Original article

Elevation of serum adiponectin in mildly decreased glomerular filtration rate

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Abstract

Background: Adiponectin secreted by adipocytes plays a key role in insulin sensitivity, anti-inflammation, and anti-atherosclerosis. It is involved in several conditions including obesity, type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease (CKD). Glomerular filtration rate is monitored to indicate the kidney function and CKD progression.

Objective: To assess the serum adiponectin levels in individuals with normal and mildly decreased glomerular filtration rate, analyze the association of serum adiponectin with various physical and biological parameters, and test whether serum adiponectin is the risk factor of mildly decreased glomerular filtration rate.

Methods: This cross-sectional study was conducted in 172 individuals with 35–60 years of age. Serum samples were collected and divided into two groups, based on estimated glomerular filtration rate (eGFR): 90 with normal eGFR (G1, eGFR ≥90 mL/min/1.73 m²) and 82 with mildly decreased eGFR (G2, eGFR = 60–89 mL/min/1.73 m²). Anthropometric data were recorded. Serum adiponectin was measured by enzyme-linked immunosorbent assay.

Results: Serum adiponectin levels were significantly increased in individuals with mildly decreased eGFR (G2), compared to G1 (8.23 ± 3.26 µg/mL and 6.57 ± 3.24 µg/mL, respectively; $P = 0.001$). Serum adiponectin was positively associated with age and high-density lipoprotein cholesterol but negatively associated with weight, body mass index, triglyceride, and waist and hip circumferences. Univariate analysis showed that serum adiponectin was significantly correlated with mildly decreased eGFR; however, when adjusting for confounding factors, there were no correlations. Furthermore, multivariate regression analysis showed that individuals at the age of 46–55 years (4.0; 95% CI: 1.9–8.3) and > 55 years (11.4; 95% CI: 3.7–35.5) were significantly correlated with mildly decreased eGFR.

Conclusions: Serum adiponectin was significantly elevated in individuals with mildly decreased eGFR and may be a modulation factor, but was not an independent risk factor for mildly kidney damage. Further study is needed to clarify its potential benefits as monitoring biomarker for CKD progression.

Keywords: adiponectin; chronic; glomerular filtration rate; renal insufficiency

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Adiponectin, also referred to as GBP28, apM1, AdipoQ, and Acrp30, is a 30-kDa polypeptide secreted exclusively by adipocyte that has functions in the regulation of glucose and lipid metabolisms [1]. Previous studies revealed the roles of adiponectin as an anti-inflammatory, anti-diabetic, and vascular protective adipokine [2, 3]. Reduction of serum adiponectin is associated with obesity [4–6], insulin resistance [7, 8], and cardiovascular diseases [9, 10]. In addition, serum adiponectin is described as an independent (inverse) risk of cardiovascular events and mortality among individuals with end-stage kidney disease [11]. Inversely, reports have shown that serum adiponectin increases in chronic kidney disease (CKD) [12–14], especially in individuals with end-stage kidney disease [15]. When the kidney is damaged or impaired, the glomerular filtration rate (GFR) decreases, resulting in an accumulation of adiponectin in blood circulation [11].

CKD is a noncommunicable disease, which is the global epidemic with increasing prevalence [16]. CKD is defined as abnormalities of kidney structure or function for >3 months [17], which may be detected by decreases in GFR and/or the presence of proteinuria. As a result, CKD individuals are classified into five stages; stage 1, normal GFR (eGFR ≥ 90 mL/min/1.73 m²); stage 2, mild kidney damage (eGFR = 60–89 mL/min/1.73 m²); stage 3, moderate kidney damage (eGFR = 30–59 mL/min/1.73 m²); stage 4, severe kidney damage (eGFR = 15–29 mL/min/1.73 m²); and stage 5, kidney failure (eGFR < 15 mL/min/1.73 m²); Moderate-to-severe kidney damage (eGFR < 60 mL/min/1.73 m²) is associated with albuminuria [18, 19]. The albuminuria categories in CKD are stratified according to urinary albumin excretion (UAE; mg/24 h) and urine albumin-to-creatinine ratio (UACR; mg/g) <30, 30–300, or >300, which fits well with the classification of normal to mildly increased, moderately, and severely increased albuminuria, respectively [20]. Stages 1 and 2 are described as the early stage of CKD and usually have no signs and symptoms. However, it can be diagnosed by slightly elevated serum creatinine and the presence of normal to mildly increased albuminuria, caused by a decline in glomerular and tubular functions [21].

As serum adiponectin markedly increases in end-stage kidney disease, it may reflect in the early stage of CKD. Therefore, this study aimed to assess levels of serum adiponectin in mildly decreased GFR, examine the relationship between serum adiponectin and other parameters, and evaluate serum adiponectin as the risk factor of mildly decreased GFR.

Materials and methods

Study population

This cross-sectional study included 172 volunteers (36 males and 136 females) at the age of 35–60 years with no history of type 1 and type 2 diabetes, cardiovascular disease, CKD with eGFR <60 mL/min/1.73 m², UACR > 300 mg/g, use of drugs that affect kidney and liver functions, such as analgesic, antipyretic, and antibiotic drugs. Based on estimated glomerular filtration rate (eGFR) defined by the Kidney Disease: Improving Global Outcomes (KDIGO: 2012) [22], they were classified into two groups: 82 cases with mildly decreased eGFR (G2, eGFR = 60–89 mL/min/1.73m²) and 90 with normal eGFR (G1, eGFR ≥ 90 mL/min/1.739m²). Anthropometric data (gender, age, weight, blood pressure, and waist and hip circumferences) were collected. This study protocol was approved by the Human Research Ethics Committee at Thammasat University (certificate of approval No. 119/2559) and informed consent was obtained from all participants.

Sample collection and biochemical analysis

Overnight (8–12 h) fasting blood and urine were collected and placed immediately on ice. Plasma and serum samples were prepared by centrifugation at 1000× g for 5–10 min and kept at –70ºC until further analysis. Fasting plasma glucose (FPG), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol) and creatinine were measured using the automated blood analyzer (Dxc800; Beckman Coulter). Calculation of eGFR was done using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, 2012 [23, 24]. Urine albumin was measured by the immunoturbidimetric assay (manufacturer). UACR was calculated using urine albumin in milligram (mg) and urine creatinine in gram (g). Serum adiponectin was analyzed using the sandwich enzyme-linked immunosorbent assay kit (DY1065, R&D system), which was verified. The percent recovery was 97.36% and the inter-assay and intra-assay coefficients of variation were 6.93% and 7.31%, respectively.

Statistical analyses

Data were reported as means ± standard deviation (SD) and analyzed using SPSS software version 23; IBM USA. Data comparisons for continuous variables between two groups were performed using the Mann–Whiney U test. The Kruskal–Wallis tests were used to analyze the statistical difference

Table 1. Anthropometric characteristics and biochemical variables of the mildly decreased eGFR (G2) and the normal eGFR (G1)

Variables	Normal eGFR (G1) (n = 90)	Mildly decreased eGFR (G2) (n = 82)	P
Sex			
Male, n (%)	14 (16)	22 (27)	
Female, n (%)	76 (84)	60 (73)	0.069[a]
Age (years)	43.52 ± 5.92	50.17 ± 6.42	<0.001*[b]
Weight (kg)	63.53 ± 12.36	62.24 ± 9.99	0.760[b]
Body mass index (kg/m^2)	24.697 ± 3.87	24.09 ± 3.10	0.624[b]
Waist (cm)	82.56 ± 10.14	83.72 ± 8.35	0.278[b]
Hip (cm)	98.94 ± 8.91	97.54 ± 7.50	0.331[b]
Waist-to-hip ratio	0.84 ± 0.07	0.86 ± 0.06	0.062[b]
DBP (mmHg)	75.89 ± 9.33	80.20 ± 10.34	<0.001*[b]
SBP (mmHg)	116.28 ± 12.46	124.32 ± 13.25	<0.001*[b]
Body adipose	30.98 ± 4.88	30.20 ± 4.96	0.274[b]
Creatinine (mg/dL)	0.70 ± 0.11	0.92 ± 0.14	<0.001*[b]
eGFR	105.02 ± 8.33	80.20 ± 6.98	<0.001*[b]
UACR (mg/g)	6.71 ± 4.27	8.13 ± 9.39	0.582[b]
FPG (mg/dL)	88.44 ± 6.56	88.91 ± 6.97	0.630[b]
Cholesterol (mg/dL)	225.56 ± 50.23	229.27 ± 45.45	0.480[b]
Triglyceride (mg/dL)	113.42 ± 54.58	125.43 ± 69.30	0.321[b]
HDL-C (mg/dL)	54.29 ± 14.54	60.61 ± 15.16	0.012*[b]
LDL-C (mg/dL)	144.36 ± 38.66	143.45 ± 40.13	0.800[b]
Serum adiponectin (mg/mL)	6.57 ± 3.24	8.23 ± 3.26	<0.001*[b]

DBP, diastolic blood pressure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; FPG, Fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Categorical variables are shown as percentage (%).
[a]Chi-square test
[b]Mann–Whitney U test
*$P < 0.05$ was considered significant.

between the three groups ($P < 0.05$). When significance was observed, a post-hoc test was used for pairwise analyses ($P < 0.05$). Spearman's rank correlation coefficients were used to examine the correlation between serum adiponectin and other parameters. Multiple linear regression analysis was used to evaluate the effects of other confounding factors for serum adiponectin. Univariate and multivariate analyses were conducted using a logistic regression with 95% confidence interval. $P < 0.05$ was considered a statistical significance. Receiver operating characteristic (ROC) curve showed the plot between specificity and sensitivity of serum adiponectin levels at a cutoff point as a predictor for mildly decreased eGFR.

Results

Baseline characteristics

Anthropometric data and biochemical variables of individuals with normal (G1, control, n = 90) and mildly decreased eGFR (G2, n = 82) are shown in **Table 1**. Ages, blood pressure, serum creatinine, HDL-cholesterol, and serum adiponectin were significantly higher in the G2 group than the G1 control. Waist circumference, waist per hip ratio (WHR), body adiposity index (BAI), triglyceride, and UACR slightly increased in the G2 group; however, there was no significant difference between the G2 and G1 groups. Both G1 and G2 groups have similar weight, body mass index (BMI), FPG, total cholesterol, and LDL-cholesterol.

Serum adiponectin in mildly decreased eGFR

Serum adiponectin was higher in individuals with mildly decreased eGFR (G2, 8.23 ± 3.26 mg/mL) than in the G1 control (6.57 ± 3.24 mg/mL) with the P value of 0.001 **(Figure 1)**. In the G2 group, females had higher serum adiponectin than males (8.92 ± 3.41 and 6.28 ± 1.76 mg/mL, respectively) with the P value of 0.002. However, the G1 control showed no significant differences in serum adiponectin between males and
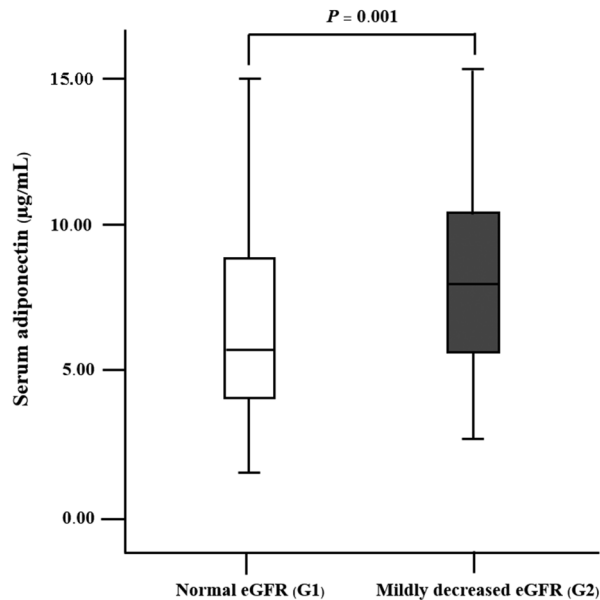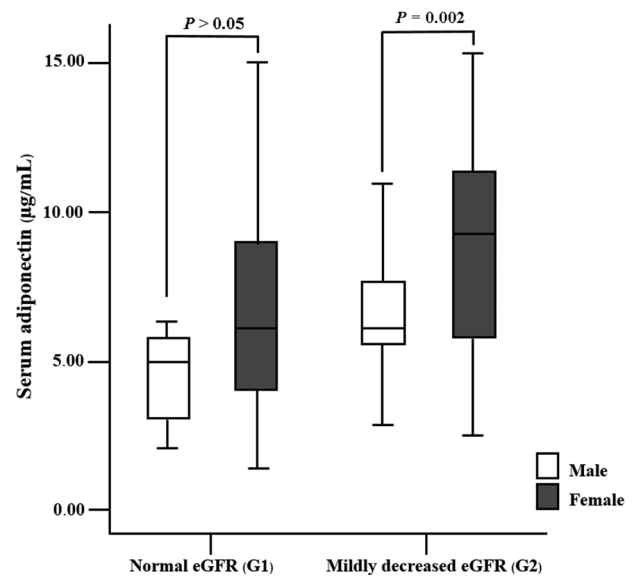
Figure 1. Comparison of the serum adiponectin between the mildly decreased eGFR (G2) and the control with normal eGFR (G1). *P*: Mann–Whiney U test

Figure 2. Comparison of serum adiponectin in male (open bars) and female (solid bars) in the mildly decreased eGFR (G2) and the control with normal eGFR (G1). *P*: Mann–Whiney U test

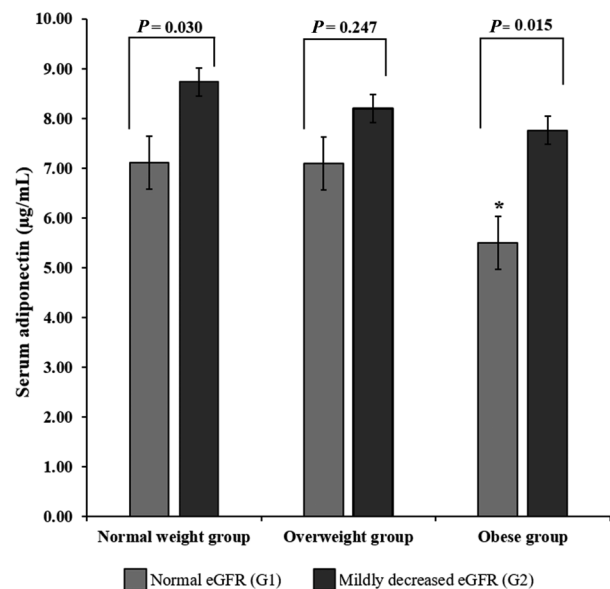females (5.39 ± 2.99 and 6.79 ± 3.26 mg/mL, respectively) with the *P* values of 0.101 **(Figure 2)**.

When data were classified based on Asian BMI criteria [25] as normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), and obesity (≥25.0 kg/m^2), it was shown that serum adiponectin in each group was higher in the G2 than the G1 control. However, the significant difference ($P < 0.05$) was found only in G1 control. Serum adiponectin levels were significantly lower in the obesity than the overweight and the normal weight with *P* value of 0.025 and 0.034, respectively **(Figure 3)**.

The Spearman's rank correlation coefficient test revealed the correlations between serum adiponectin and anthropometric parameters and biochemical variables **(Table 2)**. Serum adiponectin was significantly correlated with ages ($r = 0.355$), gender ($r = 0.196$), weight ($r = -0.306$), BMI ($r = -0.217$), waist circumference ($r = -0.236$), hip circumference ($r = -0.256$), eGFR ($r = -0.257$), triglyceride ($r = -0.204$), and HDL-cholesterol ($r = 0.444$), but not significantly correlated with WHR, BAI, creatinine, UACR, FPG, total cholesterol, LDL-cholesterol, and blood pressure. Multiple linear regression analysis setting serum adiponectin as a dependent factor showed that ages, HDL-cholesterol, and LDL-cholesterol were independently and significantly associated with serum adiponectin **(Table 3)**.

The univariate and multivariate logistic regression analyses for a predictive index of mildly decreased eGFR

Figure 3. Comparison of serum adiponectin between the normal eGFR (gray bar) and the mildly decreased eGFR (black bar) among normal weight, overweight, and obesity based on Asian BMI. The Kruskal–Wallis test followed by a post-hoc test was used to determine the differences between three independent groups and all pairwise comparisons. (*$P < 0.05$ vs normal weight group and obese group and overweight group and obese group)

are summarized in **Table 4**. Univariate regression showed that individuals older than 46 years, hypertension (systolic blood pressure [SBP] ≥130 mmHg, diastolic blood pressure

Table 2. Bivariate spearman's rank correlation coefficients between serum adiponectin with anthropometric characteristics and biochemical variables

Variables	Serum adiponectin (µg/mL)	
	r	P
Age (year)	**0.355**	**<0.001***
Weight (kg)	**−0.306**	**<0.001***
Body mass index (kg/m²)	**−0.217**	**0.004***
Waist (cm)	**−0.236**	**0.002***
Hip (cm)	**−0.256**	**0.001***
Waist-to-hip ratio	−0.105	0.168
DBP (mmHg)	−0.071	0.358
SBP (mmHg)	0.004	0.963
Body adiposity index	−0.068	0.379
Creatinine (mg/dL)	−0.073	0.344
eGFR	**−0.257**	**0.001***
UACR (mg/g)	0.108	0.159
FPG (mg/dL)	−0.005	0.947
Cholesterol (mg/dL)	−0.056	0.469
Triglyceride (mg/dL)	**−0.204**	**0.007***
HDL-C (mg/dL)	**0.444**	**<0.001***
LDL-C (mg/dL)	−0.082	0.283

Spearman's rank correlation coefficients, *$P < 0.05$ was considered significant.

[DBP] ≥ 85 mmHg), and serum adiponectin (cutoff = 5.7 mg/mL) were significantly associated with the mildly decreased eGFR (G2). Multivariate regression analysis showed that individuals at the ages of 46–55 years (4.0; 95% CI: 1.9–8.3) and >55 years (11.4; 95% CI: 3.7–33.5) were significantly correlated with the mildly decreased eGFR after adjusting for age, SBP, DBP, and serum adiponectin (**Table 4**). ROC curve analysis of serum adiponectin for detection of mildly decreased eGFR (G2) showed 70.7% specificity and 50% sensitivity at the cutoff value of 5.70 mg/mL. The area under the ROC curve was 0.652 (95% CI: 0.570–0.733, $P = 0.001$).

Discussion

The present study revealed, for the first time, that serum adiponectin increased in individuals with mildly decreased eGFR (G2) compared to normal (G1) in all groups; normal weight, overweight, and obesity. This was consistent with previous studies showing that serum adiponectin levels increase in CKD patients [12–14]. The possible explanation was that inflammatory stimuli found in CKD induce adiponectin expression in renal tubular cells to trigger a feedback response [26], leading to increases in circulating adiponectin levels.

Table 3. Multiple linear regression with adiponectin as a dependent variable ($N = 172$)

Independent variables	Unstandardized coefficients		Standardized coefficients	t	P < 0.05
	B	Std. Error	Beta		
Constant	22.190	36.021		0.616	0.539
Age (year)	0.117	0.052	0.244	2.248	0.026*
Weight (kg)	0.244	0.247	0.822	0.989	0.324
BMI (kg/m²)	−0.595	0.643	−0.627	−0.926	0.356
Waist (cm)	−0.078	0.264	−0.216	−0.295	0.769
Hip (cm)	−0.094	0.343	−0.233	−0.275	0.784
Waist-to-hip ratio	3.976	24.328	0.084	0.163	0.870
DBP (mmHg)	−0.050	0.032	−0.150	−1.534	0.127
SBP (mmHg)	0.019	0.025	0.077	0.783	0.435
Body adiposity index	0.182	0.485	0.268	0.375	0.708
Creatinine (mg/dL)	−1.451	4.985	−0.073	−0.291	0.771
eGFR	−0.030	0.053	−0.129	−0.562	0.575
UACR (mg/g)	0.021	0.031	0.045	0.664	0.508
FPG (mg/dL)	0.054	0.035	0.108	1.554	0.122
Cholesterol (mg/dL)	0.020	0.011	0.289	1.909	0.058
Triglyceride (mg/dL)	−0.006	0.005	−0.103	−1.152	0.251
HDL-C (mg/dL)	0.053	0.020	0.241	2.651	0.009*
LDL-C (mg/dL)	−0.030	0.012	−0.351	−2.537	0.012*

Constant = 22.190; $R = 0.600$; $R^2 = 0.280$; $SE_{est} = ±2.82$; $F = 4.494$; $P < 0.05$

Serum adiponectin = 22.190 + 0.117 (Age) +0.053 (HDL-C) -0.030 (LDL-C).

Table 4. Univariate and multivariate analyses of risk for mildly decreased eGFR

Variables	Case N (%)	Control N (%)	Crude OR (95%CI)	P	Adjusted OR (95%CI)	P
Sex						
Male	22 (26.8)	14 (15.6)	1			
Female	60 (73.2)	76 (84.4)	0.5 (0.2–1.1)	0.072		
Age (years)						
35–45	20 (24.4)	60 (66.7)	1		1	
46–55	38 (46.3)	25 (27.8)	4.5 (2.2–9.3)	<0.001*	4.0 (1.9–8.3)	<0.001*
>55	24 (29.3)	5 (5.5)	14.4 (4.9–42.8)	<0.001*	11.4 (3.7–35.5)	<0.001*
Body mass index (kg/m²)						
Normal	30 (36.6)	30 (33.3)	1			
Overweight	27 (37.9)	30 (33.3)	0.9 (0.4–1.9)	0.776		
Obese	25 (30.5)	30 (33.3)	0.8 (0.4–1.7)	0.626		
Waist-to-hip ratio						
Male ≤0.90, Female ≤0.85	52 (63.4)	63 (70.0)	1			
Male >0.90, Female >0.85	30 (36.6)	27 (30.0)	1.3 (0.7–2.5)	0.360		
SBP (mmHg)						
<130	57 (69.5)	77 (85.6)	1		1	
≥130	25 (30.5)	13 (14.4)	2.6 (1.2–5.5)	0.013*	1.2 (0.4–3.4)	0.689
DBP (mmHg)						
<85	53 (64.6)	75 (83.3)	1		1	
≥85	29 (35.4)	15 (16.7)	2.7 (1.4–5.9)	0.006*	2.2 (0.8–5.5)	0.112
Glucose (mg/dL)						
<100	78 (95.1)	89 (5.6)	1			
≥100	4 (4.9)	1 (1.1)	4.5 (0.5–41.7)	0.179		
Cholesterol (mg/dL)						
<200	18 (22.0)	28 (31.1)	1			
≥200	64 (78.0)	62 (68.9)	1.6 (0.8–3.2)	0.177		
Triglyceride (mg/dL)						
<150	58 (70.7)	71 (78.9)	1			
≥150	24 (29.3)	19 (21.1)	1.5 (0.8–3.1)	0.219		
HDL-C (mg/dL)						
Male ≥40, Female ≥50	14 (17.1)	23 (25.6)	1			
Male <40, Female <50	68.6 (82.9)	67 (74.4)	1.6 (0.8–3.5)	0.179		
LDL-C (mg/dL)						
<100	11 (12.6)	9 (10.0)	1			
≥100	76 (87.4)	81 (90.0)	0.8 (0.3–2.1)	0.647		
Serum adiponectin (mg/mL)						
<5.70	24 (29.3)	45 (50.0)	1		1	
≥5.70	58 (70.7)	45 (50.0)	2.4 (1.3–4.5)	0.006*	1.7 (0.8–3.5)	0.147

OR, odd ratio; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*$P < 0.05$ was considered significant.

Adiponectin was significantly higher in normal glucose tolerance group than in impaired fasting glucose and type 2 diabetes mellitus groups [27]. Diabetes mellitus was an exclusion criterion in our study. Even though, 5% of total volunteers (9/172 persons) were presented with impair glucose tolerance (IGT) state. There were four persons in the G1 group and five persons in the G2 group with FPG values of 100–107 mg/dL (The cutoff for IGT was defined as FPG = 100−125 mg/dL,

according to current American Diabetes Association (ADA) criteria [28]). Similar results as shown in **Table 1** were found after nine persons with IGT were excluded. Serum adiponectin was still higher in the mildly decreased eGFR group (7.35 ± 3.35 μg/mL) than the normal eGFR group (6.54 ± 3.19 μg/mL) with statistical significance at $P < 0.05$.

Previous reports have shown that obese individuals have lower serum adiponectin than normal weight [29, 30].

Similarly, our study showed that serum adiponectin levels were lower in obesity than normal weight individuals. In addition, low levels of serum adiponectin increase risks of CKD in the obese [3]. Obesity causes marked structural changes in kidneys, leading to loss of nephron function, increases in arterial pressure, and severe renal injury [31]. Furthermore, we observed that serum adiponectin was higher in females than males. Similar findings were shown by Eglit et al. [32], Cnop et al. [33], and Nishizawa et al. [34] that serum adiponectin concentrations were higher in females than in males. This can be explained that males have higher testosterone levels and the hormone suppresses the secretion of adiponectin [33, 34].

Moreover, our results indicated that serum adiponectin levels were positively correlated with age, and HDL-cholesterol, but negatively correlated with weight, BMI, eGFR, triglyceride, and waist and hip circumferences (**Table 2**). These findings are consistent with the previous studies in healthy, obesity, type-2 diabetes, CKD, and end-stage kidney disease subjects, showing that serum adiponectin was negatively related with BMI, weight, triglyceride, eGFR, and waist and hip circumferences [12, 14, 35, 36] and positively related with age [37] and HDL-cholesterol [5, 38].

We also found that serum adiponectin depended on age, HDL-cholesterol, and LDL-cholesterol (**Table 3**). The univariate analysis found that serum adiponectin was correlated with mildly decreased eGFR (**Table 4**). However, after adjustment for gender, age, and blood pressure, the associations between serum adiponectin and mildly decreased eGFR did not reach statistical significance. Therefore, serum adiponectin was not considered an independent risk factor for mildly kidney damage. Multivariate regression analysis showed that only age was significantly correlated with the mildly decreased eGFR. Hypertension is defined by SBP $\geq$ 130 mmHg and/or DBP $\geq$ 85 mmHg, and the present study revealed that 30.5% and 35.4% of individuals with mildly kidney damage had SBP $\geq$ 130 mmHg and DBP $\geq$ 85 mmHg, respectively. Hypertension is not only a cause but also a consequence of CKD [39, 40]. Therefore, hypertension might be the main cause of mildly decreased eGFR in this study.

ROC curve analysis of serum adiponectin for classifying a mildly decreased eGFR from a normal eGFR showed 70.7% specificity and 50% sensitivity when using 5.70 μg/mL as a cutoff value. The area under the ROC curve was 0.652 (95% CI: 0.570–0.733, $P = 0.001$). It is known that serum adiponectin decreases in diseases, such as obesity, diabetes mellitus, and cardiovascular diseases [4–10]; however, increases in adiponectin in blood circulation are found in kidney damage or CKD. Therefore, it is possible that serum adiponectin levels can be useful as a follow-up biomarker to predict the CKD progression.

Conclusion

Serum adiponectin significantly increased in individuals with mildly decreased eGFR. These findings suggested that increases in serum adiponectin reflected the reduction of kidney functions. In addition, univariate and multivariate analyses implied that serum adiponectin may be a modulating factor, but is not an independent risk factor for mildly kidney damage.

Author contributions. All the authors contributed substantially to the conception and design of this study and to the acquisition of data. AM and PS analyzed, interpreted the data, and drafted the manuscript. All the authors contributed substantially to its critical revision, approved the final version submitted for publication, and take responsibility for the statements made in the published article.

Conflict of interest statement. The authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

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