Adiponectin is not associated with renal function decline in community-dwelling elderly adults

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Abstract
Adiponectin secreted by adipocytes plays an important role in the regulation of glucose and fatty acid metabolism. Contrary to findings in patients with chronic kidney disease (CKD), no prospective data about the association of serum adiponectin with renal function decline in the general population have yet appeared. Our objective was to analyze the relationship of total and high molecular weight (HMW) adiponectin with renal function decline as measured by cystatin C in community-dwelling elderly adults without moderate or severe CKD.

In a prospective observational analysis, a total of 216 healthy elderly volunteers with eGFRcys ≥60 mL/min/1.73 m² underwent anthropometric and laboratory tests at baseline and at follow-up visits. A subgroup with serum samples collected 5 years apart was further analyzed.

There were no differences in either total or HMW adiponectin level between subjects subsequently undergoing rapid renal function decline and subjects with normal physiologic renal function decline (P = .71, P = .81). On univariate linear regression, neither total nor HMW adiponectin were associated with annual renal function decline (β = −0.23; P = .71, β = −0.057; P = .90). Multivariate analysis did not show a significant contribution of either total or HMW adiponectin to annual renal function decline (β = −0.50; P = .46, β = 0.01; P = .98). In the logistic regression analysis, we did not observe any statistically significant association of serum adiponectin levels with rapid renal function decline or incidence of CKD.

Contrary to findings in populations with CKD, neither total nor HMW adiponectin had a substantial association with renal function decline in an elderly population with eGFRcys ≥60 mL/min/1.73 m². Our results and conclusions should not be extrapolated to subjects with other characteristics.

Abbreviations: BMI = body mass index, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, eGFRcys = eGFR estimated by cystatin C, eNOS = endothelial nitric oxide synthase, GA = glycated albumin, HDL = high-density lipoprotein, HMW = high molecular weight, LMW = low molecular weight, MAP = mean arterial pressure, MEXT = Ministry of Education, Culture, Sports, Science & Technology, MMW = middle molecular weight.

Keywords: adiponectin, aging, kidney function decline

1. Introduction
In elderly adults, renal function decline, even in its early stages, has been suggested to be contribute to atherosclerosis. Atherosclerosis in turn leads to cardiovascular and cerebrovascular disease with their attendant morbidity and mortality.[1–6] Risk factors for renal dysfunction include obesity, hypertension, and diabetes mellitus.[7,8]

Adiponectin, a major adipokine secreted by adipose tissue, plays an important role in the regulation of glucose and fat metabolism by enhancing insulin sensitivity and decreasing free fatty acid production.[9] It has antiatherogenic, antiinflammatory, and hypoglycemic properties.[10,11] High adiponectin levels are associated with reduced plasma glucose, reduced serum triglyceride levels, and decreased blood pressure.[10–12] Low adiponectin levels have been associated with insulin resistance,[13] metabolic syndrome,[14] and hypertension.[15] In humans, adiponectin circulates in high molecular weight (HMW) oligomer, middle molecular weight (MMW) hexamer, and low molecular weight (LMW) trimer forms.[16] Recently, HMW adiponectin has been demonstrated to have greater biological activity than either the LMW or MMW forms.[17–19]

Cross-sectional studies have recently shown that high adiponectin levels might be an independent predictor of renal disease progression in patients with chronic kidney disease (CKD).[20,21] Some prospective studies showed that a high adiponectin level was an independent predictor of renal disease progression.[22,23] Conversely, other studies have suggested that adiponectin might have nephroprotective effects.[24–26] In a cross-sectional analysis, Kawamoto et al[27] demonstrated that a higher serum HMW adiponectin level is associated with a reduced odds
ratio of mild renal dysfunction in Japanese adults. However, in the general healthy population, no prospective data for the association between serum adiponectin levels with renal function decline have yet appeared.

Here, given these conflicting published results and the lack of evidence for an association of serum adiponectin levels with renal function decline in the general population, we sought to prospectively analyze the relationship of total and HMW adiponectin levels with renal function decline, as measured by cystatin C, in community-dwelling elderly adults with estimated glomerular filtration rate (eGFR) $\geq 60 \text{mL/min/1.73 m}^2$.

2. Methods

2.1. Study design

This was a prospective observational study of community-dwelling elderly adults to evaluate changes in renal function and adiponectin levels with increasing age. All participants provided written informed consent to participate at their first visit and the study protocol was approved by the Ethics Committee of Nihon University School of Medicine in accordance with the Declaration of Helsinki. This study from 2004 to 2015 was conducted in Ogano-machi, a town of approximately 12,000 residents located in Saitama Prefecture in Japan. Volunteers were recruited using pamphlets disseminated throughout the city. In addition, postal mail was sent to invite participants in the study to undergo a 5-year follow-up examination. A total of 1034 residents had enrolled by 2015. Participating subjects underwent annual evaluations at the Ogano assembly hall in the morning, which included standardized questionnaires, anthropometric measurements, and physical function and laboratory tests, including the collection of blood samples.

Participants with $\geq 60 \text{mL/min/1.73 m}^2$ at baseline were included in the present study and if they were assessed 2 or more times (between 2004 and 2015). Participants with no blood sampling, motor dysfunction, mental disorder, or cognitive impairment at baseline or at the time of follow-up were excluded. Frozen sera stored at $-70^\circ \text{C}$ to $-80^\circ \text{C}$ taken at 2 different times from each subject were used to measure changes in serum total adiponectin, glycated albumin (GA), albumin, creatinine, and cystatin C. In cases where $>2$ samples were drawn, we used the sample with the longest period of time from baseline. Furthermore, to analyze the incidence of CKD, we selected subjects whose follow-up period was 5 years from the included subjects.

2.2. Data collection

As in our previous study,[28] participants were administered a standard questionnaire regarding past/current medical history and family history by trained interviewers, who assured the quality and accuracy of answers. Height and body weight measurements were conducted with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated using the formula weight (kg)/height (m$^2$). Waist circumference was defined as the smallest girth midway between the lowest rib and the iliac crest at the end of normal expiration. Blood pressure was measured twice from the right arm with a standard mercury sphygmomanometer after a 5-minute rest period in a seated position, and the mean of these 2 measurements was recorded as the blood pressure value.

2.3. Measurement of physical function

Physical function measurements included hand-grip strength, knee extension strength, and one-leg standing time. Participants were guided by trained instructors in how to perform the procedures before each examination. Hand-grip strength was measured in each hand with a dynamometer adjusted to fit the participant’s hand size, and the test was performed in the standing position. Knee extension strength was measured in 2 maximum knee extension efforts against a force sensor placed bilaterally while the participant was seated. For hand-grip strength and knee extension strength, the means of each recorded value were used for analysis. One-leg standing time was measured using a stopwatch once for each leg with eyes open, and the better time was used for analyses of one-leg standing time unless participants performed the test incorrectly.

2.4. Reagents and measurement of variable parameters

Non-fasting blood samples were drawn from all participants from the antecubital vein and laboratory parameters measured at the annual evaluations including serum HMW adiponectin, high-density lipoprotein (HDL) cholesterol levels, total cholesterol levels, and triglyceride levels. HMW adiponectin levels were determined by chemiluminescent enzyme immunoassay using a Lumipulse f analyzer (Fujirebio, Tokyo, Japan). The intraassay and interassay coefficients of variation were 5.2% to 6.9% and 2.8% to 4.5%, respectively. Direct measurement of HDL cholesterol was conducted at a central laboratory (SRL, Inc., Tokyo, Japan). In addition to the abovementioned measurement of parameters, in 2016 we thawed the baseline sera samples, which had been stored at $-70^\circ \text{C}$ to $-80^\circ \text{C}$ and measured additional parameters, including serum cystatin C, total adiponectin, creatinine, albumin, and GA levels at baseline, and compared them to the follow-up values. Serum cystatin C was measured with a colloidal gold particle-enhanced colorimetric immunoassay (Nescoauto GC Cystatin C, Alfresa Pharma, Osaka, Japan). The coefficient of variation for the cystatin C assay was $\leq 10\%$ during the testing period, and the analytical measurement range for cystatin C was 0.20 to 8.00 mg/L. Total adiponectin was measured with a latex turbidimetric immunoassay using a Human Adiponectin Latex Kit (LSI Medience Corporation, Tokyo, Japan). The coefficient of variation for total adiponectin was $\leq 10\%$ during the testing period, and the analytical measurement range for total adiponectin was 0.5 to 25 mg/L. Albumin was determined with a bromocresol purple dye-binding assay (PureAuto S ALB; Kainos, Tokyo, Japan). GA was measured using the LUCICA GA-L kit (Asahi Kasei Pharma Corporation, Tokyo, Japan). Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. eGFR estimated by cystatin C (eGFRcys) was calculated using the following equations: eGFRcys in male subjects = $104 \times \text{cystatin C}^{-1.098} \times 0.996^{\text{Age}} - 8$; eGFRcys in female subjects = $(104 \times \text{cystatin C}^{-1.019} \times 0.996^{\text{Age}} \times 0.929) - 8$[29]

2.5. Renal outcomes

Decline in renal function was evaluated as continuous and dichotomized variables. Annual eGFRcys decline was calculated by dividing the difference between the initial and follow-up eGFRcys values by the duration between the 2 measurements, and expressed in mL/min/1.73 m$^2$ /y. In a study conducted in the United States, “rapid” renal decline was defined as eGFR $\geq 3$ mL/min/1.73 m$^2$/y;[30] however, it has been reported that eGFR decline in the Japanese general population is slower than that in the United States ($-0.36$ vs $-0.75$ mL/min/1.73 m$^2$/y).[31] Accordingly, we defined rapid eGFR decline as $-2.5$ mL/min/1.73 m$^2$/y.[32,33]
“Incident CKD” was defined as the development of eGFRcys <60 mL/min/1.73 m² and a decline in eGFRcys of >1 mL/min/1.73 m²/yr at follow-up in persons without CKD at baseline.34,35

2.6. Statistical analysis

Statistical analysis was performed with SPSS version. 24 (SPSS, Inc., Chicago, IL). Continuous variables were expressed as median with interquartile range (25–75%) and the Mann–Whitney U test was used to compare the 2 groups. Comparisons for categorized variables were tested with the χ² test. The associations between variables were assessed by Spearman rank correlations. We used multivariable linear regression models to evaluate associations of baseline eGFRcys and annual eGFRcys decline with log transformed serum adiponectin levels. Multivariable logistic regression models were used to evaluate the effect of serum adiponectin level on rapid renal function decline and incident CKD. In multivariable linear regression for baseline eGFRcys, we adjusted for demographic characteristics (age and sex) and other important covariates (BMI, MAP, GA, total cholesterol, HDL cholesterol, antihypertensive medications, and antidiabetic medications). Multivariable linear regression for annual eGFRcys decline was additionally adjusted for baseline eGFRcys. Next, we conducted a nested case-control analysis to reveal the association of rapid eGFRcys decline and incident CKD with adiponectin levels. In multivariable logistic regression analysis for rapid eGFRcys decline and incident CKD, model 1 was additionally adjusted for age, sex, BMI, MAP, and eGFRcys, while model 2 was additionally adjusted for total cholesterol, HDL cholesterol, GA, antihypertensive medications, and antidiabetic medication. Sample size calculation using Cohen’s equation d = 0.45 (α = 0.05, β = 0.80) gave an estimated minimum sample sized for 2-tailed hypotheses of 79 per group (total 158). Because of their skewed distribution, total adiponectin level, HMW adiponectin level, MAP, HDL cholesterol, and GA were log-transformed in linear regression analysis.

3. Results

3.1. Baseline characteristics of participants categorized by eGFRcys decline

Among the pool of 1034 participants, 584 subjects were assessed 2 or more times (between 2004 and 2015). Among these participants, 312 subjects were excluded because of refusal to provide blood for sampling, motor dysfunction, mental disorder, or cognitive impairment at baseline or at the time of follow-up. In addition, 56 participants with <60 mL/min/1.73 m² at baseline were excluded from this analysis, resulting in 216 subjects being included and analyzed. The mean follow-up period was 4.7 years. Table 1 shows the value of each variable categorized by rapid and gradual eGFRcys decline. The median age was 72.2 (68.0–77.0) years and 73% were women. Median serum total adiponectin level was 12.0 (8.6–17.4) µg/mL, and median serum HMW adiponectin level was 7.1 (4.4–10.9) µg/mL at baseline. Baseline eGFRcys was significantly higher in the rapid eGFRcys decline group than in the gradual eGFR decline group (P < .001). In contrast, there was no significant difference in metabolic variables, including total adiponectin, HMW adiponectin, total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides between the 2 groups (P = .71, P = .81, P = .19, P = .39, P = .35, P = .14, respectively). Table 2 shows the correlations of age, BMI, eGFRcys, MAP, total adiponectin level, HMW adiponectin level, total cholesterol, HDL cholesterol, GA, hand-grip strength, knee extension strength, total one-leg standing time, and a history of stroke, coronary artery disease, diabetes, and smoking status.

Data are shown as median (25th and 75th percentiles).

DBP = diastolic blood pressure, eGFRcys = cystatin C-based estimated glomerular filtration rate, GA = glycated albumin, HDL cholesterol = high-density lipoprotein cholesterol, HMW adiponectin = high molecular weight adiponectin, LDL cholesterol = low-density lipoprotein cholesterol, MAP = mean arterial pressure, SBP = systolic blood pressure, TG = triglyceride.
Association of serum adiponectin levels with risk of rapid eGFRcys decline and incident CKD

Among the 216 participants, we selected 161 subjects whose follow-up period was 5 years to analyze the incident CKD. In our cohort, 80 of a total of 216 participants developed rapid declines in renal function, and 40 of 161 participants developed incident CKD. In multivariable logistic regression analysis, we did not observe any statistically significant interaction between rapid eGFRcys decline or incident CKD and serum adiponectin levels in model 1 (total adiponectin, \( \beta = -4.0, P = .25; \beta = -0.50, P = .46; \) HMW adiponectin, \( \beta = -2.7, P = .27; \beta = 0.11, P = .98, \) respectively).

3.3. Association of serum adiponectin levels with risk of rapid eGFRcys decline and incident CKD

The linear regression analyses for baseline eGFRcys and annual eGFRcys decline were performed to investigate the association with serum adiponectin levels (Table 3). Univariate analysis showed no significant association of serum adiponectin levels with baseline eGFRcys and annual eGFRcys decline (total adiponectin, \( \beta = -3.6, P = .31; \beta = -0.23, P = .71; \) HMW adiponectin, \( \beta = -4.7, P = .063; \beta = -0.057, P = .90, \) respectively). After multivariable adjustment, associations of total adiponectin level and HMW adiponectin level with eGFRcys and annual eGFRcys decline also remained nonsignificant (total adiponectin, \( \beta = -4.0, P = .25; \beta = -0.50, P = .46; \) HMW adiponectin, \( \beta = -2.7, P = .27; \beta = 0.11, P = .98, \) respectively).

### Table 3

Association of baseline eGFRcys and annual eGFRcys decline with adiponectin levels.

| Unadjusted | Adjusted |
|------------|----------|
|             | Coefficient | 95% CI       | P    | Coefficient | 95% CI       | P    |
| Baseline eGFRcys |            |              |      |            |              |      |
| Log total adiponectin | -3.6 | -10.5 to 3.4 | .31 | -4.0 | -11.9 to 2.9 | .25 |
| Log HMW adiponectin | -4.7 | -9.7 to 0.25 | .063 | -2.7 | -7.5 to 2.1 | .27 |
| Annual eGFRcys decline |          |              |      |            |              |      |
| Log total adiponectin | -0.23 | -1.5 to 1.0 | .71 | -0.50 | -1.8 to 0.8 | .46 |
| Log HMW adiponectin | 0.057 | -0.83 to 0.94 | .90 | 0.011 | -0.91 to 0.94 | .98 |

CI = confidence interval, eGFRcys = cystatin C-based estimated glomerular filtration rate, HMW adiponectin = high molecular weight adiponectin.
addition, one prospective study showed that a high total kidney function.

HMW adiponectin activation of the renin system, systemic oxidative stress, endothelial oxidative damage, and have revealed some possibilities. For example, hypoadiponecti- and/or antiin have been developed with the expectation that it will suppress function decline in elderly without CKD. Further, we also found that high adiponectin level might not be a prognostic factor for renal function decline through the mechanism of energy expenditure or adiponectin resistance, contrary to findings in previous studies.

A majority of reports have demonstrated that adiponectin itself has antiatherogenic, antiinflammatory, and antiinflammatory effects. An adiponectin receptor agonist, AdipoRon, has been developed with the expectation that it will suppress cardiovascular disease and cancer by way of its antiatherogenic and/or antiinflammatory properties. Although the mechanism of these effects is not completely understood, several studies have revealed some possibilities. For example, hypoadiponecti- nemia may cause insulin resistance. Insulin resistance increases systemic oxidative stress, endothelial oxidative damage, and activation of the renin–angiotensin–aldosterone system. Moreover, adiponectin also has been shown to exert a vascular protective effect by its potentiation of endothelial nitric oxide synthase (eNOS) activity and NO production.

Contrary to these findings, populations with different conditions showed a negative effect of adiponectin. A recent investigation of patients with type 2 diabetes found that increased concentrations of adiponectin were independent predictors of all cause mortality. In addition, this relationship between high adiponectin levels and increased mortality risk has been repeatedly showed in several clinical sets including general population, cardiovascular disease, and reduced kidney function. This paradoxical association of adiponectin values has also been observed in patients with CKD.

Negative effects were also observed in the association between physical performance and serum adiponectin levels. Huang et al demonstrated that high adiponectin levels predicted decreased muscle strength among Japanese adults aged 70 years or older, which is similar to the results of this study, showing an inverse relation between both forms of adiponectin, and hand-grip and knee extension.

The negative aspects of high adiponectin levels on renal function in these previous studies may be explained by several mechanisms. For example, it has been shown that adiponectin increases energy expenditure, which might be not beneficial for patients with chronic heart failure or CKD. A second hypothesis is that the presence of CKD may cause dysfunction of adiponectin or its receptor, with a paradoxical increase in adiponectin secretion. Given this, we excluded the influence of renal function impairment on adiponectin by including only participants with eGFR ≥ 60 mL/min/1.73 m². This improved the credibility of our results, and we could also explain why our results differ from those of other authors.

Contrary to the findings in CKD patients, the negative association between renal function and adiponectin level in our study might be explained by the pathophysiological differences of renal function decline in baseline renal function or existence of chronic inflammation. A previous study reported that individuals with a propensity toward baseline GFR, especially >80 mL/min/1.73 m², display a greater rate of annual reduction in GFR than those with normal GFR, and this trend was getting stronger with age. Similarly, we demonstrated that the baseline eGFRcys was higher in subjects belonging to the rapid eGFRcys decline group in the elderly population. These results suggest that, with age, annual renal function decline in subjects with normal to high GFR grows increasingly more dependent upon baseline GFR than other factors, such as adiponectin.

Most of the participants of this study were healthy without any underlying health conditions. The protective effect of adiponectin might be more prominent under chronic inflammatory conditions, such as diabetes mellitus, albuminuria, or decreased renal function, than in the normal state. Consistent with this postulation, it was demonstrated that increased adiponectin expression in state of albuminuria indicates a renoprotective effect. Kim et al have recently shown that AdipoRon ameliorates glomerular endothelial cell and podocyte injury induced by diabetes-induced oxidative stress and apoptosis by activating the intracellular Ca²⁺/iver kinase B1–AMP-activated protein kinase/peroxisome proliferative-activated receptor-α pathway.
4.1. Limitations
This study had several limitations. First, we could not fully evaluate gender differences. Kollerits et al.[23] showed a male-gender-specific association of adiponectin with progression of CKD. We analyzed the association of adiponectin with renal function decline in men and women separately and found that there was no statistically significant association with gender (data are not shown). However, a conclusive answer to this question would require a larger-scale study. Second, we did not record information regarding cholesterol-lowering medications taken by participants. Use of these medications may have confounded our findings. Finally, we did not measure urinary protein levels, and could not evaluate the role of adiponectin in proteinuria.

5. Conclusions
Our study suggests that adiponectin, regardless of its biological form, might not meaningfully protect renal function in elderly general population without moderate or severe CKD. Furthermore, high adiponectin levels might not be a prognostic factor for renal function decline through the mechanism of energy expenditure or adiponectin resistance. Our results and conclusions should not be extrapolated to subjects with other characteristics.

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