	2.7±1.6	4.2±1.7 †	4.4±1.6 †
Serum hsCRP, mg/dL	0.22±0.33	0.40±0.48	0.30±0.48	0.23±0.46

Variables are presented as mean±SD or percentage. CKD, chronic kidney disease; HD, hemodialysis; HMW, high molecular weight; TNF, tumor necrosis factor; hsCRP, high-sensitivity C-reactive protein. *P<0.05 vs men of same group and †P<0.05 vs same sex of CKD.

Table 3. Univariate Correlation between plasma HMW adiponectin and other parameters in hemodialysis patients

	Men	Women
Age	0.128	-0.080
Duration of dialysis	0.233 *	0.119
Body mass index	-0.346 **	-0.126
Waist circumference	-0.362 ***	-0.0091
Visceral fat area	-0.487 ***	-0.311 *
Subcutaneous fat area	-0.286 **	-0.154
Plasma total adiponectin	0.951 ***	0.945 ***
HMW to total ratio	0.833 ***	0.758 ***
Plasma TNF-α	0.182	0.265
Serum hsCRP	0.018	0.098
Hypertension	0.064	0.105
Diabetes	-0.240 *	0.048
Dyslipidemia	-0.347 ***	-0.388 **
Smoking	-0.080	-0.010
Prior CVD	0.116	-0.019
Systolic BP	0.047	-0.041
Pulse pressure	0.039	-0.149
Hemoglobin	-0.065	0.070
Hematocrit	0.002	0.066
Serum total cholesterol	0.001	-0.055
Serum triglycerides	-0.355 ***	-0.303 *
Serum HDL- cholesterol	0.225 *	0.259 *
Serum LDL- cholesterol	0.086	-0.052
Serum uric acid	-0.280 **	-0.029
Serum potassium	0.134	
Serum calcium	0.121	0.240
Serum phosphate	0.097	-0.047
Serum intact PTH	0.134	-0.037
Serum albumin	-0.068	0.037
Serum urea	-0.073	-0.162
Serum creatinine	-0.206	-0.253
Hemoglobin A1c	-0.145	-0.186
Kt/V urea	0.046	0.278

Abbreviations are the same as Table 1 and 2. ***P<0.001.; **P<0.01.; *P<0.05.

Table 4. Multiple Regression Analysis of the Correlation of HMW adiponectin in hemodialysis patients

	B	B	95% CI	*P*
Age	0.108	0.027	-0.017 to 0.071	0.229
Sex (man=1, woman=0)	-0.146	-0.891	-1.930 to 0.149	0.092
Duration of dialysis	0.161	0.004	-0.001 to 0.009	0.083
BMI	0.098	0.100	-0.105 to 0.304	0.336
Visceral fat area	-0.367	-0.024	-0.036 to -0.011	<0.0001
Hypertension	0.052	0.628	-1.222 to 2.479	0.503
Diabetes	-0.056	-0.368	-1.461 to 0.725	0.507
Dyslipidemia	-0.295	-1.829	-2.836 to -0.818	0.082
Smoking	0.103	0.297	-0.214 to 0.807	0.253
Prior CVD	0.040	0.270	-0.797 to 1.336	0.618
Hemoglobin	-0.015	-0.037	-0.445 to 0.371	0.859
Serum albumin	0.033	0.335	-1.418 to 2.087	0.706
Serum uric acid	-0.118	-0.258	-0.613 to 0.096	0.151

Model $R^2 = 0.310$; $P<0.0001$

β, standardized coefficients; B, unstandardized coefficients; CI, confidence interval.

Table 5. Characteristics of patients treated with RAS inhibitors or CCBs in hemodialysis patients

RAS inhibitors	(-)	(-)	(+)	(+)
CCBs	(-)	(+)	(-)	(+)
Number	65	23	18	38
Age, y	59.9±11.6	63.7±11.3	58.7±11.9	61.9±11.4
Sex, men, %	66	56	61	61
Duration of dialysis, months	138.8±105.3	94.5±89.8	129.4±111.2	140.6±111.9
Waist circumference, cm	83.3±9.4	82.4±9.0	83.1±11.3	84.3±10.1
Visceral fat area, cm^2	84.3±9.4	82.4±9.0	83.1±11.3	84.4±10.1
Subcutaneous fat area, cm^2	90.7±45.0	86.3±45.8	105.3±52.5	96.9±56.9
Systolic BP, mmHg	139.4±22.2	146.7±24.3	150.1±24.7	152.8±20.4
Diastolic BP, mmHg	78.7±12.5	82.3±13.6	84.7±14.1	84.9±12.8
Pulse pressure, mmHg	59.8±17.7	64.3±15.9	65.4±17.8	67.9±17.1

Figure 1A

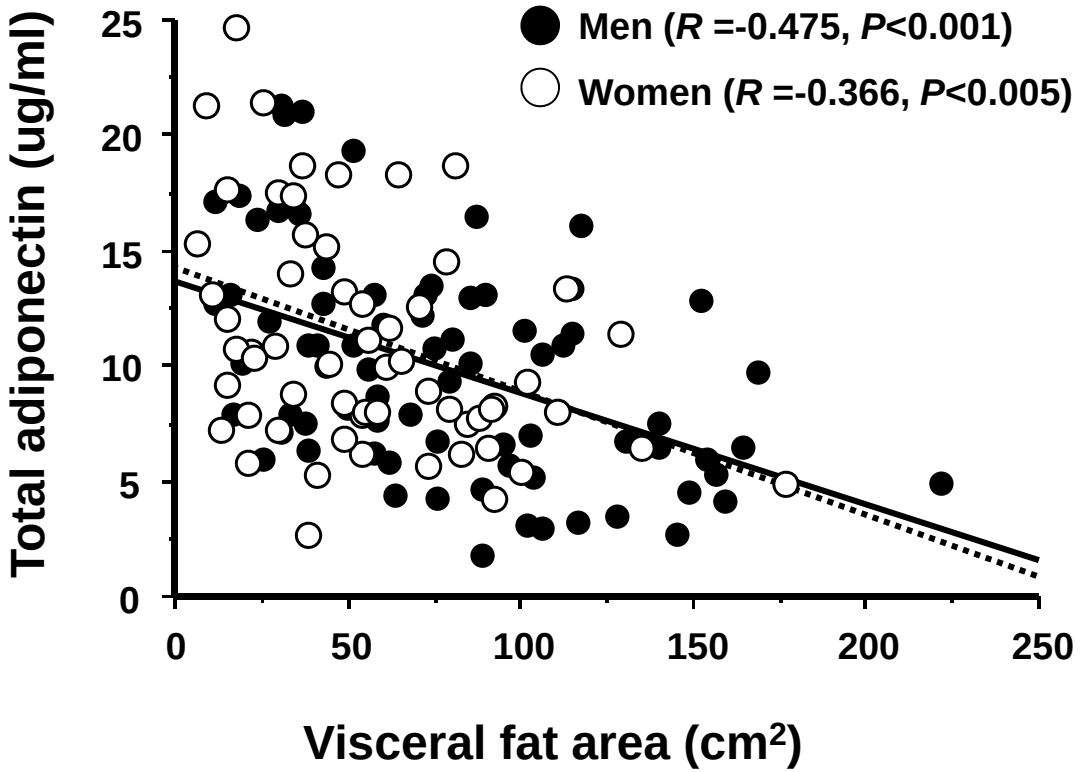

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Figure 1B

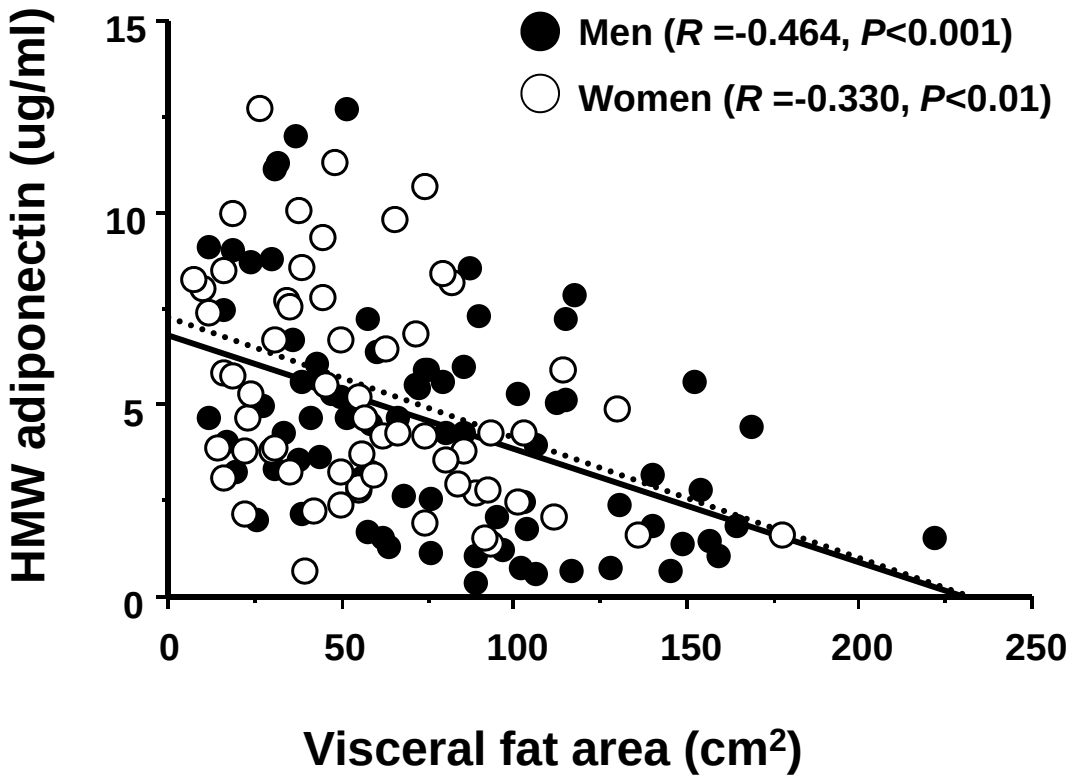

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Figure 2A

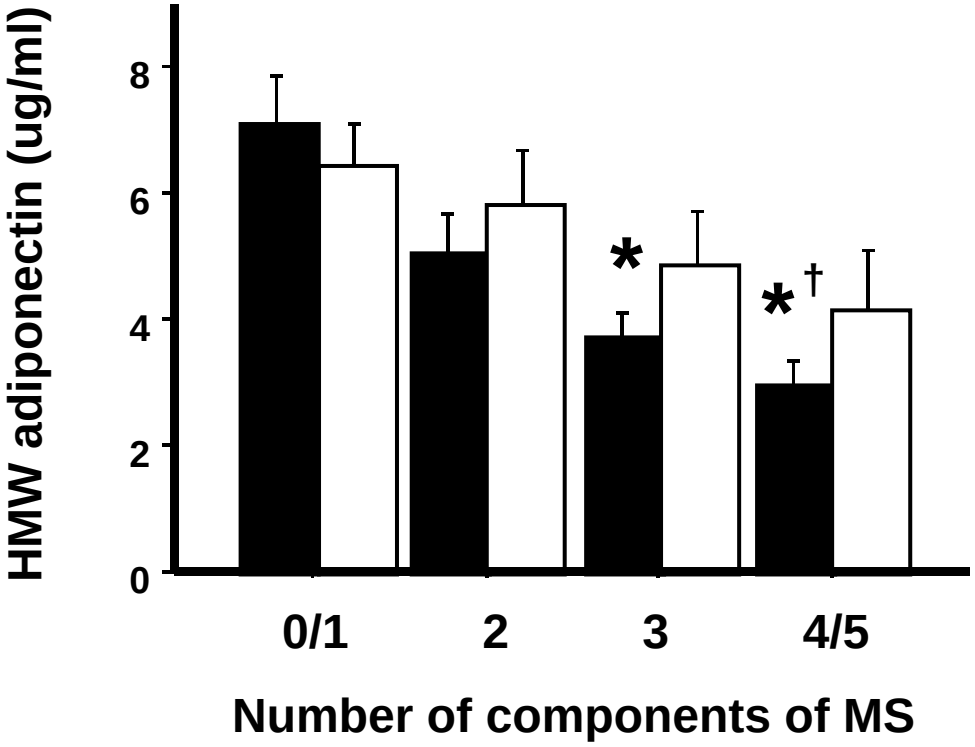

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Figure 2B

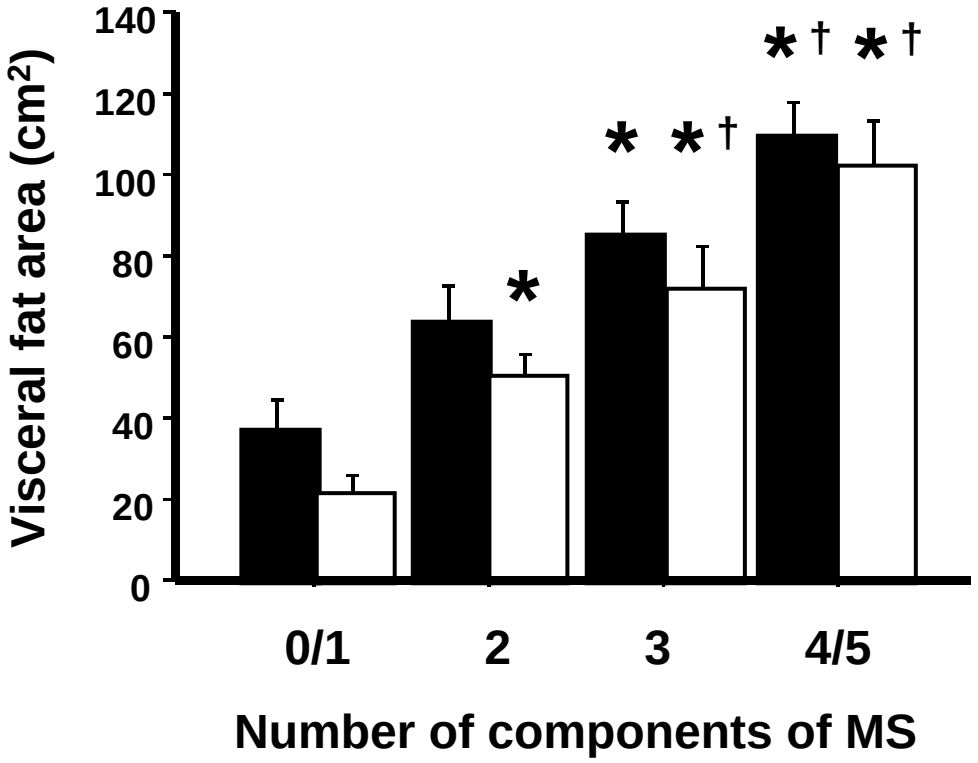

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Figure 3A

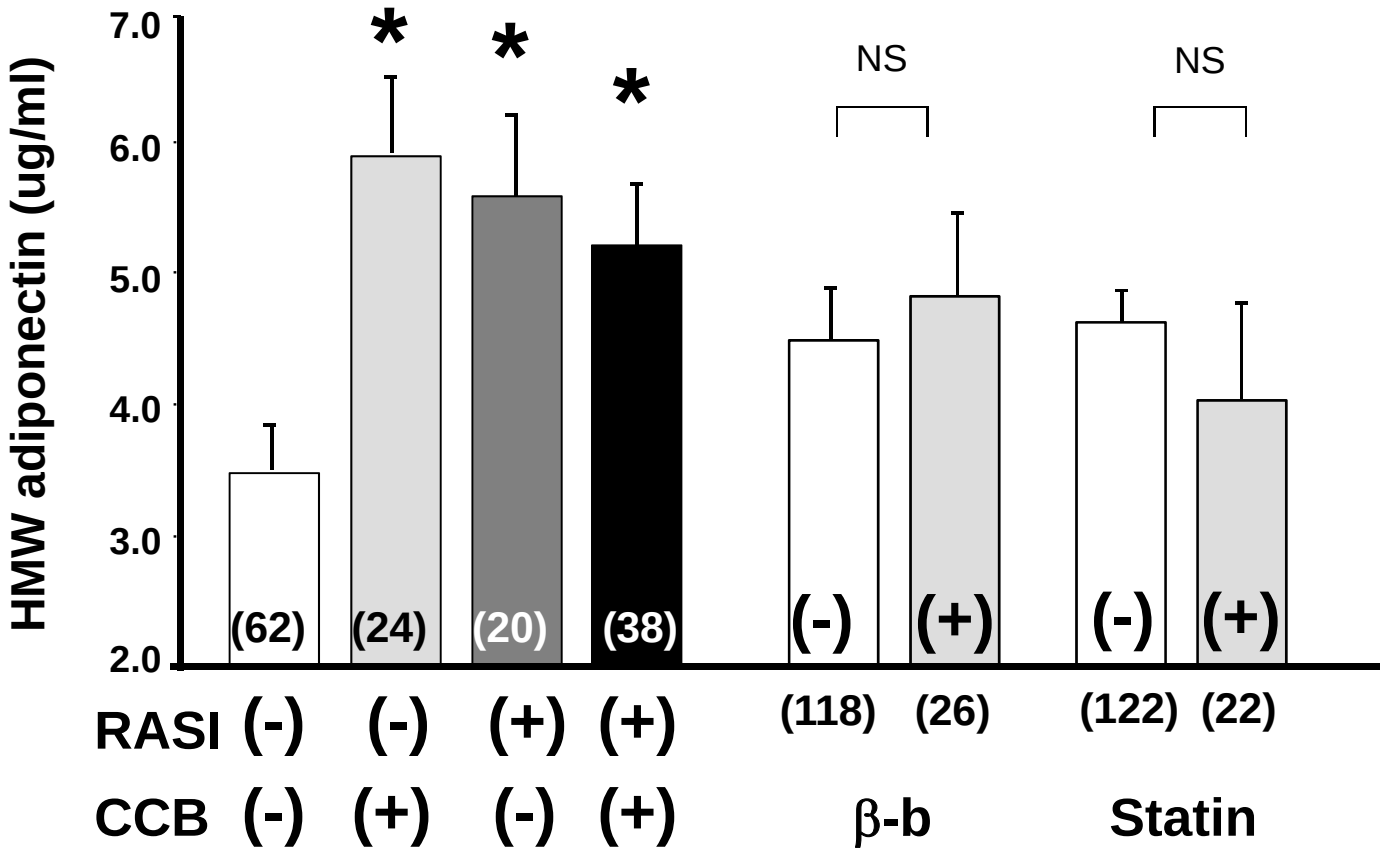

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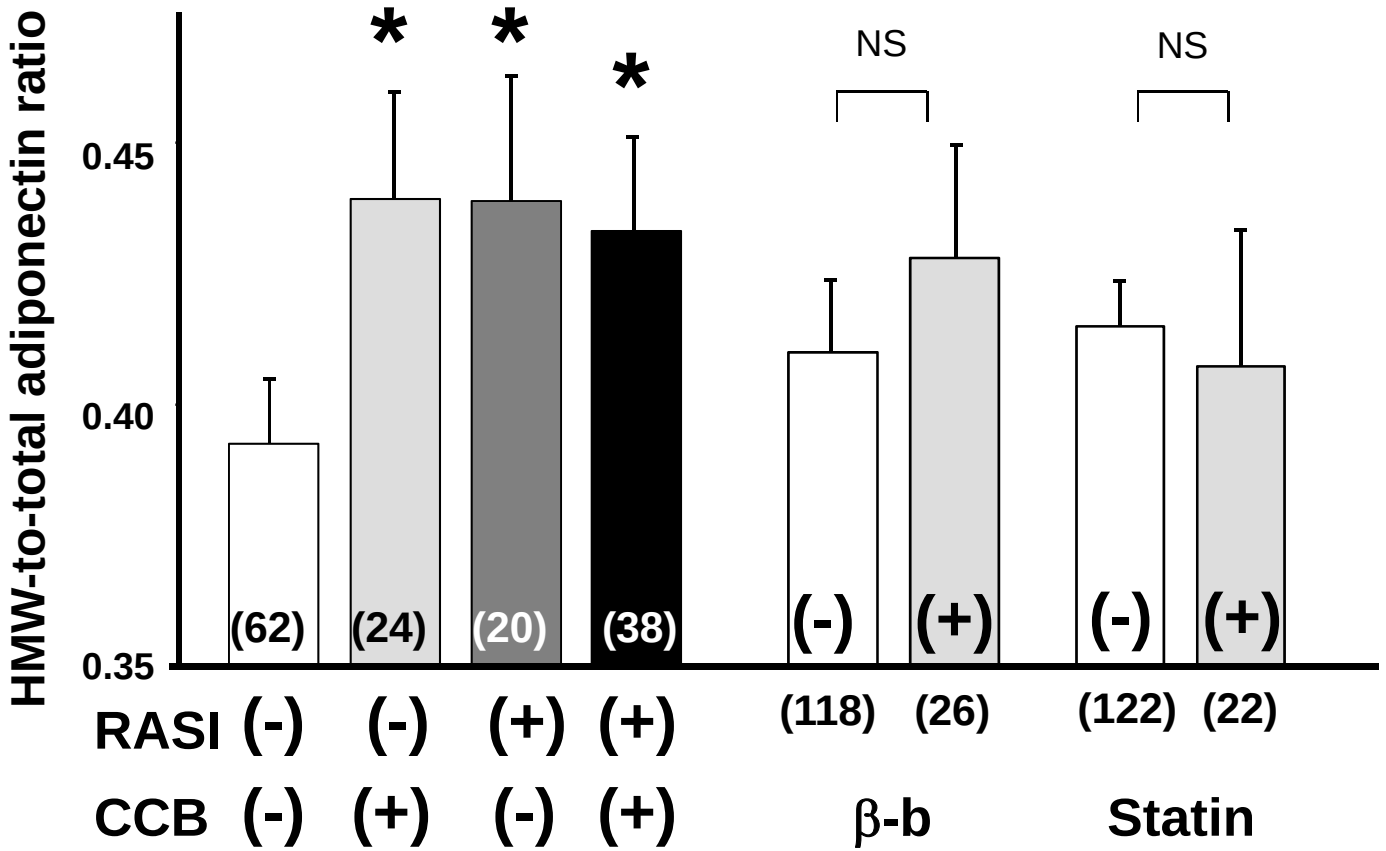
Figure 3B



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