Original Article

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ISSN: 1735-0344 *Tanaffos 2013; 12(3): 53-57*

TANAFFOS

Adiponectin Level in Serum and BAL Sample of Patients with Chronic Obstructive Pulmonary Disease

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Received: 26 May 2013
Accepted: 2 August 2013

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Background: Chronic obstructive pulmonary disease (COPD) is the only cause of mortality and morbidity with an increasing incidence. Adiponectin has recently gained the spotlight for its possible association with COPD or its exacerbation. This study evaluated the association of serum and alveolar adiponectin levels with COPD-related variables.

Materials and Methods: This analytical cross-sectional study was carried out on 45 COPD patients. Number of cigarettes smoked (packs), years of smoking, number of disease exacerbations per year and BMI were all recorded. Patients underwent spirometry and their disease severity was determined based on BODE index. Venous blood sample was obtained to measure the adiponectin serum level, ESR and CRP. Bronchoscopy and BAL were performed as well and alveolar secretions were collected to assess the alveolar fluid level of adiponectin.

Results: The mean serum level of adiponectin in COPD patients was significantly higher than the upper limit of normal range in healthy individuals (P=0.000). Level of alveolar adiponectin in smoker patients was significantly higher than non-smokers (P=0.043) but serum adiponectin was not significantly different between them. Serum adiponectin level had a significant reverse correlation with BMI and a direct correlation with number of exacerbations per year and CRP. Level of alveolar adiponectin had a direct association with number of exacerbations per year and number of smoked cigarettes.

Conclusion: Based on the obtained results, smoking cessation is very important in COPD and more emphasis should be placed on patient's weight control especially those with low BMI as well as rehabilitation programs for these patients.

Key words: Alveolar adiponectin, Serum adiponectin, Chronic Obstructive Pulmonary Disease (COPD)

INTRODUCTION

COPD is defined as progressive and irreversible airflow limitation in airways (1). At present, COPD is the 4th cause of death in the United States and the only cause of morbidity and mortality with an increasing incidence (2). Smoking is the most common cause of COPD in industrial countries; however, in developing countries environmental pollutants and wood smoke exposure are the main causes of COPD (3). The main site of increased resistance in most COPD patients is 2mm≥ airways showing metaplasia of goblet cells and Clara cell (producing surfactant) replacement with infiltrations of mononuclear inflammatory cells and mucus-producing cells. This process is induced by cigarette smoke. The mentioned processes along with hypertrophy of smooth airway muscles lead to constriction and obstruction of airways (4). Also, long-term exposure to cigarette smoke leads to infiltration of inflammatory cells in terminal air spaces namely respiratory bronchioles, alveolar ducts and alveoli and subsequent release of destructive proteases by these

cells that damage the intercellular matrix and cause the death of pulmonary parenchymal cells and eventual emphysema (4). Thus, it seems that inducing the infiltration of inflammatory cells such as macrophages, neutrophils and lymphocytes (CD8+), release of proteases and production of IL-8, TNF-alpha and other inflammatory cytokines and chemokines due to oxidants produced by cigarette smoke are the most important pathologic mechanisms involved in COPD (4).

Adiponectin is a mediator with possible association with development and exacerbation of COPD that has recently gained the spotlight (5-10). Adiponectin is a protein compound released by the adipose tissues with a confirmed role in maintaining homeostasis and protecting the body against insulin resistance and atherosclerosis (5, 7). Adiponectin as a cytokine has both pro-inflammatory and anti-inflammatory properties and by stimulating the release of other cytokines particularly interleukins plays a part in development, exacerbation or control of inflammation (4-7,9). Due to this property, researchers suspected that adiponectin may have a role in development and exacerbation of COPD and investigated this issue in several studies (9, 10). If the pathologic role of adiponectin in COPD or its association with disease severity or number of COPD exacerbations is confirmed, future studies may focus on the effectiveness of its antagonists or factors reducing adiponectin level to help control and treat COPD and decrease its related morbidity and mortality.

This study evaluated the association of serum and alveolar adiponectin levels with COPD-related variables.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted on COPD patients. Patients with absolute contraindications for bronchoscopy such as treatment-resistant hypoxia, treatment-resistant arrhythmia, patient's non-compliance and comorbidities related to adipose tissue hormones such as diabetes mellitus, metabolic syndrome, and obesity were excluded from the study and a total of 45 patients were evaluated. The study design was thoroughly explained to subjects, patients' questions were answered and written informed consent was obtained from them.

The study was carried out in 4 phases. In the first phase, number of smoked cigarettes (packs), years of smoking and number of exacerbations per year were recorded. Pack-year was calculated by multiplying the number of cigarette packs smoked per day by the number of smoking years. Height (using a tape measure) and weight (using digital scale) of patients were measured and body mass index (BMI) was calculated.

In the 2nd phase, subjects underwent spirometry (Spirometer, Japan) and severity of airway constriction was determined based on FEV1. Patients were then subjected to 6-minute walk-test and the distance walked was determined in meter. Severity of dyspnea was calculated based on patient's history and MMRC table and scored from 0 to 4. Eventually, their disease severity was determined using BODE Index (MMRC, 6-minute walk distance, BMI, FEV1)(score 0 to 10).

In the third phase, 5 ml of venous blood sample was aspirated and poured into 3 sterile tubes. The first tube contained citrate and used for determining ESR. The second tube contained citrate too and used for determining the CRP using Bionik kit.Co (Iran). The two tubes sent to the lab. The third tube was used for determination of the level of adiponectin and after separation of serum, the tube was stored in a freezer at -20°C until the ELISA test. In the final phase, subjects underwent bronchoscopy (Pentax, Japan) Patients' BAL was collected, poured into sterile falcon tubes and stored in a freezer at -20°C until the ELISA test for measurement of adiponectin level. After sampling, the collected samples were tested for adiponectin level using ELISA technique and Diagnost kit (Germany).

Obtained data were statistically analyzed. Descriptive statistics were used for description of data and Pearson's

correlation coefficient, ANOVA, t-test, linear regression model and SPSS version 21 software were used for data analysis.

Healthy control group was not used in our study because bronchoscopy is an invasive and costly procedure and there was no healthy volunteer for the study. Thus, adiponectin serum level of patients was compared with the normal range mentioned in previous studies (5-10 µg/ml). On the other hand, no normal range was found for alveolar adiponectin level in the literature and thus, we could not make any comparisons in this respect.

RESULTS

A total of 45 COPD patients were evaluated including 39 males and 6 females. Of all understudy variables, only pack-year smoking in females was significantly lower than in males and other variables were not significantly different between the two genders. The mean serum adiponectin level was 14.27±7.31 in patients that was significantly higher than the upper limit of normal range in healthy individuals (P=0.000). Alveolar adiponectin level was 4.43±1.10 in patients.

Serum adiponectin level was not significantly different in smoker and non-smokers but alveolar fluid adiponectin level was significantly higher in smokers compared to non-smokers (P=0.043).

Serum adiponectin level had a significant reverse correlation with BMI and a direct association with number of exacerbations per year and CRP. Alveolar fluid adiponectin had a significant relationship with number of exacerbations per year and number of smoked cigarettes (table 1).

Table 1. Association of serum and alveolar adiponectin levels with COPD-related variables.

Variables	Serum adiponectin	Alveolar fluid adiponectin	BMI	Exacerbations per year	Pack/ Year	BODE Index	ESR	CRP	FEV1
Serum adiponectin	-	0.623	0.001	0.044	0.879	0.101	0.814	0.002	0.510
Alveolar fluid adiponectin	0.623	-	0.256	0.000	0.002	0.687	0.458	0.815	0.206
BMI	0.001	0.0256	-	0.868	0.412	0.055	0.973	0.054	0.905
Pack/Year	0.879	0.002	0.412	0.137	-	0.408	0.934	0.150	0.239
Exacerbations per year	0.044	0.000	0.868	-	0.137	0.500	0.500	0.195	0.650
BODE Index	0.101	0.687	0.055	0.500	0.408	-	0.118	0.357	0.000
ESR	0.814	0.458	0.973	0.500	0.934	0.118	-	0.933	0.151
CRP	0.002	0.815	0.54	0.195	0.150	0.357	0.933	-	0.594

DISCUSSION

This study showed that serum adiponectin level of COPD patients was significantly higher than that of normal subjects. Several studies have evaluated this topic. Chan et al, in 2010 evaluated three groups of patients in their study: COPD patients, non-smokers and never-smokers. The results showed that serum adiponectin level of COPD patients was significantly higher than the other two groups. They reported that adiponectin probably plays a role in pathogenesis of COPD (9). Other studies by Tomoda et al. (7) and Uzum et al. (11) reported similar results. We also evaluated serum and alveolar fluid adiponectin level based on smoking status which has not been performed before and revealed that serum adiponectin level was not significantly different in the two groups of smoker and nonsmoker but alveolar fluid adiponectin was significantly higher in smokers.

Our study results demonstrated that serum adiponectin level was not significantly associated with alveolar fluid adiponectin level. On the other hand, alveolar fluid adiponectin level was higher in COPD patients with higher

number of smoked cigarettes but serum adiponectin level was not influenced by the number of cigarettes smoked by patients. We may state that the direct effect of smoking on lung tissue and the resultant local inflammation and injury lead to an increase in alveolar fluid adiponectin level and serum adiponectin level in this process has less sensitivity. No study has evaluated alveolar fluid adiponectin level or its association with serum adiponectin. The relationship of pack-year and adiponectin has not been investigated before either.

Number of disease exacerbations per year was significantly correlated with serum and alveolar fluid adiponectin levels. Krommidas et al. evaluated 63 COPD patients and reported that leptin and adiponectin serum levels and inflammatory biomarkers significantly increased during disease exacerbations (10). Kirdar et al. obtained similar results as well. They studied 36 male COPD patients and 17 controls and demonstrated that adiponectin serum level, just like ESR and CRP, can indicate disease exacerbation (5). Our study confirmed the association of serum adiponectin level and CRP but no correlation was found with ESR. Alveolar fluid adiponectin had no relationship with CRP or ESR. As expected, BMI had a significant reverse correlation with serum adiponectin and the higher the serum adiponectin level, the thinner the patient and this may be the reason why COPD patients are mostly thin. The results of Tomoda et al. are in accord with our findings. They evaluated normal weight and under-weight subjects and reported that serum adiponectin level was higher in COPD patients and had a significant association with weight loss (7).

Serum and alveolar fluid adiponectin levels had no significant correlation with BODE index which is indicative of the severity of COPD. In other words, serum and alveolar fluid adiponectin levels in stable COPD patients had no association with degree of disease severity. Similar results were obtained by Kirdar et al, in 2009. They showed that serum adiponectin level in stable COPD patients had no correlation with FEV1, FEV1/FVC or severity of airway obstruction (5).

Based on the obtained results, smoking cessation is very important in COPD and more emphasis should be placed on patient's weight control especially those with low BMI as well as rehabilitation programs for these patients.

All our understudy patients were in the stable phase and none of them were in the exacerbation phase. Evaluation of patients in exacerbation phase may further elucidate the results. We had no healthy control group and serum adiponectin levels were compared with the standard range reported in the literature. Furthermore, no standard range for alveolar fluid adiponectin level was found in the literature for comparison and we could not find out whether the alveolar fluid adiponectin level in our patients was different from the level in healthy individuals or not.

Future studies are recommended to focus on alveolar fluid adiponectin level in smoker and non-smoker COPD patients in both stable and exacerbation phases and compare it with that of healthy individuals. Alveolar fluid adiponectin level should be compared between COPD patients and healthy subjects and its correlation with smoking and disease exacerbation needs to be investigated as well.

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