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High serum adiponectin levels predict incident falls among middle-aged and older adults: a prospective cohort study

Cong Huang[1], Haruki Momma[1], Kaijun Niu[2], Masahiko Chujo[3], Atsushi Otomo[3], Yufei Cui[1], Ryoichi Nagatomi[1]

[1]Division of Biomedical Engineering for Health and Welfare, Tohoku University Graduate School of Biomedical Engineering, Sendai, Japan
[2]Department of Epidemiology, School of Public Health, Tianjin Medical University, Tianjin, China
[3]Department of Medicine and Science in Sports and Exercise, Tohoku University Graduate School of Medicine, Sendai, Japan

Address correspondence to: R. Nagatomi. Tel/Fax: (+81) 22 717 8586. Email: nagatomi@med.tohoku.ac.jp

Abstract

Background and objective: adiponectin is an adipocyte-derived hormone with anti-obesity and anti-diabetic properties. However, higher circulating adiponectin levels are related to poor muscle function and physical disability, which suggests a potential link between adiponectin and risk of falls. Nevertheless, no direct association between circulating adiponectin levels and incident fall risk has been reported. Therefore, this study aimed to investigate the relationship between serum adiponectin levels and incident falls in a population of middle-aged and older adults.
Design: a prospective cohort study.
Setting: Oroshisho Center in Sendai City, Japan.
Subjects: Japanese adults who were ≥45 years old (n = 430).
Measurements: serum adiponectin levels were measured at baseline, and the subjects were divided into sex-specific tertiles. Data regarding a history of falls were collected via participant recall using a self-reported questionnaire. Incident falls were defined as falls that were experienced by people without a history of falls at baseline.
Results: during the 2-year follow-up, 15.6% (67/430) of the subjects experienced an incident fall. In the univariate logistic regression analysis, incident falls were significantly more frequent across the increasing sex-specific serum adiponectin tertiles (P for trend = 0.008). Adjusted odds ratios (95% confidence interval) for incident falls were 2.31 (1.07–4.98) in the middle tertile and 3.61 (1.63–7.99) in the highest tertile; this risk was significantly higher than that for the lowest adiponectin tertile (P for trend = 0.002).
Conclusions: the findings of this prospective cohort study indicate that higher serum adiponectin levels may be a predictor of incident falls.

Keywords: *adiponectin, fall risk, biomarker, prevention, geriatrics*

Introduction

Adiponectin is an adipocyte-derived hormone that is considered beneficial to human health, due to its positive effect on metabolic syndrome and type II diabetes [1]. Studies have demonstrated that adiponectin may protect against these metabolic diseases via its effect on fatty acid utilisation and promoting insulin sensitivity [2]. However, in middle-aged and older adults, circulating adiponectin levels increase with age, and these increased levels have been proposed as an indicator for the incidence of cardiovascular disease [3, 4] and mortality [3–5]. The potentially paradoxical role of adiponectin in physical function has also been reported in a previous prospective study, which found that higher circulating adiponectin levels contributed to the increased incidence of physical disability among the elderly subjects [5]. Moreover, growing amounts of evidence from population-based cross-sectional studies reveal that circulating adiponectin levels are associated with several factors that indicate a poor health status, such as decreased muscle strength [6], low bone mineral density [7] and poor nutrition status [5]. As all of these factors are strong determinants of falls [8–10], it is possible that there is a correlation between circulating adiponectin levels and the risk of falling. However, no study has examined whether adiponectin levels accurately predict incident falls.

In Japan, the fall rate for people who are ≥65 years old is 12.8% for men and 21.5% for women [11]. As a geriatric syndrome, falls occur in one-third of community-dwelling older adults aged 72 years and older in America [12], and these falls are responsible for ∼70% of all unintentional injuries that are observed in this population [13, 14]. Moreover, fall-induced injuries are one of the common causes of disability [15] and mortality [16], and contribute to ∼5% of the total healthcare and long-term care costs in Japan [17]. As in the older population, falls among middle-aged adults are also an important source of fatal and non-fatal injuries [18]. Therefore, falls in both middle-aged and older people have become a serious public health problem.

Although these epidemiological observations suggest a possible correlation between circulating adiponectin levels and incident falls among older people, no previous studies have examined this topic. Therefore, this prospective cohort study aimed to investigate the relationship between circulating adiponectin levels and the risk of incident falls in a population of middle-aged and older adults.

Methods

Study participants

The data for the present study were obtained during the Oroshisho Study, which was a prospective cohort study of the lifestyle-related effects on illnesses and health status among Japanese adult employees who were working at the Sendai Oroshisho Center (Sendai, Japan), which is a group composed of >120 small and medium enterprises, between 2008 and 2011. In the present study, a 2-year prospective cohort study was designed to evaluate data from 2009 to 2011, as data from this period included information regarding falls. In 2009, 1,263 participants received an annual health examination, which was performed during the second week of August. Among these participants, 1,215 employees provided their informed consent for the analyses that were planned for this study. Based on the higher prevalence of fall-related injuries among middle-aged and older people [13, 18], only participants who were ≥45 years old were included in the current study, which yielded a sample of 642 subjects. The exclusion criteria included missing data regarding baseline serum adiponectin ($n = 1$) or covariates ($n = 33$), a history of falls at baseline ($n = 78$) and missing data regarding incident falls at 2-year follow-up ($n = 100$). Based on these exclusions, 430 adults who were ≥45 years old (349 men) met the inclusion criteria for this study. Approval for the study was obtained from the institutional review board of Tohoku University Graduate School of Medicine.

Serum adiponectin measurements

Serum adiponectin levels were assessed under overnight fasting conditions using a specific sandwich enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan). The lower limit of detection for this assay was 23.4 ng/l, the detection range was 0.375–12.0 ng/ml and the intra- and inter-assay coefficients of variation were <10%. Adiponectin levels were divided into sex-specific tertiles, based on their distribution in the statistical analysis.

Measuring the incidence of falls

The self-reported experience of falls was measured at baseline (2009) and at the follow-up (2010–11) by asking 'Did you have any falls in the previous year?'. The answers to this question consisted of yes or no, and participants were questioned regarding the number of falls they experienced. In this study, incident fall was defined as any fall that was experienced during 2010–11.

Relevant covariates

Sociodemographic data (sex, age, occupation, educational levels and marital status), smoking status and drinking frequency were collected using a self-administered survey. Estimated daily intakes of energy and protein during the preceding month were calculated using an *ad hoc* computer program and data from the brief self-administered dietary history questionnaire, which contains questions regarding the frequency at which 75 principal foods are consumed [19]. Physical activity (PA) was assessed using the International Physical Activity Questionnaire [20]. Moderate PA was defined as ≥23 metabolic equivalent (MET) hours per week, which is the reference quantity for exercise, PA and fitness levels to prevent lifestyle-related diseases, as recommended by the Japanese Ministry of Health, Labour, and Welfare [21]. Anthropometric factors (height and body weight) were recorded, and the subject's body mass index (BMI) was calculated as weight (kg)/height^2 (m^2).

Several health-related variables were also examined. Using a quantitative ultrasound device (AOS-100; Aloka Co, Tokyo, Japan), the osteo-sono assessment index (OSI) of the right calcaneus was measured as an indicator of bone mineral density [22]. OSI was calculated using the equation: $OSI = TI \times SOS^2$, where TI is the transmission index and SOS is the speed of sound. As an inflammatory marker, serum high-sensitivity C-reactive protein (hs-CRP) levels were measured using the N-latex CRP-2 assay (Siemens Healthcare Japan, Tokyo, Japan). Depressive symptoms were assessed using the Japanese version of the self-rated depression scale (SDS) [23]. Participants with a total SDS score of ≥45 were considered to have depressive symptoms [24]. Metabolic syndrome was defined based on the

American Heart Association Scientific Statement criteria for individuals of Asian ethnicity (including Japanese people) [25]. Regarding the components of metabolic syndrome, waist circumference was measured according to a standardised protocol, and sitting blood pressure was measured at rest, using the upper right arm and an automatic device (Yamasu 605P; Kenzmedico, Saitama, Japan). Enzymatic methods were used with the appropriate kits to determine serum levels of fasting glucose (Eurotec, Tokyo, Japan), triglycerides and high-density lipoprotein-cholesterol (Sekisui Medical, Tokyo, Japan).

Statistical analysis

All continuous variables in this study were log-transformed prior to statistical analysis because of their skewed distribution, and then re-transformed for data presentation. Participants' characteristics according to the sex-specific serum adiponectin tertiles were analysed using analysis of variance for continuous variables and the χ^2 test for categorical variables. Data were expressed as means or estimated geometric means (95% confidence interval, CI) or percentages, as appropriate.

To determine the relationship between baseline adiponectin levels and incident falls during the follow-up period, logistic regression analysis was used to calculate the odds ratio (95% CI) for incident falls in each adiponectin tertile, using the lowest adiponectin tertile as the reference group. Multivariate analyses were divided into three statistical models, with Model 1 being adjusted for BMI and the sociodemographic variables, which included sex, age, occupation (desk work or not), educational level (≥college or not) and marital status (married or not). In addition to the covariates in Model 1, Model 2 included lifestyle-related variables, such as smoking status (never, former, current), drinking frequency (never, sometimes, every day), daily energy and protein intake, and PA (≥23 MET h/week). In addition to the covariates in Model 2, Model 3 included health status variables (OSI, hs-CRP, depressive symptoms and metabolic syndrome). An age-stratified analysis of the association between adiponectin and falls risk was also performed. In addition, cross-product terms were created to examine the interactions between serum adiponectin levels and each covariate for incident falls, and these were added to the regression model. All tests were two-tailed, and *P* values of <0.05 were considered statistically significant. All analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA).

Results

Participants' characteristics

The mean age (SD) for the study sample was 54.9 (6.3) years (range, 45–83 years), and the proportion of subjects who were ≥55 years old (pre-elderly and older) was 52.1%. In this study, 81.2% of the subjects (349/430) were men. Similar characteristics were observed when we compared the subjects who

Table 1. Baseline participants' characteristics according to sex-specific serum adiponectin tertiles

Variables	Sex-specific serum adiponectin tertiles			*P* value*
	145 (28 women)	143 (26 women)	142 (27 women)	
Adiponectin range, mg/l	Men: 1.0–5.2 Women: 2.5–9.0	Men: 5.3–7.8 Women: 9.1–12.5	Men: 7.9–27.6 Women: 12.6–24.4	
Age, years[a]	54.2 (53.1–55.1)	53.6 (52.7–54.7)	55.8 (54.8–56.9)	**0.03**
BMI, kg/m^{2}[a]	24.4 (23.9–24.9)	22.7 (22.2–23.2)	22.2 (21.7–22.7)	**<0.001**
Education (≥college), %	29.7	29.4	26.1	0.76
Occupation (desk work), %	85.5	82.5	78.2	0.26
Marital status (married), %	82.1	86.0	83.8	0.66
Smoking status				
Current, %	41.4	47.6	34.5	
Former, %	13.1	9.8	11.3	
Never, %	45.5	42.7	54.2	0.25
Drinking frequency				
Every day, %	34.5	37.1	40.8	
Sometimes, %	40.7	42.7	38.7	
Never, %	24.8	20.3	20.4	0.88
Energy intake, kcal/day[a]	1,876 (1,776–1,980)	1,806 (1,710–1,908)	1,797 (1,701–1,899)	0.28
Protein intake, g/day[a]	64.0 (60.0–68.4)	61.7 (57.8–66.0)	62.7 (58.7–67.0)	0.67
PA ≥23 MET h/week, %	35.2	39.2	43.7	0.34
High-sensitivity CRP, mg/l[a]	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.3 (0.2–0.3)	**<0.001**
OSI, arbitrary units[a]	2.7 (2.6–2.7)	2.6 (2.6–2.7)	2.6 (2.6–2.7)	0.06
Metabolic syndrome, %	49.0	25.2	16.2	**<0.001**
Depressive symptoms, %	39.3	33.6	33.1	0.47

The significance of bold values were defined as a *P* value <0.05.

Data are presented as mean (95% confidence interval), percentage or range.

BMI, body mass index; CRP, C-reactive protein; MET, metabolic equivalent; PA, physical activity; OSI, osteo-sono assessment index.

[a]Variables were log-transformed due to a skewed distribution.

*Differences were evaluated using ANOVA and the χ^2 test, as appropriate.

did and did not complete the follow-up (Supplementary data, Table S1, available in *Age and Ageing* online). A significant sex-related difference was observed in the adiponectin levels, with women having higher levels than men. Table 1 shows the participants' baseline characteristics according to the sex-specific adiponectin tertiles. Mean age increased significantly with the increasing adiponectin tertiles ($P < 0.05$). In contrast, adiponectin levels were inversely associated with BMI, hs-CRP and the prevalence of metabolic syndrome ($P < 0.001$). In addition, participants with higher adiponectin levels tended to have lower OSI, although the difference was not significant ($P = 0.06$). The sex-specific adiponectin tertiles were not correlated with the other variables at baseline. During the 2-year follow-up, 15.6% of the subjects (67/430) experienced at least one incident fall.

Table 2. Multivariate logistic regression analysis of the association between baseline sex-specific serum adiponectin tertiles and the incidence of falls at follow-up

	Odds ratio (95% confidence interval) for incident falls		
	Model 1[a]	Model 2[b]	Model 3[c]
Sex-specific serum adiponectin tertiles			
Tertile 1 (Reference)	1	1	1
Tertile 2	2.14 (1.01–4.52)*	2.17 (1.02–4.61)*	2.31 (1.07–4.98)*
Tertile 3	3.10 (1.47–6.53)†	3.36 (1.57–7.18)†	3.61 (1.63–7.99)†
P for trend	**0.003**	**0.002**	**0.002**

The significance of bold values were defined as a *P* value <0.05.
[a]Adjusted for, sex, log age, occupation (desk work), marital status (married), education level (≥college) and log body mass index.
[b]Adjusted for smoking status (current, former, never), drinking frequency (every day, sometimes, never), log daily energy intake, log daily protein intake, physical activity (≥23 metabolic equivalent h/week) and the variables in Model 1.
[c]Adjusted for log osteo-sono assessment index, log high-sensitivity C-reactive protein, depressive symptoms, metabolic syndrome and the variables in Model 2.
*$P < 0.05$.
†$P < 0.01$.

Serum adiponectin levels and the incidence of falls

Univariate logistic regression analysis (Supplementary data, Figure S1, available in *Age and Ageing* online) revealed a graded relationship between adiponectin levels and the risk of falls (odds ratio [95% CI]: Tertile 2, 1.79 [0.88–3.64]; Tertile 3, 2.51 [1.27–4.96], *P* for trend = 0.008). Multivariate analysis confirmed that this linear trend was detected in all three covariates-adjusted models (*P* for trend <0.01) (Table 2). In the fully adjusted model (Model 3), the risk of incident falls in the second and third adiponectin tertiles were 2.3-fold and 3.6-fold higher, respectively, than that in the first tertile (odds ratio [95% CI]: Tertile 2, 2.31 [1.07–4.98], $P < 0.05$; Tertile 3, 3.61 [1.63–7.99], $P < 0.01$). No significant interactions between adiponectin levels and the other covariates for incident falls were observed (data not shown). Moreover, an age-stratified analysis revealed that higher

Table 3. Age-stratified analysis of the association between baseline sex-specific serum adiponectin tertiles and the incidence of falls at follow-up

	Odds ratio (95% confidence interval) for incident falls		
	Model 1[a]	Model 2[b]	Model 3[c]
Younger middle-aged adults (45–54 years old)			
Sex-specific serum adiponectin tertiles ($n = 206$)			
No. of participants	70 (15 women)	69 (15 women)	67 (13 women)
Tertile 1 (Reference)[d]	1	1	1
Tertile 2	1.38 (0.48–3.93)	1.32 (0.45–3.90)	1.05 (0.34–3.25)
Tertile 3	2.98 (1.06–8.38)*	3.12 (1.06–9.14)*	2.53 (0.81–7.88)
P for trend	**0.032**	**0.030**	0.079
Pre-elderly and older (≥55 years old)			
Sex-specific serum adiponectin tertiles ($n = 224$)			
No. of participants	75 (13 women)	75 (13 women)	74 (12 women)
Tertile 1 (Reference)[e]	1	1	1
Tertile 2	2.81 (0.95–8.35)	3.08 (0.99–9.54)	3.68 (1.13–12.0)*
Tertile 3	3.20 (1.10–9.34)*	3.38 (1.11–10.3)*	5.27 (1.54–18.0)†
P for trend	**0.037**	**0.036**	**0.008**

The significance of bold values were defined as a *P* value <0.05.
[a]Adjusted for sex, log age, occupation (desk work), marital status (married), education level (≥college) and log body mass index.
[b]Adjusted for smoking status (current, former, never), drinking frequency (every day, sometimes, never), log daily energy intake, log daily protein intake, physical activity (≥23 metabolic equivalent h/week) and the variables in Model 1.
[c]Adjusted for log osteo-sono assessment index, log high-sensitivity C-reactive protein, depressive symptoms, metabolic syndrome and the variables in Model 2.
[d]Adiponectin range (mg/l) in younger middle-aged men (Tertile 1: 1.0–5.0, Tertile 2: 5.1–7.0, Tertile 3: 7.1–20.9) and women (Tertile 1: 2.5–6.9, Tertile 2: 7.0–12.3, Tertile 3: 12.4–24.3).
[e]Adiponectin range (mg/l) in pre-elderly and older men (Tertile 1: 1.1–5.3, Tertile 2: 5.4–8.1, Tertile 3: 8.2–27.6) and women (Tertile 1: 3.7–9.0, Tertile 2: 9.1–12.5, Tertile 3: 12.6–24.4).
*$P < 0.05$.
†$P < 0.01$.

adiponectin levels were significantly associated with increased risk of incident falls in pre-elderly and older people (≥55 years old) (odds ratio [95% CI]: Tertile 2, 3.68 [1.13–12.0]; Tertile 3, 5.27 [1.54–18.0], *P* for trend = 0.008) (Table 3).

Discussion

In this prospective study of adults who were ≥45 years old, subjects with higher levels of serum adiponectin tended to have a higher incidence of falls, compare with subjects with lower levels of circulating adiponectin. To our knowledge, the present study is the first to investigate the relationship between circulating adiponectin levels and the risk of falling, and our findings indicate that adiponectin levels were associated with the incidence of falls.

Despite there being no direct evidence in the literature for comparison, the findings of a few previous studies may partially support our observed association between adiponectin and incident falls. For example, one prospective study noted that higher serum adiponectin levels predicted incident physical disability, which was defined as experiencing difficulty in the activities of daily living and impaired mobility [5]. Most recently, our cross-sectional study of Japanese elderly found that high serum adiponectin levels were independently associated with decreased lower extremity muscle strength [6]. Loncar *et al.* [26] have also reported an inverse association between circulating adiponectin levels and muscle strength or muscle mass in 73 elderly patients with chronic heart failure. Thus, the contribution of adiponectin to incident falls in this study appears to extend the findings of these previous studies, as it is well known that the most common risk factor for falls is muscle weakness [20].

To examine the potential mechanisms underlying the relationship between adiponectin levels and incident falls, we added various PA and health status factors to our regression model, which included nutrition status (BMI, and daily energy and protein intakes), depressive symptoms, OSI, hs-CRP and metabolic syndrome. However, adjusting for these covariates did not change our findings, which suggests that these factors did not account for the relationship between adiponectin levels and incident falls. Alternatively, elderly people with low muscle strength or muscle mass have an increased risk of falls [8, 27], as declines in lower extremity muscle strength can result in loss of balance [28], and this factor may partially explain our findings. Thus, muscle weakness could be considered an essential confounding factor when performing further studies regarding the association between adiponectin levels and the incidence of falls.

One strength of the present study is the use of a prospective study design, which allowed us to assess the predictive value of adiponectin levels. Another strength is that our analysis was limited to subjects who did not have a history of falls at baseline. This is very important for evaluating the risk of incident falls, as a history of falls is a strong predictor of recurrent falls [29]. However, several limitations of the present study should also be considered. First, interpretations of our observations are limited by the lack of assessment regarding any potential mechanism(s), which include lower extremity skeletal mass and muscle strength. Further, falls assessment was performed using a self-reported questionnaire, which is subject to recall bias. In addition, detailed information regarding the date, location and cause of the falls could not be recorded. Finally, interpretation of the sex-stratified analysis in this study is complicated by the relatively small number of female subjects.

In conclusion, this population-based study is the first to provide evidence regarding the relationship between adiponectin levels and the risk of falls. At the 2-year follow-up, higher baseline serum adiponectin levels predicted a greater incidence of falls in a population of predominantly middle-aged and pre-elderly individuals. These findings suggest that adiponectin may be a useful biomarker for the incidence of falls. In the scientific literature regarding the prevention of falls and fall-related injuries, there seems to be evidence that supports the effectiveness of preventive measure. It is noteworthy that more attention should be paid to the potential role of adiponectin in physical health. Further prospective studies with different populations and a longer follow-up period are needed to confirm the association between adiponectin levels and the risk of falls, and to assess the potential mechanisms underlying these observations.

Key points

- A 2-year incidence of falls was 12.5% in predominantly middle-aged and pre-elderly individuals.
- Subjects with higher circulating levels of adiponectin tended to have increased risk of falls.
- Nutrition status, bone health and mental disorders could not explain the association between adiponectin levels and falls risk.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of interest

None declared.

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