Full Length Research Paper

Elevated circulating plasma adiponectin in normal weight male patients with stable chronic obstructive pulmonary disease (COPD)

Zhao Jian Jun, Song Yu Ming, Wang Jing, Zhao Feng Qin, Tan Ping and Yang Lei*

Respiratory Department, China-Japan Union Hospital of Ji Lin University, Changchun 130033.
Ji Lin Province, China.

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Chronic obstructive pulmonary disease (COPD) is recognized as a multi-component disease these days. There is growing evidence that persistent low-grade systemic inflammation present in COPD may contribute to the pathogenesis of atherosclerosis and cardiovascular disease. Adiponectin (APN) is a secretory protein synthesized by adipocytes and has important anti-inflammatory as well as anti-atherosclerotic and anti-obesity effects, while little is known before regarding the importance of APN in pulmonary inflammation of human or animal subjects and to determine whether hyperadiponectinemia could be an underlying mechanism for COPD and whether there is a relationship between plasma adiponectin level and pulmonary function. Plasma samples were obtained from 68 normal weight male patients with stable COPD and 36 healthy control subjects. Plasma concentrations of APN were measured by enzyme-linked immunosorbent assay. Pulmonary function testing and body mass index (BMI) were performed in all patients and control subjects. We found that plasma adiponectin levels in patients with stable COPD were significantly higher than that in control subjects (18.6 ± 2.4 μg/mL vs. 4.2 ± 0.8 μg/mL, P<0.01). There was no correlation between adiponectin and FEV₁, FEV₁/FVC in COPD patients. Our data indicate that COPD patients exhibited higher plasma APN levels compared with healthy control subjects, suggesting a peculiar role for this protein in COPD pathogenesis.

Key words: Chronic obstructive pulmonary disease (COPD), enzyme-linked immunosorbent assay (ELISA), pulmonary function, adiponectin, plasma

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major global disease that has been predicted to be the third leading cause of mortality worldwide by 2020 (Murray et al., 1997). It is a disease characterized by partially reversible airflow limitation, is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (Rabe et al., 2007). Furthermore, COPD is recognized as a multi-component disease these days, involving various extra-pulmonary manifestations like low-grade systemic inflammation and an increased prevalence of cardiovascular co morbidity (Han et al., 2007). There is growing evidence that persistent low-grade systemic inflammation present in COPD may contribute to the pathogenesis of atherosclerosis and cardiovascular disease (Sin et al., 2003).

Adiponectin (APN) is a secretory protein synthesized by adipocytes and has important anti-inflammatory as well as anti-atherosclerotic and anti-obesity effects (Pasceri et al., 2000; Wouters et al., 2007; Desruisseaux et al., 2007). It exists in trimers, hexamers, high-molecular-weight form and decreases with smoking habits, genetic factors, the use of corticosteroids and obesity-linked disorders (Arita et al., 1999; Kadowaki et al., 2005; Iwashima et al., 2005; Kadowaki et al., 2006). It also reduces the production and activity of tumor necrosis factor alpha (TNF-a) and inhibits interleukin-6 (IL-6).

*Corresponding author. E-mail: zhaojj1@hotmail.com. Tel/Fax: 086-0431-8495860.
production, and this anti-inflammatory activity is accompanied by induction of the anti-inflammatory cytokine interleukin-10 (IL-10) and interleukin-1 (IL-1) receptor antagonist. APN has a wide range of effects in pathologies with immune and inflammatory components, such as cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome and rheumatoid arthritis, while little is known before regarding the importance of APN in pulmonary inflammation of human or animal subjects (Lago et al., 2007). Until recently, there is some evidence that APN plays a significant role in the pathogenesis of lung disease. All three of the known APN receptors (AdipoR1, AdipoR2, and T-cadherin) are expressed in the lungs, and APN has been isolated from bronchoalveolar lavage fluid (Hug et al., 2004; Takemura et al., 2007; Yamauchi et al., 2007; Miller et al., 2009). In addition, exogenously administered APN was shown to suppress leukocyte recruitment, Th2 cytokine production, and airway inflammation in a murine model of allergen-induced asthma (Shore et al., 2006). Interestingly, the lungs of APN-deficient mice exhibit an emphysema-like phenotype that is associated with activated alveolar macrophages that spontaneously elaborate TNF-α and matrix metalloproteinase-12. This suggests that APN deficiency may be associated with the pathogenesis of inflammatory lung diseases, such as emphysema (Summer et al., 2008).

Given the aforementioned data and the antiprotease, antiinflammation, and antioxidant functions of APN, which have been traditionally posited as key mechanisms for COPD, we therefore hypothesized that hyperadiponectinemia could be an underlying mechanism for COPD and the key link between COPD and various comorbidities. In order to avoid several parameters that may affect the level of plasma adiponectin, including BMI, smoking, gender and treatment regimens such as the use of systemic corticosteroids, our study was deliberately designed that only male smoker with normal weight stable COPD patients were included.

SUBJECTS AND METHODS

Study subjects

We enrolled 68 male patients with stable COPD who met our entry criteria. The diagnosis and severity of COPD was established in accordance to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (Rabe et al., 2007). Patients with significant comorbidities, including tuberculosis or other lung disease except from COPD, apparent heart failure, coronary artery disease, renal or liver impairment or failure, diabetes mellitus, history of cancer in any site, metabolic syndrome, collagen and vascular disorders were excluded. In order to increase the homogeneity of the study population and avoid the affect of gender and weight, only men with current smoke and normal weight patients were enrolled in this study because visceral fat mass varies according to gender and weight. All patients were clinically stable at the time of evaluation. The medical treatment of patients at the time of the study mainly included inhaled bronchodilator therapy.

None of the patients were on regular inhaled or systemic corticosteroids treatment. The control group consisted of 36 healthy volunteers who were smokers without symptoms or signs of COPD or any of the aforementioned exclusion criteria with normal pulmonary function. Information about smoking habits, respiratory symptoms and other diseases, such as cardiovascular diseases, were obtained using a detailed questionnaire. The study was approved by the Ethics Committee of the China-Japan Union Hospital of Ji Lin University and informed consent was obtained from all participating subjects.

Pulmonary function testing

Pulmonary function testing were performed in all control subjects and patients with reversibility using standardized methods according to the American Thoracic Society guidelines, assessed by use of a short-acting β2-agonist, equivalent to 200 mg salbutamol by a metered-dose inhaler (Minato AutoPal Spirometry, Osaka, Japan). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV$_1$) were measured and expressed as percentages of the predicted normal reference values (Laszlo et al., 2006). The predicted normal reference values were obtained from our local population.

Blood sampling and analysis

Venous blood samples were taken from all subjects in the morning at 7:00 to 8:00 AM after an overnight fast. The blood was centrifuged immediately at 4°C and stored at -70°C.

Plasma adiponectin was measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Inc, Minneapolis, MN, USA) according to the prescription by the producer.

Body mass index (BMI) calculated

Body weight and height were measured and body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$) in both groups. Body height was measured to the nearest 0.1 cm. Body weight was assessed by using an electronic beam scale with digital readout to the nearest 0.1 kg after emptying the bladder and with the subjects standing barefoot and wearing light indoor clothing. The normal weight patients BMI was between 21.0 and 25.0 kg/m$^2$. 
Table 1. Characteristics of healthy controls and COPD patients.

<table>
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<tr>
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<th>Healthy controls (n=36)</th>
<th>COPD Patients (n=68)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67.8 ± 7.6</td>
<td>72.4 ± 8.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 0.6</td>
<td>21.3 ± 0.9</td>
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<tr>
<td>FEV₁ %</td>
<td>92.1 ± 14.6</td>
<td>74.2 ± 21.5</td>
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<tr>
<td>FEV₁/FVC %</td>
<td>85.7 ± 9.2</td>
<td>56.7 ± 11.6</td>
</tr>
<tr>
<td>Smoking status (pack years)</td>
<td>40 ± 3</td>
<td>39 ± 2</td>
</tr>
</tbody>
</table>

![Figure 1. Comparison of plasma APN concentrations in normal weight male patients with stable COPD and healthy controls, showing that APN levels were significantly higher in COPD patients compared with healthy controls (*P < 0.05).](image)

Statistical analyses

Data were analyzed using the SPSS® statistical package, version 11.5 (SPSS Inc, Chicago, IL, USA) for Windows®. Data of the subjects are presented as mean ± SE, comparisons between healthy control subjects and COPD patients were made using Mann–Whitney rank-sum test, as appropriate. A P-value < 0.05 was considered to be statistically significant. The relationships between the data were examined by the Spearman rank correlation coefficient. Correlations with both R≥0.4 and P < 0.05 were considered relevant.

RESULTS

Characteristics of subjects

Clinical characteristics of COPD patients and healthy control subjects are summarized in Table 1. All patients with COPD were with mild and moderate bronchial obstruction (stage I - II, GOLD 2007). There was no difference in age or BMI between the COPD and control groups.

Plasma adiponectin level in chronic obstructive pulmonary disease (COPD)

Plasma adiponectin levels in patients with COPD were significantly higher than that in control subjects (18.6 ± 2.4 μg/mL vs 4.2 ± 0.8 μg/mL, P<0.01) as shown in Figure 1.

Relationship between plasma adiponectin level and pulmonary function in patients with chronic obstructive pulmonary disease (COPD)

There was no correlation between adiponectin and FEV₁, FEV₁/FVC in COPD patients.

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is considered to be a disease which profoundly affects worldwide mortality and morbidity (Rabe et al., 2007). It is well appreciated that there is an up-regulation of airway and systemic inflammation in COPD (Hurst et al., 2006). Despite the aforementioned evidence, many aspects of the underlying mechanism of increased systemic inflammation in COPD remain speculative.

Adiponectin (APN) is secreted by the white adipose tissue. It is involved in inflammatory processes, immune response, lipid metabolism, insulin sensitivity, vascular homeostasis, angiogenesis, and regulation of energy balance (Wouters et al., 2007). Decreased circulating concentrations of adiponectin are associated with obesity, metabolic syndrome, insulin resistance, and cardiovascular disease (Wert, 2008). By contrast, serum levels of adiponectin are elevated in the presence of autoimmune diseases and chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis (Fantuzzi, 2008).

Furthermore, higher levels of adiponectin have been
reported to predict mortality in healthy elderly persons, in patients with chronic heart failure and in patients with chronic renal failure (Kistorp et al., 2005; Ohashi et al., 2008; Poehls et al., 2009). Although systemic manifestations as a result of the low-grade systemic inflammatory process are recognized by many researchers, there is little knowledge on the alterations and the role of adiponectin in COPD patients. Expression of adiponectin by bronchial epithelial cells in COPD has been described (Yoon et al., 2011). A smaller cross-sectional study has demonstrated that serum concentrations of adiponectin are elevated in patients with stable COPD when compared to healthy controls. Furthermore, both leptin and adiponectin are associated with the systemic inflammatory process during exacerbations of COPD (Kirdar et al., 2009). These studies were limited by their inability to evaluate the confounding effect of fat mass on this association. In order to increase homogeneity of the study population and to avoid several parameters that may affect the level of plasma adiponectin, including BMI, smoking, gender and treatment regimens such as the use of systemic corticosteroids, our study was deliberately designed that only male smoker patients with normal BMI were included. Moreover, the medical treatment of patients at the time of the study mainly included inhaled bronchodilator therapy. None of the patients were on regular inhaled or systemic corticosteroids treatment. In our present study, we found that plasma adiponectin levels in patients with stable COPD were significantly higher than that in control subjects. The potential role of adiponectin in COPD is that adiponectin is known predominantly to exert anti-inflammatory effects, though recent studies have also provided evidence of potential proinflammatory effects (Tilg et al., 2006). Anti-inflammatory effects of adiponectin may be mediated through several potential pathways including its capacity to suppress the synthesis of tumor necrosis factor (TNF) as well as its ability to induce the production of anti-inflammatory cytokines such as IL-10 and the IL-1 receptor antagonist (Kadowaki et al., 2006; Tilg et al., 2006). Another unexplored mechanism by which adiponectin might inhibit inflammation in COPD is through adiponectin’s known activation of peroxisome proliferator-activated receptor-α, which exerts anti-inflammatory effects through inhibition of the transcriptional activation of proinflammatory response genes.

Association studies between plasma adiponectin concentrations and lung function have yielded conflicting results. In a large population-based study of 2,056 young participants of both sexes, serum adiponectin concentrations were positively associated with forced vital capacity (FVC) and forced expiratory volume (FEV₁) without any significant change in FEV₁/FVC ratio, independent of obesity (Thyagarajan et al., 2010). On the other hand, two small previous cross-sectional studies of 31 and 15 patients with stable and established COPD, without adjustment for obesity, showed a lack of correlation between spirometric lung function and serum adiponectin concentrations (Kirdar et al., 2009). In line with Tomada et al. (2007) we did not find there was a correlation between adiponectin and FEV₁, FEV₁/FVC in COPD patients. Probably, in our study the absence of correlation between pulmonary function and plasma level of APN can be explained that all patients with COPD were with mild and moderate bronchial obstruction.

Our study has several limitations. First, we carried out the measurements in plasma, which reflects only systemic changes and may not adequately reflect the local concentrations in the lungs. Further studies involving biological samples such as bronchoalveolar lavage, induced sputum and exhaled breath condensate might shed more light locally. Second, since our study population is limited, and there are only a few related studies in the literature, the precise mechanism and significance of the associations between adiponectin and lung disease at the current stage is confusing and frankly paradoxical in places, the value of adiponectin as a biomarker of systemic inflammatory response and its role in the regulation or attenuation of systemic inflammation in COPD patients should be confirmed by further studies.

In conclusion, the results of the present study indicate that COPD may upregulate systemic and lung adiponectin expression and adiponectin may be a marker of low grade systemic inflammatory response in COPD, at least in men, since plasma adiponectin levels was elevated in COPD patients compared to healthy controls. Higher adiponectin levels of patients with COPD can be interpreted as an attempt to overcome the effects of proinflammatory cytokines such as TNF-α, IL-6 and C-reactive protein (CRP). This area of research needs additional study that may open up novel therapeutic strategies for these lung diseases.

REFERENCES


Yoon H, Li Y, Man SF, Tashkin D, Wise RA, Connett JE,