The Association of Adiponectin with Computed Tomography Phenotypes in Chronic Obstructive Pulmonary Disease

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Rationale: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder associated with systemic manifestations that contribute to its morbidity and mortality. Recent work suggests that biomarker signatures in the blood may be useful in evaluating COPD phenotypes and may provide insight into the pathophysiology of systemic manifestations. Adiponectin, primarily produced by fat cells, has been implicated in the pathophysiology of emphysema.

Objectives: To investigate the association of adiponectin with clinical and radiologic COPD phenotypes.

Methods: Adiponectin levels were determined in 633 individuals, including 432 individuals with COPD from a cohort of former or current smokers enrolled in the COPD Gene study. Univariate and multiple regression analysis were used to examine the association of adiponectin with clinical and physiologic data together with quantitative high-resolution computed tomography parameters.

Measurements and Main Results: Multiple regression analysis confirmed that higher plasma adiponectin levels were independently associated with emphysema, decreasing body mass index, female sex, older age, and lower percentage change in prebronchodilator/post-bronchodilator FEV₁.

Conclusions: The association between plasma adiponectin and computed tomography-assessed emphysema suggests a contribution of adiponectin to the development of emphysema and highlights a role for metabolic derangements in the pathophysiology of emphysema.

Keywords: phenotypes; adiponectin; chronic obstructive pulmonary disease

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There are animal data and limited human data to suggest adiponectin is associated with phenotypes in chronic obstructive pulmonary disease (COPD), especially emphysema and low body mass index. Because adiponectin is an adipokine and part of the fat-lung axis, it has been implicated in the pathogenesis of COPD, but direct evidence is lacking regarding its role as a plasma phenotypic biomarker and its association with other parameters in COPD.

What This Study Adds to the Field

This study investigates the associations of plasma adiponectin with various clinical, physiologic, and radiologic parameters, including computed tomography-assessed emphysema, in a reasonably large cohort of current or former smokers with normal lung function and COPD. Some of the findings are consistent with previous studies including associations with lower body mass index, female sex, and older age, but in addition we associate adiponectin with radiologic-assessed emphysema independent of those parameters, adding further evidence to the role of adiponectin as a potential biomarker of COPD phenotypes.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality (1). It is a heterogeneous disease, generally characterized by different phenotypes, such as airflow limitation that is not fully reversible; chronic sputum production (chronic bronchitis); and loss of normal lung tissue (emphysema). COPD is also associated with systemic manifestations that result in comorbidities, such as weight loss, depression, osteoporosis, and cardiovascular disease, which greatly contribute to poor health outcomes (2, 3). The pathophysiology of these systemic

manifestations is unclear; however, recent work on peripheral blood biomarkers suggests that there may be biomarker signatures in blood that are associated with COPD phenotypes (4). Examples of candidate biomarkers include C-reactive protein, IL-6, tumor necrosis factor- α , leptin, and adiponectin (5, 6).

Adiponectin, a 30-kDa adipokine, is highly expressed in adipocytes and possesses antiinflammatory, antiatherosclerotic, and insulin-sensitizing properties (7, 8). Adiponectin is highly abundant in plasma and is a key cytokine in the metabolic syndrome (9). It is highly expressed in bronchoalveolar lavage (BAL) fluid and airway epithelial cells in subjects with COPD and emphysema compared with control subjects (10). Tobacco smoke exposure induces adiponectin protein in murine BAL fluid and adiponectin-deficient mice are protected against cigarette smoke-induced emphysema and inflammation (11). These studies suggest adiponectin is a biomarker of COPD that may also play an important role in the pathogenesis of smoking-related lung disease.

Despite compelling animal studies, there are limited data in humans supporting adiponectin as a good biomarker to distinguish between human COPD phenotypes. Elevation of plasma adiponectin has been found in patients with stable COPD and also during acute exacerbations of COPD (12). Increased plasma adiponectin has been demonstrated in underweight patients with COPD, and

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adiponectin levels inversely associate with body mass index (BMI), the degree of airflow limitation, and adverse cardiovascular outcomes (13, 14). Women generally have higher levels of adiponectin than men (15). The relationship between plasma adiponectin levels and smoking status is less clear and may be sex related, with some studies showing lower levels in women smokers only, while another demonstrated a rise in adiponectin levels on smoking cessation in both men and women (16–18). Adiponectin has been associated with a decreased risk of cardiovascular events but increased risk of respiratory mortality in individuals with mild to moderate COPD (19).

Although studies suggest a role for adiponectin in COPD, there are no data evaluating the association of adiponectin with radiologic parameters, such as airway wall thickness or extent of emphysema on chest computed tomography (CT). To investigate what role adiponectin might play in COPD phenotypes and its relationship to clinical and radiologic parameters, we measured plasma adiponectin levels in a cohort of former or current smokers with normal lung function and with COPD that were enrolled in the COPDGene study. We examined the association of plasma adiponectin levels with various clinical, physiologic, and radiologic parameters to determine if measuring adiponectin levels would enable clinicians to better phenotype patients with COPD. Some of the results of this study have been previously reported in the form of an abstract (20).

METHODS

Study Population

COPDGene is a multicenter study of the genetic epidemiology of COPD that enrolled 10,300 non-Hispanic white and African-American individuals, aged 45–80 years old with at least a 10 pack-year history of smoking, who had not had an exacerbation of COPD for at least the previous 30 days. Additional information on the COPDGene study and the collection of clinical data has been described previously (21). A total of 2,000 subjects had fresh frozen plasma collected using a p100 tube (BD, Franklin Lakes, NJ) at just two COPDGene sites. From this cohort, we measured plasma adiponectin levels in a subset of 633 individuals. Initially selection of the individuals was planned as a nested case-control study; however, because of limited plasma samples available and the fact that individuals with COPD tended to be older with greater smoking history, it was not possible to perfectly match subjects. Therefore, individuals were taken randomly based on enrollment at the two COPDGene sites to minimize variability. The institutional review boards of participating institutions approved the study.

COPDGene Definitions

COPD was defined by a post-bronchodilator ratio of FEV₁ to FVC of less than 70%. COPD was further subdivided using Global Initiative for Chronic Obstructive Lung Disease guidelines as mild (FEV₁ >80% predicted), moderate (FEV₁ >50–79% predicted), severe (FEV₁ 30–49% predicted), and very severe (FEV₁ <30% predicted) based on post-bronchodilator FEV₁ (1). Current or ex-smokers with normal lung function were considered control subjects.

Radiologic Definitions

Study patients underwent whole-lung volumetric multidetector CT as previously described (21). Quantitative analysis of lung density was performed using Slicer software package (www.slicer.org). Emphysema was defined as percent of lung attenuation less than 950 HU. Automated airway analysis including airway wall thickness and wall percentage area was performed using Vida Pulmonary workstation, v2.0 (Vida Diagnostics, Coralville, IA) as previously described (21, 22).

Assessment of Plasma Adiponectin Levels

Blood samples were drawn from nonfasting individuals between 10 AM and 2 PM. Approximately 8.5 ml of blood was withdrawn from the

antecubital vein into a sterile 13 × 1,000 mm P100 Blood Collection Tube (BD). The sample was immediately centrifuged at 2,500 × *g*, 20 minutes at room temperature. Aliquots in 500-μl tubes were stored at –80°C until analyzed. Total adiponectin levels were determined in plasma with no extra freeze-thaw cycles using a custom Triplex panel that also included serum amyloid protein and β₂ microglobulin biomarkers (Linco Research, St. Charles, MO) on a Luminex 200 analyzer (Luminex, Austin, TX). All samples were measured in duplicate and samples with a coefficient of variation greater than 10% were repeated and only included in the final analyses if the coefficient of variation was less than 10%.

Statistical Analysis

A Wilcoxon rank-sum test with continuity correction was used to evaluate the differences in adiponectin levels between the different study groups. A chi-square test was used to evaluate differences regarding categorical data and a Student *t* test was used to evaluate differences between the groups for continuous variables. For regression analysis, adiponectin was log transformed to improve the model fit, and univariate and multiple regressions were based on the log-transformed adiponectin levels. For univariate analysis, a list of included variables is available (*see* Table E1 in the online supplement). For multiple regression analysis, variables with a *P* value less than 0.25 were considered for inclusion in the model selection procedure to determine the final model (*see* Table E2). Using Akaike Information Criterion (a measure of the relative goodness of fit) and a combination of backward and forward selection, stepwise regression was used to arrive at the final model and a *P* value of less than 0.05 was taken as statistically significant (23). Statistical analyses were performed using R and SAS 9.2 statistical software packages (24).

RESULTS

Study Population

Demographics, physiology, health scores, quantitative CT measurements, and medication use by COPD severity are listed in Table 1. There were differences between control subjects and individuals with COPD with respect to age at enrollment and pack-year history of smoking (*P* < 0.001), with older age and higher pack-years in the total COPD group. A larger proportion of control subjects were also current smokers than those with established COPD (*P* < 0.01). With regard to sex, there were no statistically significant differences in sex distribution between the control group and COPD group (*P* > 0.05). There were differences in race distribution, with more whites than African-Americans in control and COPD groups (*P* < 0.01), but ratios were similar between both groups (*P* > 0.05). There was a difference in BMI between the groups with the lowest BMI in the COPD group (*P* < 0.01).

Adiponectin Levels

There was considerable variability in adiponectin levels across all groups and adiponectin levels were log transformed for analysis to improve the model fit (*see* Figure E1). Adiponectin levels were 1.2-fold higher in individuals with established COPD compared with control subjects with normal lung function (*P* = 0.046) (Figure 1). When comparing adiponectin levels in control subjects with subsets of COPD, adiponectin was 1.3-fold higher in individuals with very severe COPD compared with control subjects (*P* < 0.02), but there were no significant differences in adiponectin levels between the other groups (*P* > 0.05).

Univariate Analysis

The association of adiponectin with various parameters measured and recorded in the COPDGene study was examined by univariate analysis (Table 2, Figure 2; *see* Table E1). There was a significant

TABLE 1. DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF THE STUDY SUBJECTS

Variable	Total	Healthy Smokers (Control)	All COPD	Mild COPD (GOLD 1)	Moderate COPD (GOLD 2)	Severe COPD (GOLD 3)	Very Severe COPD (GOLD 4)	Healthy Smokers versus All COPD
N	633	201	432	48	161	144	79	—
Age, yr	64 ± 3	61 ± 1	66 ± 1	66 ± 1	66 ± 1	66 ± 1	65 ± 1	<0.001
Sex, M/F	347/286	107/94	240/192	28/20	84/77	89/55	39/40	>0.05
Race, W/AA	588/45	173/28	415/17	46/2	158/3	137/7	74/5	>0.05
% Current smoker	38	73	21	19	27	19	16	<0.01
Pack-years	49 ± 1	37 ± 2	55 ± 1	51 ± 4	55 ± 2	55 ± 2	56 ± 3	<0.001
BMI, kg/m ²	27.7 ± 0.2	28.8 ± 0.4	27.2 ± 0.3	26.6 ± 0.6	28.3 ± 0.5	26.9 ± 0.4	25.5 ± 0.7	<0.001
Adiponectin level, µg/ml	70.7 ± 2.9	63.3 ± 2.3	74.4 ± 3.1	83.8 ± 4.0	67.4 ± 3.0	75.7 ± 2.3	81.8 ± 4.3	0.046
Physiologic								
FEV ₁ , % predicted	65.6 ± 1.2	98.1 ± 0.8	50.4 ± 1.0	89.6 ± 1.6	62.7 ± 0.7	38.9 ± 0.5	22.8 ± 0.6	<0.001
FVC, % predicted	87.2 ± 0.8	96.5 ± 0.8	82.8 ± 1.0	107.3 ± 2.1	90.6 ± 1.3	78.2 ± 1.1	60.3 ± 1.5	<0.001
FEV ₁ /FVC, %	55.5 ± 0.1	77.9 ± 0.3	50.0 ± 0.1	62.8 ± 0.8	53.4 ± 0.7	38.3 ± 0.7	29.1 ± 0.7	<0.001
Walk distance, m	400.2 ± 6.4	502.3 ± 6.4	352.5 ± 7.9	498.5 ± 10.5	400.9 ± 11.5	337.3 ± 11.8	193.15 ± 16.0	<0.001
Health outcomes								
BODE Index	1.9 ± 0.08	0.3 ± 0.05	2.8 ± 0.1	0.5 ± 0.1	1.5 ± 0.1	3.9 ± 0.1	5.5 ± 0.1	<0.001
MRC dyspnea score	1.6 ± 0.1	0.6 ± 0.1	2.1 ± 0.1	0.9 ± 0.2	1.6 ± 0.1	2.4 ± 0.1	3.2 ± 0.1	<0.001
SF-36 Gen Health	59.7 ± 1.0	50.9 ± 0.7	53.4 ± 1.2	50.9 ± 1.5	46.5 ± 0.8	38.7 ± 0.8	34.2 ± 1.1	<0.001
SGRQ Total Score	29.8 ± 0.9	12.0 ± 1.0	38.1 ± 1.0	18.1 ± 2.4	31.3 ± 1.6	42.3 ± 1.5	56.2 ± 1.7	<0.001
High-resolution computed tomography measurements								
% Emphysema	13.7 ± 0.5	2.2 ± 0.2	18.3 ± 0.6	9.4 ± 0.9	11.6 ± 0.8	21.7 ± 1.0	27.2 ± 1.5	<0.001
% Gas Trapping	35.5 ± 0.9	10.4 ± 0.5	45.7 ± 0.9	21.7 ± 1.7	34.2 ± 1.3	53.0 ± 1.2	62.0 ± 1.5	<0.001
SRWA Pi10	3.7 ± 0.01	3.7 ± 0.01	3.8 ± 0.01	3.7 ± 0.01	3.8 ± 0.01	3.8 ± 0.01	3.8 ± 0.02	<0.001
SRWA Pi15	5.2 ± 0.01	5.0 ± 0.01	5.2 ± 0.01	5.1 ± 0.04	5.1 ± 0.01	5.3 ± 0.01	5.2 ± 0.04	<0.001
% Medication use								
LABA	3	0	5	2	4	8	4	—
ICS/LABA	33	1	48	10	33	60	78	—
ICS	7	1	10	4	13	10	10	—
Tiotropium	34	1	49	19	34	63	72	—
Theophylline	3	0	4	2	2	3	9	—

Definition of abbreviations: AA = African-American; BMI = body mass index; BODE = composite of BMI, FEV₁, dyspnea score, and walk distance; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β agonist; MRC = Medical Research Council; Pi10 = square root of airway wall area at internal perimeter 10 mm; Pi15 = square root of airway wall area at internal perimeter 15 mm; SF-36 = Short Form health survey; SGRQ = St. George Respiratory Questionnaire score; W = white.

Shown are arithmetic mean ± standard error except adiponectin, which is presented as geometric mean ± standard deviation.

association between increasing age at enrollment in the study and increasing levels of adiponectin (coefficient = 0.014; $P = 0.004$). Similarly, higher adiponectin levels were associated with female sex (coefficient = 0.344; $P < 0.001$). However, increasing adiponectin levels were associated with decreasing BMI (coefficient = -0.038 ; $P < 0.001$) in the study population.

There was no association between adiponectin levels and patient-reported history of having had an exacerbation of COPD in the 12 months before enrollment in the study, including a history of severe exacerbations requiring hospitalization, in this cohort. There was an association between adiponectin levels and active current smoking status in the current study on univariate analysis, with active smoking associated with lower adiponectin levels (coefficient = -0.247 ; $P = 0.013$).

There were associations between adiponectin levels and pulmonary function test parameters on univariate analysis with adiponectin levels being negatively correlated with post-bronchodilator FEV₁ ($P = 0.001$) and FVC ($P < 0.001$). Higher adiponectin levels were also associated with lower percentage change in FEV₁ post-bronchodilator ($P = 0.034$). Overall, higher adiponectin levels were associated with poorer lung function in this cohort.

There were several associations of adiponectin levels with radiologic parameters in this study. Increasing adiponectin levels were associated with increased emphysema present by radiologic assessment of the lungs. This association included increasing percentage emphysema in total lungs (coefficient = 0.01; $P = 0.002$), increasing percentage emphysema in upper third of lungs (coefficient = 0.006; $P = 0.013$) and in lower third of the lung (coefficient = 0.011; $P = 0.003$) as assessed by Slicer software.

Conversely, higher adiponectin levels were associated with lower bronchial wall area thickness as assessed by square root of wall area at an internal perimeter of 15 mm (coefficient = -0.684 ; $P < 0.004$).

Multivariable Regression Analysis Using Model Selection

Model selection using Akaike information criterion and a combination of backward and forward selection was performed using

Figure 1. Adiponectin levels in individuals with normal lung function and individuals with established chronic obstructive pulmonary disease (COPD). Box plot of adiponectin levels in individuals with COPD ($n = 432$) and control smokers with normal lung function ($n = 201$). Central box bars represent the median and end box bars represent the first and third quartiles. Error bars represent the standard error. $P < 0.046$.

TABLE 2. VARIABLES WITH A SIGNIFICANT ASSOCIATION WITH PLASMA ADIPONECTIN LEVELS IN UNIVARIATE ANALYSIS

Variable	Standardized Beta Coefficient	P Value
Age at enrollment	0.014	0.004
Sex (female)	0.344	<0.001
Body mass index	−0.038	<0.001
Wall area Pi15 SRWA	−0.684	0.004
Current smoking	−0.247	0.013
% Emphysema lower third lung	0.011	0.003
% Emphysema upper third lung	0.006	0.013
% Emphysema total lung	0.01	0.002
FEV ₁	−0.141	0.001
FVC	−0.168	<0.001
Prebronchodilator/post-bronchodilator FEV ₁ % change	−0.009	0.034

Definition of abbreviation: Pi15 = square root of airway wall area at internal perimeter 15 mm.

variables selected from the univariate analysis (Table 3; see Table E2). Because of collinearity between variables, only FEV₁ percent predicted and bronchodilator responsiveness were included in this multivariate model and not FEV₁/FVC ratio. Similarly, only percent emphysema in lower third was included and not other emphysema parameters because of collinearity. In the final model, there were positive associations between increasing adiponectin levels and increasing age at enrollment ($P = 0.015$), female sex ($P < 0.001$), and a negative association with the presence of bronchodilator responsiveness as assessed by percentage change in post-bronchodilator FEV₁ ($P = 0.036$) and BMI ($P = 0.003$). With regard to radiologic data, increasing adiponectin levels were significantly associated with increasing percentage emphysema in lower third of lungs ($P = 0.032$) on multiple regression analysis. Multiple regression analysis for serum amyloid protein and β_2 -microglobulin were associated with neither CT-assessed emphysema nor airflow limitation (see Tables E4 and E5).

To further probe the association between plasma adiponectin levels and radiologic emphysema, multiple regression analysis was repeated with percentage emphysema in lower third of lungs as the outcome and included interaction terms for adiponectin with current smoking status and female sex. This analysis demonstrated that CT-assessed emphysema in the lower third of lungs was positively associated with plasma adiponectin levels ($P = 0.023$) and age ($P = 0.01$) and negatively associated with active current smoking ($P < 0.001$), female sex, BMI ($P < 0.001$), and FEV₁/FVC ratio ($P < 0.001$). No significant interaction was identified between plasma adiponectin levels and female sex ($P = 0.18$) or adiponectin levels and current smoking ($P = 0.07$) (see Table E3).

DISCUSSION

Adiponectin is an antiinflammatory adipokine produced mainly in fat cells. There are increased levels of plasma adiponectin in individuals with COPD, especially individuals with very severe COPD, compared with individuals with normal lung function. In the COPDGene cohort, we found that plasma total adiponectin was associated with CT-assessed emphysema and less bronchodilator responsiveness even when adjusting for covariates, such as BMI, age, and sex.

Adiponectin, although a secreted protein of fat cells, is also expressed in airway epithelium and BAL fluid in the emphysematous form of COPD (10). It possesses antiinflammatory effects, and is involved in the regulation of insulin sensitivity (25). In the lung, adiponectin exerts an antiinflammatory effect on alveolar macrophages through adiponectin receptor 1 (26–29), reduces IL-6 production and adhesion molecule expression, and inhibits nuclear factor kappa B (30). In contrast to this, adiponectin has been shown to exert proinflammatory effects on airway epithelium by inducing expression of IL-8 (10).

Animal studies on adiponectin have also demonstrated a potential role for this molecule in the pathogenesis of emphysema and its systemic manifestations. Adiponectin expression is induced in airway epithelium and BAL fluid in wild-type mice

Figure 2. Univariate analysis of the association of adiponectin with variables age at enrollment in the study; body mass index (kg/m^2); and percent emphysema on computed tomography chest scan. Each dot represents a study individual. Log-transformed adiponectin levels are on the ordinate of each graph and the variables are on the abscissa. Each line represents the line of best fit to the data. $P < 0.01$ for all comparisons.

TABLE 3. VARIABLES WITH A SIGNIFICANT ASSOCIATION WITH PLASMA ADIPONECTIN LEVELS IN MULTIPLE REGRESSION ANALYSIS

Variable	Standardized Beta Coefficient	P Value
Age at enrollment	0.11	0.015
Female sex	0.34	<0.001
Body mass index	−0.14	0.003
Prebronchodilator/post-bronchodilator FEV ₁ % change	−0.20	0.036
% Emphysema lower third lungs	0.10	0.032

on exposure to cigarette smoke (10). Adiponectin may also play a role in lung development, because mice deficient in adiponectin demonstrate airspace enlargement at 6–18 days. Interestingly, mice with a partial deficiency in adiponectin also demonstrate airspace enlargement compared with wild-type mice (31). Although adiponectin-deficient (knockout) mice may be resistant to tobacco smoke-induced emphysema (11), they also have higher levels of proinflammatory mediators, enhanced endothelial cell apoptosis, and systemic manifestations of emphysema, such as muscle atrophy, osteoporosis, and weight loss, underscoring an antiinflammatory role for adiponectin in animal models (31, 32).

Consistent with previously published studies, we found increased levels of adiponectin in subjects with COPD, especially individuals with very severe COPD. Increased adiponectin levels have been demonstrated in 12 normal weight and 19 underweight Japanese male subjects with COPD compared with control subjects, where levels correlated with body weight loss and high levels of tumor necrosis factor- α (13). Similarly, increased adiponectin levels have been found in 71 subjects with COPD (mean FEV₁ 37 $\pm$ 13% predicted) compared with healthy smokers and nonsmokers. Adiponectin levels have been shown to correlate with IL-6 levels, age, pack-years smoked, and inversely with BMI (14).

In this study, there was a negative association between plasma adiponectin levels and active smoking status on univariate analysis. CT-assessed emphysema was independently associated with adiponectin levels and negatively with current smoking, but no interaction was identified between adiponectin and current smoking on the outcome of emphysema. Other studies have suggested such a relationship, but overall this is not clear. Lower adiponectin levels have been found in men who are current smokers compared with men who are nonsmokers in a study of 2,500 Korean men (16). However, another study reported lower adiponectin levels in women smokers only and found no relationship between smoking status and adiponectin levels in men, suggesting a sex difference with regard to the effects of smoking status on adiponectin levels (17). Similarly, a rise in adiponectin levels may also occur after smoking cessation in men and women, suggesting active smoking may lower adiponectin levels (18).

In our multivariable analysis we found several factors associated with adiponectin levels. Female sex was significantly associated with higher adiponectin levels than male sex, which has also been reported in healthy subjects and COPD subjects (15). Similarly, as previously reported, we found a strong negative correlation between plasma adiponectin and BMI. The relationship between BMI and adiponectin has been studied in many conditions associated with cachexia, such as anorexia nervosa, end-stage renal failure, chronic heart failure, and COPD (14, 33, 34). The higher adiponectin levels may reflect a generally increased systemic inflammatory response or a metabolic state similar to starvation, which has been shown to cause emphysema in animals and humans (35, 36).

Besides emphysema, in this study those with lower percentage change in FEV₁ post-bronchodilator had higher adiponectin levels. This finding is interesting given that higher adiponectin levels have negatively correlated with risk of asthma (7).

Adiponectin plays a role in insulin sensitivity and fatty acid oxidation, and is associated with the metabolic syndrome. It may lower the risk of type 2 diabetes mellitus and may be cardioprotective (22). Lower levels of adiponectin have been associated with insulin resistance and the presence of the metabolic syndrome in individuals with COPD (9). Those individuals with the metabolic syndrome tended to have less severe COPD in a study of 114 patients, but may represent a different COPD phenotype with increased insulin resistance. Others have demonstrated adiponectin as a predictor of future cardiovascular events in individuals with COPD, with lower adiponectin levels associated with increased risk of adverse cardiovascular outcomes (19). One explanation for this may lie in the antiatherogenic and insulin-sensitizing properties of adiponectin, highlighting a potential role for adiponectin as a biomarker of cardiovascular risk in COPD.

Our study is one of the larger studies of adiponectin in individuals with and without COPD and the first to report that adiponectin levels are associated with CT-assessed emphysema, and includes almost 50% women; however, there are some limitations regarding interpretation of the data. There was a large amount of collinearity among the different quantitative emphysema measurements (total emphysema, upper-third emphysema, and lower-third emphysema). Thus, although we found that emphysema in the lower third of the lung was the most significant in the multivariable model, we cannot rule out that other emphysema parameters contribute to the association with plasma adiponectin levels. Additionally, our subject population was predominantly non-Hispanic white subjects; thus, we do not know whether this relationship is true in other populations.

Conclusions

We demonstrate that adiponectin is associated with CT-assessed emphysema and other covariates, such as decreasing BMI, albeit that the association with CT-assessed emphysema is weaker than the associations with BMI, sex, and age. The precise role adiponectin plays in the pathophysiology of COPD is not clear, because adiponectin exerts proinflammatory and antiinflammatory effects. Although it is beyond the scope of this study to determine the underlying mechanisms for the association of plasma adiponectin with CT-assessed emphysema, one possible explanation is that increased systemic inflammation in COPD leads to increased plasma adiponectin as a counterinflammatory molecule. This is a more favorable explanation because most studies suggest adiponectin has largely antiinflammatory properties. An opposing mechanism is that adiponectin exerts its proinflammatory effects on airway epithelium or fat cells and the subsequent derangement in metabolism contributes to the functional loss of lung tissue (emphysema), implicating adiponectin as a phenotypic biomarker of COPD, but further studies are required to evaluate this hypothesis.

Author disclosures are available with the text of this article at www.atsjournals.org.

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