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ORIGINAL ARTICLE

Association of serum adiponectin level with albuminuria in chronic kidney disease patients

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Abstract

Background Adiponectin, a peptide hormone secreted from adipocytes, exerts anti-diabetic, anti-atherogenic, and anti-inflammatory properties. We aimed to determine the relationship between serum adiponectin levels and albuminuria, and evaluate determinant factors for serum adiponectin in patients with chronic kidney disease (CKD).

Methods In total, 1442 CKD patients were included and divided into three groups according to their albumin-to-creatinine ratios: patients with normoalbuminuria ($N = 228$), microalbuminuria ($N = 444$), and macroalbuminuria ($N = 761$). Serum adiponectin was specifically assayed with a commercially available enzyme-linked immunosorbent assay kit.

Results Serum adiponectin was significantly higher in patients with macroalbuminuria than in those without macroalbuminuria (9.7 ± 6.0, 12.4 ± 9.0, and 14.9 ± 11.0 μg/mL in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively). Univariate linear regression analysis showed that the serum adiponectin concentrations were correlated with age, the albumin-to-creatinine ratio, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, whereas they were negatively correlated with body mass index, the estimated glomerular filtration rate, and serum albumin and triglyceride levels. The stepwise regression multiple analysis showed that sex; the estimated glomerular filtration rate; body mass index; total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; and logarithm of the albumin-to-creatinine ratio were independently associated with the logarithm of serum adiponectin levels ($r = 0.55$, $p < 0.001$).

Conclusion Serum adiponectin concentrations are higher in patients with increasing albuminuria, and these levels are associated with renal insufficiency and lipid profiles.

Keywords Serum adiponectin · Albuminuria · Chronic kidney disease

Introduction

Obesity is associated with metabolic syndrome, which is characterized by hyperinsulinemia, insulin resistance, diabetes mellitus (DM), hypertriglycemia, and decreased high-density lipoprotein (HDL) cholesterol levels. In addition, obesity is recognized as a major risk factor for chronic kidney disease (CKD) progression to end-stage renal disease [1]. Adiponectin is a 30 kDa collagen-like protein secreted from adipocytes. Interestingly, plasma concentrations are inversely correlated with the amount of body fat in obesity [2].

Experimental evidence showed the direct role of renoprotective effects such as the anti-inflammatory and anti-fibrotic effects of adiponectin [3, 4]. However,

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human studies investigating the relationship between serum adiponectin and albuminuria have shown conflicting results [5]. In addition, serum adiponectin levels are an inverse predictor of cardiovascular outcomes [6]. Most research about adiponectin has been conducted on a relatively small population and limited number of patients with DM or obesity. Moreover, some medications affecting serum adiponectin and albuminuria such as renin–angiotensin system blockers or thiazolidinedione were not considered.

We aimed to determine the relationship between serum adiponectin levels and albuminuria in DM and non-DM patients, and evaluate determinant factors for serum adiponectin in patients with CKD.

Patients and methods

Study subjects

The design of the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) study has been described in detail in a previous study (NCT01630486) [7]. KNOW-CKD is a patient-based, multicenter cohort study comprised nine clinical centers of major university-affiliated hospitals of South Korea. The KNOW-CKD enrolled ethnic Korean patients with CKD who ranged in age between 20 and 75 years. Specific causes of CKD were defined and classified into four sub-cohorts: glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, and polycystic kidney disease. Patients with other causes were categorized as unclassified. Serum and urine samples were subsequently collected on a regular basis according to the standardized protocol. All data, including clinical information, laboratory results, and outcomes, were entered into a web-based, electronic, case-reporting form.

A baseline survey was administered from February 2011 through May 2015 in an ongoing prospective cohort study in collaboration with a multicenter cohort study. In total, 1529 patients were included in this analysis, and we excluded 87 patients with missing data of serum adiponectin and creatinine. Ultimately, 1442 participants were included in the final analysis. These subjects were classified into three groups according to their urine albumin-to-creatinine ratio (UACR): patients with normoalbuminuria (UACR <30 mg/g; $N = 228$), microalbuminuria (30 mg/g ≤UACR <300 mg/g; $N = 444$), and macroalbuminuria (UACR ≥300 mg/g; $N = 761$). CKD was defined by a calculated value of the estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [8].

Clinical data and laboratory analyses

Clinical data, including detailed demographic information and baseline laboratory results, were extracted from the electronic data management system (PhactaX, Seoul, Korea). The adiponectin level was measured using an enzyme-linked immunosorbent assay (Adipogen, Seoul, Korea). Adiponectin is secreted into the bloodstream as three oligomeric complexes, including a trimer [low molecular weight (LMW)], hexamer (middle molecular weight), and multimer [high molecular weight (HMW)] comprised at least 18 monomers that possess distinct biological activities. Adiponectin does not circulate in biological fluids as monomers or dimers [9]. The Adiponectin (human) ELISA Kit, which we used, was a total adiponectin kit that detected the sum of values of low-, middle-, and high-molecular-weight adiponectin. The intra- and interassay coefficients of variation were 3.3 and 7.4 %, respectively.

Statistical analysis

Continuous variables with normal distributions are presented as mean ± SD and were compared using one-way analysis of variance. Pearson's Chi-square test was used to evaluate differences between categorical variables. Simple linear regression analysis was used to examine the relationship between serum adiponectin and various parameters and the relationship between eGFR; body mass index (BMI); systolic blood pressure; diastolic blood pressure; UACR; and fasting blood glucose, serum albumin, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol levels. Multiple stepwise regression analysis was used to determine the contribution of various factors to serum adiponectin levels. All statistical tests were performed using the Statistical Package for Social Sciences software, version 18.0 (IBM Corp., Armonk, NY). P values <0.05 were considered significant.

Results

Baseline characteristics

In total, 1442 patients (mean age: 53.6 ± 12.3 years; men, 61.6 %) were included in this study. Table 1 summarizes the baseline general characteristics, including 324 with diabetic nephropathy, 309 with hypertensive nephropathy, 455 with glomerulonephropathy, and 246 with autosomal dominant polycystic kidney disease. Table 2 presents the demographics and clinical features according to the albuminuria categories. At baseline, 15.8 % ($N = 228$) of patients had normoalbuminuria, 30.7 % ($N = 444$) had microalbuminuria, and 52.7 % ($N = 761$) had

Table 1 General patient characteristics according to primary renal disease

	Total cohort	DN	HTN	GN	PKD	p value
Total participants[a]	1442	324	309	455	246	
Age (years)	53 ± 12	58 ± 9	58 ± 10	49 ± 12	46 ± 10	<0.001
Men (%)	882 (61.2)	210 (64.8)	219 (70.9)	263 (57.8)	122 (49.6)	<0.001
Body mass index (kg/m^2)	24.3 ± 3.3	25.1 ± 3.2	25.1 ± 3.4	23.9 ± 3.3	23.3 ± 3.0	<0.001
Waist–hip ratio (m/m)	0.89 ± 0.06	0.92 ± 0.05	0.90 ± 0.06	0.87 ± 0.06	0.87 ± 0.06	<0.001
Systolic blood pressure (mmHg)	127 ± 16	135 ± 18	127 ± 15	122 ± 14	127 ± 13	<0.001
Diastolic blood pressure (mmHg)	76 ± 11	75 ± 11	77 ± 11	75 ± 10	79 ± 10	<0.001
CKD stage						
1	217 (15.0)	9 (2.8)	19 (6.1)	96 (21.1)	86 (35.0)	<0.001
2	267 (18.5)	26 (8.0)	53 (17.2)	107 (23.5)	68 (27.6)	
3	540 (37.4)	131 (40.4)	140 (45.3)	156 (34.3)	58 (23.6)	
4	313 (21.7)	113 (34.9)	79 (25.6)	71 (15.6)	22 (8.9)	
5	105 (7.3)	45 (13.9)	18 (5.8)	25 (5.5)	12 (4.9)	
Creatinine (mg/dL)	1.87 ± 1.18	2.44 ± 1.39	1.96 ± 1.04	1.68 ± 1.14	1.38 ± 0.97	<0.001
Cystatin C (mg/L)	1.80 ± 0.95	2.33 ± 1.00	1.86 ± 0.83	1.60 ± 0.89	1.33 ± 0.79	<0.001
eGFR (mL/min/1.73 m^2)	51 ± 30	35 ± 20	44 ± 23	58 ± 31	72 ± 33	<0.001
Adiponectin (μg/mL)	13.4 ± 10.0	15.1 ± 11.6	12.3 ± 9.3	13.1 ± 9.4	12.4 ± 9.0	0.001
UACR (mg/g)	802 ± 1493.2	1787 ± 2220.0	501 ± 1137.2	693 ± 967.9	133 ± 278.5	<0.001
ACEIs or ARBs (%)	1219 (84.5)	287 (88.6)	261 (84.5)	409 (89.9)	191 (77.6)	<0.001
Statin (%)	719 (49.9)	207 (63.9)	169 (54.7)	226 (49.8)	57 (23.2)	<0.001
Thiazolidinedione (%)	20 (1.4)	19 (5.9)	1 (0.3)	0	0	<0.001
Total cholesterol (mg/dL)	173 ± 37.5	164 ± 38.8	173 ± 35.1	179 ± 39.1	178 ± 32.0	<0.001
Triglyceride (mg/dL)	154 ± 96.0	168 ± 104.3	163 ± 104.0	155 ± 93.6	126 ± 70.8	<0.001
LDL cholesterol (mg/dL)	96 ± 30.9	88 ± 30.9	97 ± 29.8	101 ± 32.4	101 ± 27.2	<0.001
HDL cholesterol (mg/dL)	49 ± 15.7	44 ± 14.6	47 ± 15.0	52 ± 17.0	54 ± 13.7	<0.001

Numbers denote mean $\pm$ SD or number (%)

DN diabetic nephropathy, *HTN* hypertensive nephropathy, *GN* glomerulonephropathy, *PKD* autosomal dominant polycystic kidney disease, *UACR* urine albumin-to-creatinine ratio, *ACEIs* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

[a] Total participants included those in 4 subgroups and the other unclassified kidney diseases

macroalbuminuria. With increasing albuminuria, patients had a higher BMI; systolic blood pressure; and fasting blood glucose, triglyceride, and adiponectin levels, whereas they had lower levels of serum albumin and HDL cholesterol. Increasing albuminuria was associated with a higher prevalence of DM, and use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). LDL cholesterol and total cholesterol levels were higher in patients as albuminuria increased. There were no differences in sex and age among the groups. As expected, eGFR decreased with increasing albuminuria. Mean eGFRs were 72 ± 30, 53 ± 28, and 44 ± 28 mL/min/1.73 m^2 in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively.
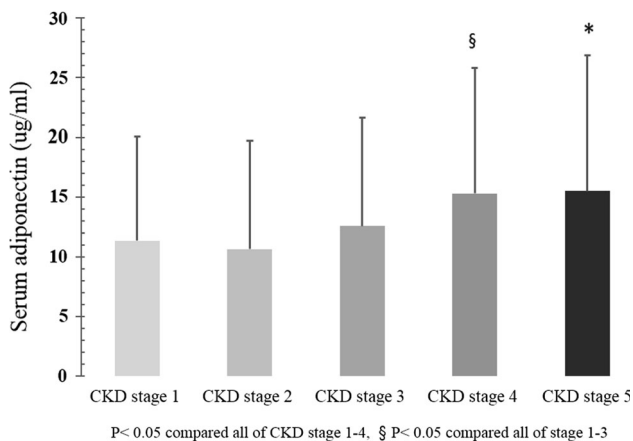
Levels of serum adiponectin according to the CKD stage

Patients were divided into five eGFR groups corresponding to strata used to define the CKD stages: GFR ≥ 90; $60 \leq$ GFR < 90; $30 \leq$ GFR < 60; $15 \leq$ GFR < 30; and GFR <15 mL/min/1.73 m^2 [10]. Figure 1 shows the serum adiponectin levels according to the CKD stages. There was no difference in the adiponectin concentration among CKD stages 1, 2, and 3, but the serum adiponectin concentration in patients with CKD stage 4 was higher than those in patients with CKD stages 1–3. The serum adiponectin concentrations were higher in patients with CKD stage 5 than in those with CKD stages 1–4 (Fig. 2).

Table 2 Baseline characteristics and clinical features of patients according to the albuminuria categories

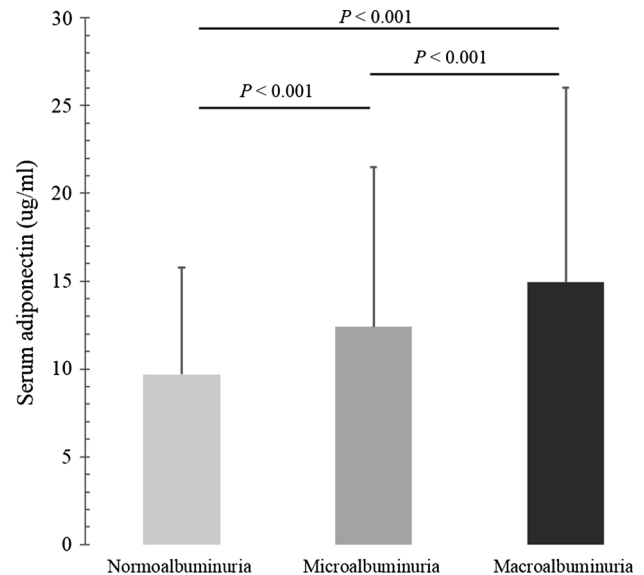|	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	p
N	228	444	761	
Men (%)	148 (64.9)	258 (58.1)	469 (61.6)	0.207
Age (years)	52 ± 13	53 ± 12	53 ± 12	0.6730
Diabetes (%)	30 (13.6)	106 (24.8)	321 (43.6)	<0.001
Body mass index (kg/m^2)	23.9 ± 3.2	24.1 ± 3.2	24.7 ± 3.4	0.001
Systolic blood pressure (mmHg)	125 ± 14	125 ± 15	130 ± 17	<0.001
Diastolic blood pressure (mmHg)	76 ± 10	75 ± 10	77 ± 11	0.176
eGFR (mL/min/1.73 m^2)	72 ± 30	53 ± 28	44 ± 28	<0.001
UACR (mg/g)	12.3 ± 7.7	134.7 ± 80.6	1520.6 ± 1357.5	<0.001
Fast blood glucose (mg/dL)	101 ± 20.5	102 ± 25.2	112 ± 42.8	<0.001
Albumin (mg/dL)	4.3 ± 0.2	4.3 ± 0.2	4.0 ± 4.3	<0.001
Total cholesterol (mg/dL)	174 ± 32	169 ± 33	175 ± 40	0.007
Triglyceride (mg/dL)	132 ± 76	139 ± 77	170 ± 107	<0.001
LDL cholesterol (mg/dL)	101 ± 31	94 ± 27	96 ± 32	0.028
HDL cholesterol (mg/dL)	51 ± 15	49 ± 14	48 ± 16	0.041
ACEIs or ARBs (%)	169 (74.1)	374 (84.2 %)	668 (87.8 %)	<0.001
Statin (%)	75 (33.0)	188 (42.3)	452 (59.4)	<0.001
Thiazolidinedione (%)	1 (0.4)	5 (1.1)	14 (1.8)	<0.001
Adiponectin (μg/mL)	9.7 ± 6.0	12.4 ± 9.0	14.9 ± 11.0	<0.001

Data are presented as number (%) or mean ± SD

eGFR estimated glomerular filtration rate, *UACR* urine albumin-to-creatinine ratio, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ACEIs* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers

Fig. 1 Serum adiponectin concentration according to the chronic kidney disease stage

Levels of serum adiponectin according to albuminuria

We compared a group of patients with macroalbuminuria with groups of patients with normoalbuminuria and microalbuminuria. The serum adiponectin level was significantly higher in patients with macroalbuminuria than in

Fig. 2 Serum adiponectin concentration according to the degree of albuminuria

those without microalbuminuria (9.7 ± 6.0, 12.4 ± 9.0, and 14.9 ± 11.0 μg/mL in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively).

Association between the serum adiponectin level and clinical parameters

The serum adiponectin level correlated with age; UACR; and total cholesterol, triglyceride, LDL cholesterol, and HDL cholesterol levels, whereas BMI, eGFR, and the serum albumin level correlated inversely with this protein (Table 3). In stepwise multiple regression analysis, sex; eGFR; BMI; the total cholesterol, HDL cholesterol, and triglyceride levels; and the logarithm of UACR were independent predictors of the logarithm of serum adiponectin (Table 4). However, age, DM, the LDL cholesterol levels, ACEIs or ARBs, statins, thiazolidinedione, the fasting blood glucose level, and systolic blood pressure were not determinants. Additional analysis was performed in DM patients and non-DM patients. Similarly, in both DM and non-DM patients, sex; eGFR; total cholesterol, HDL cholesterol, and triglyceride levels; and the logarithm of UACR were common determinants. In non-DM patient, BMI and the fasting blood glucose level were included with independent predictors of the logarithm of serum adiponectin.

Discussion

In the present study, the serum adiponectin level was much higher in patients with macroalbuminuria than in patients with normoalbuminuria or microalbuminuria. Albuminuria and the HDL cholesterol level were positively correlated with serum adiponectin, whereas serum albumin, BMI, and eGFR were inversely correlated with this protein. In stepwise multiple regression analysis, the logarithm of UACR;

Table 3 Univariate linear regression analysis between serum adiponectin and the clinical parameters

	R	p
Age (years)	0.060	0.022
Body mass index (kg/m²)	−0.247	<0.001
Systolic blood pressure (mmHg)	0.049	0.061
Diastolic blood pressure (mmHg)	0.024	0.360
eGFR (mL/min/1.73 m²)	−0.257	<0.001
UACR (mg/g Cr)	0.269	<0.001
Fast blood glucose (mg/dL)	0.042	0.113
Serum albumin (mg/dL)	−0.295	<0.001
Total cholesterol (mg/dL)	0.110	<0.001
Triglyceride (mg/dL)	−0.198	<0.001
LDL cholesterol (mg/dL)	0.061	0.020
HDL cholesterol (mg/dL)	0.262	<0.001

eGFR estimated glomerular filtration rate, *UACR* urine albumin-to-creatinine ratio, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *Cr* creatinine

sex; eGFR; BMI; and total cholesterol, HDL cholesterol, and triglyceride levels were independent predictors of the logarithm of serum adiponectin. This result strongly suggests that renal proteinuria is compensated by a substantial increase in adiponectin synthesis in CKD patients with high levels of albuminuria.

Adiponectin is a peptide hormone secreted from adipocytes that has insulin-sensitizing, anti-artherogenic, and anti-inflammatory properties [11, 12]. It was reported that serum adiponectin is inversely related to eGFR [6, 13]. Adiponectin circulates as various isoforms and polymers [14–16], and its monomers (28 kDa) and dimers can cross the normal glomerular filtration barrier and is cleared by the kidney. It seems that a higher-molecular-weight adiponectin is not secreted in urine, thus a high-molecular-weight adiponectin can be a marker of adiponectin production independent of eGFR.

Adiponectin receptors (AdipoR) 1 and 2 are found in the kidney and are located in the intrarenal arterioles, endothelium, podocytes, mesangial cells of the glomerulus, and proximal tubular cells [17, 18]. AdipoR 1 can activate the AMP-activated protein kinase (AMPK) pathway that inhibits high-glucose-induced protein synthesis and reactive oxygen species protein. Sharma et al. reported that adiponectin knockout (Ad$^{-/-}$) mice exhibited increased albuminuria and podocyte effacement compared with wild-type mice. In addition, Ad$^{-/-}$ mice treated with adiponectin exhibited normalization of albuminuria with increased glomerular AMPK activation [19]. Furthermore, rats with adenine-induced chronic renal failure had increased renal expression of AdipoR 1 and 2, and its receptors were positively correlated with serum and urinary adiponectin levels [20]. These findings indicate that renal injury may cause a compensatory up-regulation of AdipoR 1 and 2 in the kidneys to reduce further renal injury.

In most clinical human study settings, serum adiponectin level was elevated with increasing albuminuria [21, 22]. Because studies demonstrating the beneficial effects of adiponectin regarding the reduction in albuminuria were performed exclusively in animal experiments [19, 23, 24], it is necessary to cautiously interpret the relevance between human and rodent studies. The underlying mechanism is unknown, but a plausible explanation for increasing serum adiponectin in patients with macroalbuminuria or nephropathy is a beneficial compensatory mechanism that has a protective role of adiponectin against the development of albuminuria. Considering the anti-inflammatory and anti-atherosclerotic properties of adiponectin, it is postulated that increased adiponectin levels serve to protect patients at high risk of cardiovascular disease against the harmful actions of pro-inflammatory and atherosclerotic agents, as recently suggested [25].

Table 4 Multiple regression model for the determinants of serum adiponectin (logarithm transformed)

Independent variable	Total cohort (N = 1442)		Non-DM patients (N = 915)		DM patients (N = 458)	
	β	p	β	p	β	p
Sex	−0.147	<0.001	−0.173	<0.001	−0.095	0.024
Body mass index (kg/m^2)	−0.164	<0.001	−0.208	<0.001	–	–
Fast blood glucose (mg/dL)	–	–	−0.063	0.030	–	–
eGFR (mL/min/1.73 m^2)	−0.325	<0.001	−0.338	<0.001	−0.292	<0.001
Total cholesterol (mg/dL)	0.094	0.001	0.078	0.020	0.106	0.042
HDL cholesterol (mg/dL)	0.175	<0.001	0.166	<0.001	0.208	<0.001
Triglyceride (mg/dL)	−0.202	<0.001	−0.098	0.004	−0.325	<0.001
Logarithm of UACR (mg/g Cr)	0.153	<0.001	0.130	<0.001	0.159	<0.001

Adjusted clinical factors including age, sex, diabetes, eGFR, body mass index, ACEIs or ARBs, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, fasting blood glucose, systolic blood pressure and the logarithm of UACR, HMG-CoA reductase inhibitors, thiazolidinedione

eGFR estimated glomerular filtration rate, *UACR* urine albumin-to-creatinine ratio, *ACEI*s angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Albuminuria is associated with DM and obesity, and increasing albuminuria constitutes an adverse cardiovascular risk factor [2, 26, 27]. Albuminuria is associated with increased renal endothelial permeability and endothelial dysfunction [28]. Adiponectin is also related to endothelial dysfunction, as it binds to the major collagen components of the intima of blood vessels and accumulates in the vascular wall when the endothelial barrier is damaged [29]. Thus, serum adiponectin may be an early and novel biomarker for cardiovascular risk together with albuminuria.

In the present study, the logarithm of serum adiponectin was determined by sex (women had a higher serum adiponectin); eGFR; BMI; total cholesterol, HDL cholesterol, and triglyceride levels; and the logarithm of UACR. Christous et al. demonstrated that serum HDL cholesterol induces adiponectin production and a positive relationship between the levels of HDL cholesterol and serum adiponectin [30]. Although the underlying mechanism was not clear, serum HDL cholesterol showed effects against albuminuria in an observational study, and it was supposed that HDL cholesterol may have a role in increased adiponectin. Women have higher circulating serum adiponectin concentrations than men [31]. As shown recently, the sex difference in adiponectin develops during puberty, and it is negatively associated with serum levels of androgen, which is believed to suppress adiponectin synthesis [32]. It has been reported that age was also related to serum adiponectin [31], but our data did not show age as a determinant factor for adiponectin. This may be explained by the fact that age was preserved in a healthy population, whereas it was absent in patients with albuminuria.

Because the signal transduction of AdipoR seems to involve activation of AMPK and p38 mitogen-activated protein kinase and peroxisome proliferator-activated receptor-α [33], we assumed that a statin or thiazolidinedione may be a determinant for serum adiponectin, but our analysis showed that they were not related factor. This may be because the number of patients taking thiazolidinedione among DM patients was only 20, which was relatively small.

This study has several limitations. Lo et al. [34] concluded that the ratio between high-molecular-weight adiponectin and low-molecular-weight adiponectin may be an important biomarker of high cardiovascular risk. We measured the total serum adiponectin so the ratio could not be determined. Second, because it was a cross-sectional analysis of baseline data of a cohort study, we could not determine the association between serum adiponectin and cardiovascular events or mortality. Third, although we adjusted for multiple confounding factors, it is possible that some unmeasured confounders remained.

In conclusion, the relationship between serum adiponectin and albuminuria was significant in patients with CKD, independent of eGFR. Furthermore, serum adiponectin was associated with renal insufficiency and lipid profiles. Adiponectin may be key in understanding the pathophysiological roles of association among obesity and CKD, and albuminuria.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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