Serum adiponectin as a biomarker for chronic obstructive pulmonary disease and lung cancer and its relation to severity

Amany T. Gayed[a], Riham H. Raafat[b]

Introduction 'Chronic obstructive pulmonary disease' (COPD) is an inflammatory disorder associated with airway narrowing and airflow limitation in response to air pollution, gases, and smoking and is associated with morbidity and mortality. Cancer is also considered as a systemic inflammatory disorder where pro-inflammatory cytokines and mediators are released.

Aim To evaluate serum adiponectin level in COPD and lung cancer and its importance in detecting and predicting severity.

Patients and methods A total of 40 patients were recruited in the study: 20 had stable COPD and 20 had lung cancer. Moreover, another 10 age-matched and sex-matched individuals were included as a control group. All were subjected to routine laboratory chest radiography, spirometry, and serum adiponectin level measurement.

Results The results showed an increase of adiponectin level in both patients with COPD and those with lung cancer, and significant correlation was found between adiponectin level and forced expiratory volume in 1 s and performance status.

Conclusion Adiponectin serum level is elevated in both COPD and lung cancer and significantly elevated in severe cases.

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Keywords: adiponectin, body mass index, chronic obstructive pulmonary disease, lung cancer

[a]Chest Departments, Ainshams University, [b]Ainshams University Hospitals, Cairo, Egypt

Correspondence to Riham H. Raafat, MD, 8th Mahdy Ebn Baraka Street, District 7, Nasr City, Cairo, 11765, Egypt. Tel: +20 100 094 8672; e-mail: dr_riham80@yahoo.com

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Introduction

'Chronic obstructive pulmonary disease (COPD)' is an inflammatory disorder, where airway narrowing and airflow limitation is progressive and associated with inflammatory response in airways [1] and spread of inflammatory mediators from the lungs all over, resulting in systemic inflammatory response of COPD [2]. Annual forced expiratory volume in 1 s (FEV_1) change is highly variable in COPD [3], as COPD progresses to a severe form in association with emphysematous bullae, there is progressive decline in FEV_1 [4]. Reliable blood biomarkers are needed to predict patients' prognosis; if these markers could be easily measured, it could reduce the burden of COPD [5]. Adiponectin plays a role in the pathogenesis of metabolic syndrome and was noted as a contributing factor to COPD [6]. Tomoda *et al.* [7] noticed an increase in adiponectin levels in severe and malnourished patients with COPD. Higher adiponectin levels were associated with a higher risk of mortality in patients with COPD, as was have lately demonstrated [8]. It was shown that adiponectin as a COPD complex biomarker was associated with an increased risk of respiratory mortality [9]. Serum levels of adiponectin were elevated with BMI and insulin resistance and were inversely correlated with body weight [10]. Cancer as a systemic inflammation, pro-inflammatory cytokines and cytokines have a role in catabolism and acute phase protein production and early they have a protective effect but unlimited contribution of inflammation has adverse effects and associated with poor outcome in advanced cancer [11]. The role of 'adipokines' in induced systemic inflammation by advanced cancer has not been studied. Obese populations have higher leptin levels, the protein hormone that controls appetite, and lower adiponectin level, which regulates glucose level and the breakdown of fatty acids [12]. Lung cancer death rate is decreased with obesity, with BMI more than 30; loss of weight in patients with cancer is related to hypercatabolic state associated with the loss of skeletal mass and adipose tissue [11]. A complex network of peripheral mediators, such as hormones, neuropeptides, and cytokines, regulate food intake and energy homeostasis. Adiponectin is one of these mediators. Body weight loss and inflammatory mediators affect quality of life [10].

The aim of the study was to evaluate adiponectin level as a biomarker in COPD and lung cancer and its relation to severity.

Patients and methods

This cross-sectional analytic study included 40 male patients from Chest Department and Clinic in Ain Shams University Hospital from June 2015 to December 2015. There were 20 patients with lung

cancer who were cytologically confirmed and 20 patients with stable COPD, with their typical history regarding coughing, sputum production, dyspnea, and history of exposure to a risk factor associated with postbronchodilator spirometric criteria according to global obstructive lung disease (GOLD) guidelines [13]. Moreover, 10 healthy age-matched and sex-matched individuals as a control group were included in the study. All patients after their approval were subjected to the following:

(1) Full history and clinical examination.
(2) Chest radiography.
(3) Laboratory investigations.
(4) ECG.
(5) Spirometry.
(6) Blood samples were collected from the antecubital vein between 7 and 9 a.m. after overnight fasting, to detect level of adiponectin. The blood samples were immediately transferred to chilled tube containing EDTA and centrifuged. The serum samples obtained were immediately frozen at −70°C until further analysis for adiponectin determination using 'Avi Bion Human adiponectin ELISA kits, Finland.'
(7) BMI was calculated as weight (kg) divided by square of height (m^2) [14].
(8) Performance status was evaluated by Karnofsky scoring; it runs from 100 to 0, where 100 is perfect health and 0 is death [15].

Patients with other chest diseases or comorbidities were excluded from the study.

Statistical analysis

IBM SPSS statistics was used for data analysis. Data were expressed as mean±SD for quantitative parametric measures. The following tests were used:

(1) Comparison between two independent mean groups for parametric data using Student's *t* test.
(2) Pearson's correlation test was used to study the possible association between each two variables among each group for parametric data. The probability of error at 0.05 was considered significant, whereas at 0.01 and 0.001 highly significant.
(3) Diagnostic validity test: it includes the following:
    (a) Diagnostic sensitivity: it is the percentage of diseased cases truly diagnosed among total diseased cases (true positive (TP)+false negative (FN)).
    (b) Diagnostic specificity: it is the percentage of nondiseased truly excluded by the test (true negative (TN)) among total nondiseased cases (TN+false positive (FP)).
    (c) 'Predictive value' for a positive test: it is the percentage of cases truly diagnosed among total positive cases.

Results

Our study included 20 patients with stable COPD, 20 patients with lung cancer, and 10 male age-matched and sex- matched individuals as a control group from Ain Shams University Hospital.

Our results showed there was a significant difference between COPD and control regarding adiponectin level, so that COPD mean was 9.875±1.64 μg/ml and control mean was 4.9±1.33 μg/ml (Table 1).

There was a significant difference between adiponectin level in patients with cancer and control, with mean of 9.9±2.6 and 4.9±1.33 μg/ml, respectively. Moreover, there was a significant difference between patients with lung cancer and control group regarding performance status, with mean of 56±10.5 and 100±0.00, respectively, and BMI, with mean of 21.1±1.33 and 25.6±2.91 kg/m^2, respectively (Table 2).

There was no significant difference between patients with COPD and patients with lung cancer regarding adiponectin level, as both were ∼9 μg/ml (Table 3).

A highly significant difference was seen between adiponectin level and FEV_1, so there was an inverse

Table 1 Demographic and biochemical parameters in patients with chronic obstructive pulmonary disease and control

Parameters	COPD (*n*=20)	Controls (*n*=10)	*P* value
Age (mean±SD) (years)	58.55±7.35	53.8±7.42	0.115 NS
Adiponectin level (mean±SD) (μg/ml)	9.875±1.64	4.9±1.33	0 HS

COPD, chronic obstructive pulmonary disease; HS, highly significant.

Table 2 Demographic and biochemical parameters in patients with lung cancer and control

Parameters	Lung cancer (*n*=20)	Controls (*n*=10)	*P* value
Age (mean±SD) (years)	55.45±10.5	53.8±7.42	0.62 NS
Performance status (mean±SD)	56±10.5	100±0.00	<0.0001
Adiponectin (mean±SD) (mg/ml)	9.9±2.6	4.9±1.33	0 HS
BMI (kg/m^2)	21.1±1.33	25.6±2.91	<0.0001 HS

HS, highly significant.

Table 3 Demographic and biochemical parameters in patients with lung cancer and patients with chronic obstructive pulmonary disease

Parameters	COPD (*n*=20)	Lung cancer (*n*=20)	*P* value
Age (mean±SD) (years)	58.55±7.35	55.45±10.5	0.28 NS
Adiponectin (mean±SD) (μg/ml)	9.87±1.64	9.9±2.68	0.972 NS

COPD, chronic obstructive pulmonary disease.

relation between FEV_1 and adiponectin level (when severity of COPD increased, the level of FEV_1 decreased whereas the level of adiponectin level increased) (Table 4).

Table 5 showed no significant relation between BMI and adiponectin level, but there was a significant negative correlation between adiponectin and performance status of patients with lung cancer. Adiponectin level was a predictor of severity of patients with cancer with respect to performance status.

Discussion

Adiponectin is an adipocytokine derived from adipocytes. It inhibits the expression of pro-inflammatory cytokines such as TNF-alpha and alters the macrophages (MQs) phenotype from pro-inflammatory MQs to anti-inflammatory MQs [16].

COPD is a major worldwide inflammatory disorder where there is exaggeration of inflammation during exacerbation, and also there is an increased systemic inflammation response. Therefore, it would be a great advantage to find a biomarker that helps in diagnosis and prediction of outcomes [17].

Cancer is a systemic inflammation driven by pro-inflammatory cytokines, which have role in catabolism, gluconeogenesis, and acute phase protein production, leading to poor outcome in advanced cancer [11].

The present study was done on 40 patients (20 COPD and 20 lung cancer) and control group of 10 sex-matched and age-matched healthy persons.

The results showed that there was an increase in adiponectin level in patients with COPD; this result goes hand in hand with Krommidas *et al*. [18], who studied 63 patients with COPD exacerbation and measured serum levels of leptin and adiponectin, and the results proved that leptin and adiponectin are associated with systemic inflammatory process during COPD exacerbation.

Table 4 Demographic and biochemical parameters in serum adiponectin level and age, forced expiratory volume in 1 s, and forced expiratory volume in 1 s/forced vital capacity

Parameters	Age	FEV_1	FEV_1/FVC
Adiponectin			
R	–0.152	–0.571	–0.332
P	0.523	0.009	0.153
Significance	NS	HS	NS

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HS, highly significance.

Table 5 Demographic and biochemical parameters in serum adiponectin level and body mass index and performance status of lung cancer

Parameters	BMI	Performance status
Adiponectin	*R*=–0.39	–0.47
	P=NS	*P*=0.035 (S)

S, significant.

Kirdar *et al*. [19] studied 36 male patients with COPD and 17 age-matched and sex-matched healthy participants and measured the adiponectin and leptin levels and found that the adiponectin level was significantly higher than control, and this was in agreement with our study.

Another study [3] involving COPD quantification using computed tomography chest, biomarkers, and quality of life had shown a lung function decline associated with leptin to adiponectin ratio, and this was in accordance with the present study, which showed significant correlation between adiponectin level and FEV_1 in COPD cases. Adiponectin level is inversely related to FEV_1. Our results also matched with Sato *et al*. [20], who found that there is an inverse correlation between plasma adiponectin level and annual changes in FEV_1. Bruno *et al*. [21] found that leptin and adiponectin are expressed in human lung and were increased in the bronchial mucosa of COPD compared with normal participants, owing to airway inflammation and airflow obstruction.

Lung cancer is the commonest cause of cancer death, associated with progressive weight loss, which leads to reduction in performance status and quality of life owing to the presence of systemic inflammatory response (especially in advanced lung and gastrointestinal cancers), which acts as a survival predictor independent of stage in cancer [22].

Our results showed there was an increase in adiponectin level in patients with cancer lung, and they also had poor performance state and poor prognosis. This result is consistent with a meta-analysis of 16 prospective studies involving 14 063

participants, which showed that high adiponectin level is associated with increased morality in patients with cardiovascular disease [23]. These findings seem paradoxical as many studies have shown that adiponectin has significant antidiabetic, anti-inflammatory, and anti-carcinogenic activity [24]. The possible two explanations for adiponectin paradox are that adiponectin promotes AKT-medicated activation of cancer cells and such activation is a significant predictor of worse survival [25], and promotes tumor angiogenesis [26]. Performance status was evaluated using Karnofsky scoring [15]. In this study, performance status mean in patients was 56±10.5 in comparison with control 100 ±0.00, with a very high significance (<0.0001). Our results were in agreement with Singh *et al.* [27] who studied the prevalence of low BMI among newly diagnosed patients with lung cancer in India and its association with smoking and demonstrated that performance status of those patients were significantly lower than control. Scott *et al.* [28] showed similar results in a prospective study of the effect of weight loss and the systemic inflammatory response on quality of life in patients with inoperable nonsmall cell lung cancer and realized that Karnofsky performance status and quality of life were lower ($P<0.05$) in patients compared with control.

On the contrary, our results were different from the results of Barb *et al.* [29], who searched for 'adiponectin: a link between obesity and cancer' and found that adiponectin had a negative correlation with BMI in patients with lung cancer. Moreover, our results go with the results of Serter *et al.* [30] on studying 'the value of adiponectin as an inflammatory marker in lung cancer' and found that adiponectin and interleukin-6 levels were significantly higher in lung cancer group than in control group and concluded that adiponectin was involved in inflammatory processes with interleukin-6, which might be a cause in developing lung cancer.

Limitations

Small sample size as well as limited time were the limitations of the study. Therefore, to generalize the results, a larger number of participants and longer duration of the study must be taken into account for future studies.

Conclusion

Adiponectin could be used as 'a biomarker for COPD and lung cancer' especially in severe cases, and it can be used as a predictor of severity.

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Conflicts of interest

There are no conflicts of interest.

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