Research Paper

Association between Plasma Adiponectin Levels and Decline in Forced Expiratory Volume in 1 s in a General Japanese Population: The Takahata Study

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Abstract

Background: Adiponectin is an anti-inflammatory and cardio-protective cytokine. However, several studies have demonstrated that plasma adiponectin levels were inversely associated with pulmonary function in patients with chronic obstructive pulmonary disease, suggesting a proinflammatory or pulmonary-destructive role. It is still unclear whether adiponectin is a potent biomarker predicting declines in pulmonary function. The aim of this study was to investigate the association between adiponectin and pulmonary function among Japanese individuals who participated in an annual health check-up.

Methods: Spirometry and blood sampling, including measurements of plasma adiponectin, were performed for 3,253 subjects aged 40 years or older who participated in a community-based annual health check-up in Takahata, Japan from 2004 to 2006. In 2011, spirometry was re-performed, and the data from 872 subjects (405 men and 467 women) were available for a longitudinal analysis.

Results: Plasma adiponectin levels were found to be significantly associated with age, body mass index (BMI), and alanine aminotransferase (ALT), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-c) levels among both men and women in the study population. Plasma adiponectin levels were found to be associated with lifetime cigarette consumption (Brinkman index, BI) in men only. Plasma adiponectin levels were inversely correlated with forced expiratory volume in 1 s (FEV_1) per forced vital capacity in both men and women. In addition, the annual change in FEV_1 was inversely associated with plasma adiponectin levels in both genders. A multiple linear regression analysis revealed that this association was independent of other confounding factors such as age, BMI, BI, ALT, TG, and HDL-c.

Conclusions: The results of the present study suggest that adiponectin levels are predictive of declines in FEV_1 in the general population.

Key words: Adiponectin; Decline in FEV_1; General population; Pulmonary function; Spirometry.

Introduction

Long-term cigarette smoking induces many pulmonary diseases. Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory disorders in the elderly population [1]. Given the tremendous impact of COPD on death and chronic disability, the prevention of COPD is particularly

important. COPD is thought to involve chronic inflammation not only in the respiratory system, but also in the rest of the body resulting from the spread of inflammatory mediators from the lungs [2].

Metabolic syndrome is a predominant comorbidity of COPD [3-7]. Adipocytokines, including adiponectin, play a significant role in the pathogenesis of metabolic syndrome [8], and were noted as factors contributing to COPD. Tomoda et al. demonstrated an increase in plasma adiponectin levels in underweight COPD patients [9]. Recently, it was demonstrated that higher adiponectin levels were associated with a higher risk of all-cause mortality in COPD patients [10]. In addition, the Lung Health Study analysis demonstrated that adiponectin is a complex biomarker in COPD that is associated with a decreased risk of cardiovascular events, but an increased risk of respiratory mortality [11]. These results suggest that adiponectin plays a proinflammatory or pulmonary-destructive role in the pathogenesis of COPD.

However, studies using adiponectin gene-targeted mice have yielded controversial results. Two studies reported that adiponectin-null mice developed a COPD-like phenotype [12, 13]. In contrast, others have demonstrated that adiponectin knockout mice were protected from the development of emphysema induced by long-term exposure to cigarette smoke [14]. These contrasting results from animal studies complicate the interpretation of the role of adiponectin. Thus, whether adiponectin plays a pulmonary-protective or pulmonary-destructive role in the pathogenesis of COPD remains unclear.

To date, the relationship between plasma adiponectin levels and pulmonary function has not been demonstrated in a general population. This study aimed to investigate this relationship in order to determine the role of adiponectin in the lungs.

Methods

Study population

This study formed part of the Molecular Epidemiological Study of the Regional Characteristics of the 21st Century Centers of Excellence (COE) Program and the Global Centers of Excellence Program in Japan [3, 15-22]. The study was approved by the Ethics Committee of Yamagata University School of Medicine, and all participants provided their written informed consent.

The study used data from an annual community health check-up in which all residents of Takahata, a town in northern Japan, aged 40 years or older were invited to participate. From 2004 to 2006, 1,579 men and 1,941 women (total, 3,520 subjects) enrolled in the study and underwent initial spirometric examina-

tions. We excluded 267 subjects from the analysis because their spirometry data did not meet the specified criteria. The data from 3,253 subjects (1,500 men and 1,753 women) were utilized in the final statistical analysis. The subjects' medical histories, smoking habits, current use of medications, and clinical symptoms were documented using a self-reported questionnaire. The lifetime consumption of cigarettes was expressed as the Brinkman index (BI: number of cigarettes per day × years of smoking) [3, 19]. In 2011, spirometry was re-performed on 873 subjects. After the exclusion of 1 subject resulting from an error in spirometry measurements, the data from 872 subjects (405 men and 467 women) were used for a longitudinal analysis.

Measurements

Fasting blood samples were taken from the antecubital vein of the subjects, and immediately transferred to chilled tubes. Plasma adiponectin levels were measured by using an enzyme immunoassay (Otsuka Pharmaceutical Co., Tokyo, Japan) [23].

Spirometric parameters (FVC and FEV_1) were measured using standard techniques, with subjects performing FVC maneuvers on a CHESTAC-25 part II EX instrument (Chest Corp., Tokyo, Japan) according to the guidelines of the Japanese Respiratory Society (JRS) [24]. A bronchodilator was not administered prior to spirometry. The highest value of at least 3 FVC maneuvers by each subject was used for the analysis. The results were assessed by 2 pulmonary physicians, who visually inspected the flow-volume curves and excluded subjects with inadequate data as defined by the JRS criteria [24]. Subjects' pulmonary functions were classified as follows: normal, %FVC ≥ 80 and FEV_1/FVC ≥ 0.7; restrictive, %FVC < 80 and FEV_1/FVC ≥ 0.7; obstructive, %FVC ≥ 80 and FEV_1/FVC < 0.7; and mixed disorder, %FVC < 80 and FEV_1/FVC < 0.7. The annual change in FEV_1 (%/year) was calculated as ([value of 2011 spirometry – value of initial spirometry]/value of initial spirometry) × 100/ time between observations (years).

Statistical analyses

For continuous variables, data are presented as the mean and standard deviation (SD). For multiple comparisons, a 1-way analysis of variance was used along with Tukey's test. Correlations between 2 variables were evaluated using Pearson's product moment correlation coefficient. A multiple linear regression analysis was performed to determine whether plasma adiponectin levels contributed to annual changes in FEV_1 after adjustment for all other variables included in the model. Statistical significance was inferred for 2-sided *P*-values < 0.05. All statistical

analyses were performed using JMP version 8 software (SAS Institute Inc., Cary, NC, USA).

Results

The median (interquartile range) of plasma adiponectin levels was 7.1 µg/mL (5.2, 10.0) in men and 10.5 µg/mL (7.5, 15.0) in women. Table 1 shows the characteristics of the subjects according to their adiponectin level quartile. Age and high-density lipoprotein-cholesterol (HDL-c) increased in accordance with increased adiponectin level quartile in both men and women. In contrast, body mass index (BMI), alanine aminotransferase (ALT), triglycerides (TG), and FEV_1/FVC decreased with increasing adiponectin level quartile in both men and women. BI decreased with increases in adiponectin level only in men. FVC% predicted and FEV_1% predicted in both men and women and BI in women remained unchanged with increases in adiponectin levels.

Table 2 shows the mean plasma adiponectin levels according to the spirometric classifications (i.e., normal, restrictive, obstructive, and mixed ventilatory disorders). Plasma adiponectin levels in patients with obstructive disorders were significantly higher than those in normal subjects (Tables 2A and B). The plasma adiponectin levels in women with obstructive disorders were higher than in those with restrictive disorders (Table 2B).

Figure 1 shows the relationship between plasma adiponectin levels and FEV_1/FVC in men (Figure 1A) and women (Figure 1B). There was a significant inverse relationship between adiponectin levels and FEV_1/FVC in both men and women. Because the degree of airflow obstruction is usually evaluated by FEV_1, we evaluated whether adiponectin is predictive for airflow obstruction progression in a general population by assessing the relationship between plasma adiponectin levels and longitudinal changes in FEV_1. An inverse relationship was observed in both men and women (Figure 2). A multiple linear regression analysis revealed that adiponectin was a significant determinant of annual changes in FEV_1 in both men and women, and independent of other confounding factors such as age, BMI, BI, ALT, TG, and HDL-c (Table 3). Next, the relationships between adiponectin and annual changes in FEV_1 were assessed separately according to smoking status. As shown in Table 4, this relation was significant in men who had never smoked and in current smokers, but not in men who were ex-smokers. In women, this relation did not reach statistical significance for any smoking status, although there was a trend that higher adiponectin levels were associated with a greater decline in FEV_1 in women who had never smoked ($P = 0.0594$, women who never smoked, Table 4).

Table 1. Characteristics of the subjects according to adiponectin level quartile.

Men					
	Q1 (n = 390)	**Q2 (n = 390)**	**Q3 (n = 394)**	**Q4 (n = 398)**	*P*-value
Age, years	59.2 (9.9)	61.5 (9.9)*	62.9 (10.2)*	67.9 (9.8)*#¶	< 0.0001
BMI, kg/m²	24.5 (2.7)	23.9 (2.9)*	23.4 (2.8)*	22.1 (2.9)* #¶	< 0.0001
BI, cigarettes × years	485.7 (487.4)	467.8 (495.3)	433.5 (529.9)	369.9 (447.9)*	0.0158
ALT, U/L	30.3 (15.7)	27.6 (19.3)	24.1 (12.0)* #	21.3 (11.1)* #¶	< 0.0001
TG, mg/dL	151.8 (93.4)	126.4 (84.1)*	108.3 (69.2)* #	86.3 (51.0)* #¶	< 0.0001
HDL-c, mg/dL	50.4 (12.0)	53.8 (14.1)*	57.4 (14.0)* #	62.9 (14.8)* #¶	< 0.0001
%FVC	96.2 (12.9)	97.4 (14.1)	98.3 (15.0)	97.1 (17.1)	0.2494
%FEV_1	94.8 (15.7)	96.4 (15.8)	95.6 (17.7)	95.0 (20.2)	0.5937
FEV_1/FVC, %	77.7 (7.6)	77.9 (7.9)	76.4 (9.5)	76.1 (10.2) #	0.0081
Women					
	Q1 (n = 463)	**Q2 (n = 484)**	**Q3 (n = 476)**	**Q4 (n = 482)**	*P*-value
Age, years	60.1 (10.3)	61.1 (10.3)	63.2 (10.0)* #	64.4 (10.3)* #	< 0.0001
BMI, kg/m²	24.7 (3.3)	23.8 (3.3)*	23.4 (3.3)*	22.1 (3.2)*#¶	< 0.0001
BI, cigarettes × years	22.7 (99.9)	20.4 (112.9)	9.4 (54.5)	16.7 (90.3)	0.14
ALT, U/L	24.8 (14.8)	21.2 (11.7)*	20.5 (13.1)*	19.2 (10.3)*	< 0.0001
TG, mg/dL	115.7 (52.9)	105.7 (50.3)*	93.4 (39.6)* #	79.6 (34.4)* #¶	< 0.0001
HDL-c, mg/dL	55.8 (12.9)	58.9 (12.6)*	62.0 (13.7)* #	69.2 (14.5)* #¶	< 0.0001
%FVC	98.3 (13.9)	100.4 (13.2)	100.5 (14.5)	100.4 (15.5)	0.0686
%FEV_1	99.1 (14.9)	100.1 (14.9)	99.9 (15.3)	99.9 (16.6)	0.7634
FEV_1/FVC, %	81.0 (5.8)	79.9 (6.1)	79.4 (6.6)*	79.4 (7.4)*	0.0011

Men: Q1 [adiponectin (µg/mL) < 5.2]; Q2 [5.2 ≤ adiponectin (µg/mL) < 7.1]; Q3 [7.1 ≤ adiponectin (µg/mL) < 10.0]; Q4 [adiponectin (µg/mL) ≥ 10.0] .

Women: Q1 [adiponectin (µg/mL) < 7.5]; Q2 [7.5 ≤ adiponectin (µg/mL) < 10.5]; Q3 [10.5 ≤ adiponectin (µg/mL) < 15.0]; Q4 [adiponectin (µg/mL) ≥ 15.0].

*: $P < 0.05$ vs. Q1, #: $P < 0.05$ vs. Q2, ¶: $P < 0.05$ vs. Q3.

Values are expressed as the mean and standard deviation (SD). Differences among the quartiles were evaluated by a 1-way analysis of variance and Tukey's method.

BMI, body mass index; BI, Brinkman index; ALT, alanine aminotransferase; TG, triglycerides; HDL-c, high density lipoprotein-cholesterol; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

Table 2. Mean plasma adiponectin levels according to the type of spirometric disorder.

Men

	Normal (n = 1161)	Restrictive (n = 96)	Obstructive (n = 184)	Mixed (n = 55)	*P*-value
Adiponectin (µg/mL)	7.9 (4.5)	8.9 (5.3)	9.5 (5.0)*	8.6 (3.9)	< 0.0001

Women

	Normal (n = 1525)	Restrictive (n = 96)	Obstructive (n = 80)	Mixed (n = 18)	*P*-value
Adiponectin (µg/mL)	11.6 (5.8)	11.1 (6.1)	13.5 (6.0)*#	14.8 (7.5)	0.0025

Adiponectin concentrations were not available for 384 men and 410 women.

Values are expressed as the mean (SD). Differences between the groups were evaluated by a 1-way analysis of variance and Tukey's method.

*: $P < 0.05$ vs. the normal group, #: $P < 0.05$ vs. the restrictive group.

Table 3. Multiple linear regression analysis: correlations between variables and annual changes in FEV_1.

	Men		**Women**	
Explanatory variables	**β**	***P***	**β**	***P***
Age, years	-0.108	0.057	-0.063	0.194
BMI, kg/m²	0.000	0.994	-0.088	0.100
BI, cigarettes × years	-0.023	0.685	-0.050	0.289
ALT, U/L	-0.045	0.432	0.010	0.845
TG, mg/dL	0.032	0.605	0.006	0.910
HDL-c, mg/dL	-0.020	0.757	0.020	0.717
Adiponectin, µg/mL	-0.166	0.006	-0.120	0.020

Dependent variable: annual change in FEV_1 (%/year).

β, standard partial regression coefficient; BMI, body mass index; BI, Brinkman index; ALT, alanine aminotransferase; TG, triglycerides; HDL-c, high density lipoprotein-cholesterol.

Table 4. Univariate linear regression analysis: correlations between annual change in FEV_1 and plasma adiponectin levels according to gender and smoking status.

Gender	Smoking status from 2004–2006	n	β	*P*
Men	never	148	-0.28	0.0006
Men	current	106	-0.25	0.0087
Men	past	151	0.002	0.9713
Women	never	426	-0.09	0.0594
Women	current	21	-0.291	0.1998
Women	past	9	-0.28	0.4653

Explanatory variable: plasma adiponectin level (µg/mL).

Dependent variable: annual change in FEV_1 (%/year).

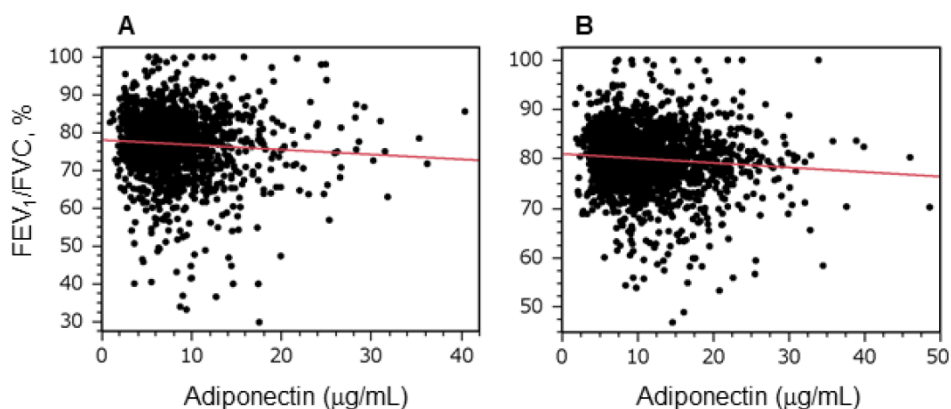β, standard partial regression coefficient.

Figure 1. Plasma adiponectin levels were inversely correlated with forced expiratory volume in 1 s per forced vital capacity. Graphs show the relationships between forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] and plasma adiponectin levels in men (A) and women (B). Correlations were evaluated using Pearson's product moment correlation coefficient. A statistically significant relationship was observed in both men and women (A, $r = -0.07$, $P = 0.01$; B, $r = -0.08$, $P = 0.001$).
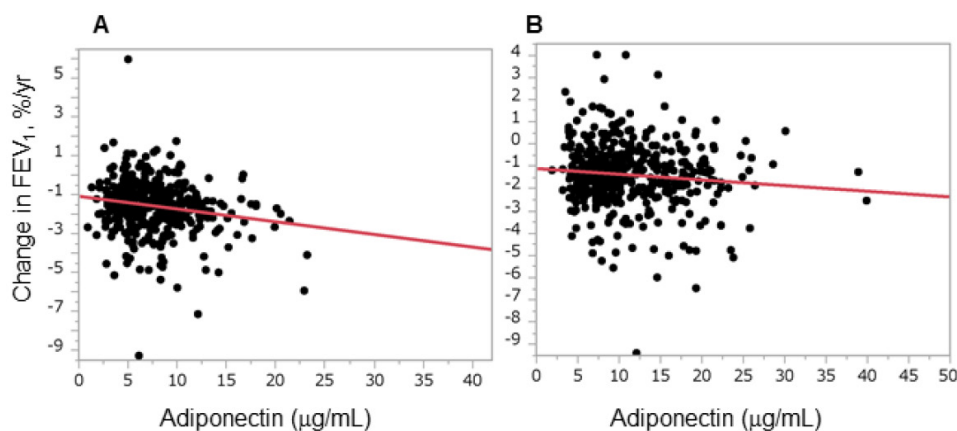
Figure 2. Plasma adiponectin levels were inversely correlated with annual changes in forced expiratory volume in 1 s. The graphs show the relationships between annual decline in forced expiratory volume in 1 s (FEV_1) and plasma adiponectin levels in men (A) and women (B). Correlations were evaluated using Pearson's product moment correlation coefficient. A statistically significant relationship was observed in both men and women (A, r = -0.17, P = 0.001; B, r = -0.10, P = 0.033).

Discussion

In the present study, we demonstrated an inverse correlation between plasma adiponectin levels and FEV_1/FVC in a general Japanese population (Figure 1). In addition, plasma adiponectin levels were inversely associated with annual changes in FEV_1 (Figure 2), even after adjusting for confounding factors such as age, BMI, BI, ALT, TG, and HDL-c (Table 3). This association was significant not only in men who were current smokers, but also in those who had never smoked (Table 4).

Adiponectin is an adipocytokine that is derived from adipocytes. Adiponectin inhibits the expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha [25]. Low levels of adiponectin have been reported to be related to high levels of C-reactive protein, a biomarker of inflammation, in patients with obesity, type 2 diabetes, or coronary artery disease [25]. In addition, adiponectin alters the phenotype of macrophages from pro-inflammatory macrophages (M1) to anti-inflammatory macrophages (M2) [26]. Therefore, there is accumulating evidence that suggests the role of adiponectin in anti-inflammatory, anti-atherosclerotic, and cardio-protective pathways [25].

To date, 3 institutes have reported on pulmonary phenotypes in adiponectin-deficient mice. Summer's and Nakanishi's groups demonstrated the development of emphysematous changes in adiponectin-deficient mice [12,13]. In null mice, alveolar macrophage activation and the secretion of matrix metalloproteinase-12, a macrophage-derived protease that promotes emphysema, were confirmed [13]. In addition, they observed emphysematous development in accordance with aging; further, the extra-pulmonary phenotypes were commonly observed in human COPD patients, such as weight loss, fat atrophy, and osteoporosis [12]. These results are in accordance with evidence that adiponectin has anti-inflammatory properties, and that the loss of adiponectin results in a reduced protective capacity against the development of emphysema. However, as many studies have shown, circulating adiponectin levels in patients with COPD were not reduced; in fact, they were increased [9, 27-29]. Even if adiponectin is anti-inflammatory and pulmonary-protective, the elevation of adiponectin levels is not enough to suppress the impairment of pulmonary function in COPD patients. In contrast, Miller et al. demonstrated that adiponectin deficiency protected mice from tobacco-induced inflammation and increased emphysema [14]. Thus, their new evidence showing the pro-inflammatory effects of adiponectin challenges the established theory regarding the anti-inflammatory role of adiponectin. They demonstrated that adiponectin deficiency suppressed the production of pro-inflammatory cytokines such as TNF-alpha and keratinocyte-derived chemokines in the lungs, which resulted in the protection of the lungs from cigarette smoke in adiponectin-null mice. Their study on adiponectin-deficient mice agrees with clinical evidence that shows an elevation of adiponectin in COPD patients.

Globular adiponectin is a proteolytic cleavage fragment consisting of the globular C-terminal domain of full-length adiponectin [30]. Proteases secreted from leukocytes are thought to cleave adiponectin to generate a globular fragment of adiponectin. In contrast to full-length adiponectin, it has been reported that globular adiponectin has the potential to induce inflammation [14, 31, 32]. In addition, the receptor for globular adiponectin is adiponectin receptor 1, and has been reported to be expressed in airway epithelial cells in COPD patients [33, 34]. Be-

cause the kit for adiponectin detection in the present study used 2 antibodies that recognize the collagenous domain of adiponectin, the measured adiponectin concentration demonstrated in the present study did not contain those in globular form. According to the instruction manual of another commercial enzyme-linked immunosorbent assay kit for human globular adiponectin (Alpha Diagnostic International, San Antonio TX, USA) [35], the mean serum level of globular adiponectin was 0.16 μg/mL (0.06–0.65 μg/mL). Although the concentrations of globular adiponectin of subjects in the present study are currently unknown, those in subjects with reduced FEV_1 values may be elevated by the proteolytic milieu in obstructive subjects [1], resulting in the promotion of airway inflammation linked to airflow obstruction. Further investigations are required regarding this point.

Previously, we demonstrated that hyperhomocysteinemia and lower serum iron levels were predictive of a rapid decline in FEV_1 in men who were continuing smokers using the Takahata Study database between 2004–2006 (Visit 1) and 2009 (Visit 2) (n = 147) [16, 19]. In 2011 (Visit 3), we re-performed the pulmonary function measurements for 873 participants in this study. Not only men who were current smokers, but also women and other subjects with smoking status were included in the analyses. During the follow-up period, many active smokers quit smoking. During Visit 1, the active smokers included 521 men (total male subjects, 1500) and 99 women (total female subjects, 1753) [17, 18]. Finally, during Visit 3, there were 50 men who were continuing smokers (total male subjects, 405) and 9 women (total female subjects, 467). Neither homocysteine nor serum iron levels were associated with changes in FEV_1 between Visit 1 and Visit 3, suggesting that these variables predict declines only in continuing smokers (data not shown). In contrast, adiponectin predicted declines in FEV_1 for both genders and for any smoking status.

The present study has other limitations because it was not hospital-based. Further, the lack of the information regarding chest radiography findings, the final pulmonary disease diagnosis, and current medication use, which could affect adiponectin values, may be potential limitations. In addition, there is the possibility of a sampling bias among the subjects who participated in the present study, specifically resulting from the socioeconomic status of these patients.

In conclusion, we demonstrated an inverse relationship between plasma adiponectin levels and FEV_1/FVC in a healthy Japanese population. In addition, adiponectin levels were inversely associated with annual changes in FEV_1, even after the adjusting for possible confounding factors. In contrast to clinical evidence regarding the cardio-protective role of adiponectin, many studies demonstrated elevation of adiponectin in clinical COPD patients, suggesting pro-inflammatory and destructive roles in the lungs. The results of the present study were in accordance with previous clinical studies regarding adiponectin levels in COPD patients. Since adiponectin levels were significantly associated with annual declines in FEV_1, they predict declines in pulmonary function in the general population, both in smokers and in those who have never smoked.

Ethics committee approval

This study was approved by the Institutional Ethics Committee of Yamagata University and all participants gave written informed.

Conflicts of interest

The authors have declared that no competing interest exists.

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