Serum adiponectin level in obese and non-obese COPD patients during acute exacerbation and stable conditions

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KEYWORDS
Obesity;
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Abstract  Aim: To assess serum adiponectin in obese & non obese COPD during exacerbation and stable conditions and its relation to ventilatory functions.

Subjects and methods: The study was conducted on 40 male COPD patients during exacerbation and stable conditions with 15 age matched healthy control subjects. Patients and control were divided into non-obese and obese according to their body mass index. Subjects were submitted to full history taking, Complete physical examination, plain chest X-ray, Complete blood count, Erythrocyte sedimentation rate, Liver and kidney functions, Fasting and post prandial blood sugar, Ventilatory functions, and Venous blood samples for Adiponectin measurement.

Results: There was Significant difference in serum adiponectin between exacerbated nonobese COPD and nonobese controls ($P < 0.005$) and significant difference in serum adiponectin between exacerbated obese COPD patients and obese controls ($P < 0.05$). Significant difference was observed in serum adiponectin between nonobese stable COPD and nonobese controls ($P < 0.005$). Significant difference was observed in serum adiponectin between exacerbated nonobese COPD and stable nonobese COPD ($P < 0.05$). Significant difference was observed in serum adiponectin between nonobese COPD and obese COPD patients during exacerbation and stable states ($P < 0.001$). Non significant correlation was found between changes in serum adiponectin in nonobese COPD and obese COPD (exacerbation and stable conditions) and...
following ventilatory functions, FVC (% pred), FEV₁ (% pred), FEV₁/FVC and FEF25-75 (% pred).

Conclusion: Serum adiponectin was significantly higher in obese and nonobese COPD than controls, the rising is more during exacerbation than stable condition and more in non obese than obese COPD and non significant correlation between changes in adiponectin and ventilatory functions was found.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [10]. An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD [4]. COPD affects about 10% of the general population, but its prevalence among heavy smokers can reach 50% [6]. Adiponectin is a secretory protein synthesized by adipocytes and has important anti-inflammatory, anti-atherosclerotic and antiobesity effects [28]. Adiponectin is a mediator with possible association with the development and exacerbation of COPD that has recently gained the spotlight (5–10). 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 the development of exacerbation or control of inflammation [5]. Due to this property, researchers suspected that adiponectin may have a role in the development and exacerbation of COPD and investigated this issue in several studies [13].

Aim of the work

Was to assess the level of serum adiponectin in obese & non obese chronic obstructive pulmonary disease patients (COPD) during acute exacerbation and in stable conditions and to determine whether changes in its level correlate with changes in the ventilatory functions or not.

Subjects and methods

This study was conducted on 40 male patients with COPD and 15 age matched healthy subjects as controls (all COPD & controls are smokers). All COPD patients were in acute exacerbation as defined by [7]. All COPD patients and the control group were divided into non-obese and obese according to their body mass index (BMI). Those with BMI < 25 & > 18.5 were considered non-obese. Those with BMI > 30 were considered obese. Those with BMI between 25 and 30 were considered overweight and were not included in this study [19]. They were admitted to the chest department in Benha University hospital in the period between July 2010 and July 2011. The diagnosis of COPD had been established on the basis of the Global Initiative for Chronic Obstructive Lung Disease [10]. All patients for acute exacerbation COPD received adequate treatment until reach stable state with disappearance of symptoms and signs of exacerbation such as increased dyspnea, increased sputum purulence, increased sputum volume, increased cough, increased wheeze, chest tightness, increased fatigue, increased respiratory rate more than 25 breath/minute and increased heart rate by 20% above baseline. All subjects were submitted to:

(1) Full history taking (including smoking history) and clinical examination.
(2) Body mass index (BMI).
(3) Radiological examination (plain chest X ray postero-anterior and lateral views)
(4) Ventilatory function tests (spirometry) done to all cases during exacerbation and stable condition before and after bronchodilatation by using a Sensor-medics V max series, 2130 spirometer, V6200 Autobox, and 6200 DL.
(5) Laboratory tests: complete blood count, liver functions, kidney functions, ESR and fasting, postprandial blood sugar.
(6) Blood samples for adiponectin measurement: Venous blood samples were obtained between 8:00 am and 9:00 am after an overnight fast. After clotting at 48 °C, the serum was separated by centrifugation at 1000 g for 5 min at room temperature and stored at −70 °C until analysis. The serum levels of adiponectin were quantified using a sandwich enzyme–linked immunosorbent assay kit according to manufacturer’s protocol.

Principle of the assay

Adiponectin, also referred to as Acrp30, AdipoQ and GBP-28, is an 244 aminoacids protein, which is physiologically active, specifically and highly expressed in adipose cells (adipokine). Adiponectin forms homotrimers, which are the building blocks for higher order complexes found circulating in serum. This Enzyme Linked Immuno Sorbent Assay (ELISA) is based on the competition between free adiponectin and
coated adiponectin, in the presence of a known quantity of HRP labeled adiponectin antibody (tracer).

**Measurement of serum adiponectin concentration**

The serum adiponectin concentration was measured by the double antibody sandwich ELISA method with an antibody specific for human adiponectin (R&D systems).

**Exclusion criteria**

1. History of any other co-morbidities that may raise the adiponectin as, malignancy, hepatic cirrhosis, end-stage renal disease, rheumatoid arthritis and any systemic infection or inflammation [15].
2. By spirometry: reversibility in post bronchodilator FEV1 (% pred) more than 12% or 200 ml.

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation, linear correlation coefficient, analysis of variance [ANOVA] test and chi-square test by SPSSV [29].

**Results**

See Tables 1–9.

**Discussion**

COPD is considered as a multicomponent disease including weight loss, nutritional abnormalities, skeletal muscle dysfunction, risk of myocardial infarction, angina, osteoporosis, bone fracture, depression and sleep disorders [26]. Adiponectin is an adipocyte-specific protein secreted by visceral fat tissue that has anti-inflammatory as well as anti-obesity effects [17]. In patients with metabolic syndrome, adiponectin levels in plasma decreased in proportion with the increase in body weight [2]. Hypoadiponectinemia correlated with both insulin resistance [24], and atherosclerosis resulting in cardiovascular disease [14]. Adiponectin is a predominantly anti-inflammatory adipokine. Adiponectin inhibits proinflammatory cytokines, such as TNF-α, IL-6, and nuclear factor k B [16], as well as induces anti-inflammatory cytokines, such as IL-10 and IL-1-receptor antagonist [14].

The demographic data of the studied groups are illustrated in Table 1. The study included 55 subjects (7 control obese, 8 control nonobese, 20 obese COPD patients and 20 nonobese COPD patients) in this study the range of age in obese control subjects was from 43 to 59 years with the mean age 48.75 ± 5.4 years while in nonobese control subjects from 43 to 60 years with the mean age 47.75 ± 6.43 years while in obese COPD patients the range was from 45 to 60 years with the mean age 53.13 ± 5.08 years and in nonobese COPD patients the range was from 47 to 63 years with the mean age 54.88 ± 5.25 years. The range of body mass index (kg/m²) in obese control subjects was from 31.7 to 35.8 (kg/m²) with the mean body mass index 34 ± 1.3(kg/m²). While in nonobese control subjects from 22.6 to 24.9 (kg/m²) with the mean body mass index 23.5 ± 2 (kg/m²) and, in obese COPD patients the range was from 30.2 to 35.9 (kg/m²) with the mean body mass index 32.9 ± 1.9(kg/m²) and in nonobese COPD patients the range was from 19.2 to 24.9 (kg/m²) with the mean body mass index 22 ± 1.7 (kg/m²). These demographic data revealed no significant difference between control obese and non obese as regarding age while there was significant difference in body mass index between both of them. Also, there was no significant difference between obese COPD patients and non-obese COPD patients as regarding age while there was significant difference in body mass index between both of them. In this study, there was significant difference in serum adiponectin level between nonobese COPD patients during exacerbation and nonobese controls (P < 0.005) and significant difference in serum adiponectin level between obese COPD patients during exacerbation and obese controls (P < 0.05) (Table 2). And there was a significant difference in serum adiponectin between nonobese stable COPD cases and nonobese controls (P ≤ 0.005) (Table 3). Also there was a significant difference in serum adiponectin between nonobese COPD cases during exacerbation and nonobese stable COPD cases (P ≤ 0.05) (Table 4). These results were in agreement with the work done by Tomoda et al. [25] who made their study on 31 male COPD patients in stable states, they were classified according to their body mass index into groups under weight (BMI ≤ 20 kg/m. n = 19), normal weight (BMI ≥ 23 kg/m. n = 12) and age matched healthy male control subjects (n = 12). Adiponectin was measured by ELIZA. They found that the adiponectin level was significantly higher in COPD cases (under weight and normal weight) than control subjects (P ≤ 0.01). Tomoda et al. [25] study was done only on stable COPD patients but this study was done during exacerbation and during stable states. This study was in agreement with the work done by Kirdar et al. [13] who made their study on 36 male patients with

| Demographic data of studied subjects as regards, number, sex, age, & body mass index. |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Obese                           | Non Obese       | t-test          | p-value         |
| **Control**                     |                 |                 |                 |
| No.                             | 7 (100%)        | 8 (100%)        | 3.4             | > 0.05          |
| Age/years                       | 48.75 ± 5.4 R:43–59 | 47.75 ± 6.43 R:43–60 | 0.093          | > 0.05          |
| BMI (kg/m²)                     | 34 ± 1.3 R:31.7–35.8 | 23.5 ± 2 R:22.6–24.9 | 12.6           | < 0.005         |
| **COPD**                        |                 |                 |                 |
| No.                             | 20 (100%)       | 20 (100%)       | 3.8             | > 0.05          |
| Age/years                       | 53.13 ± 5.08 R:45–60 | 54.88 ± 5.25 R:47–63 | 0.677          | > 0.05          |
| BMI (kg/m²)                     | 32.9 ± 1.9 R:30.2–35.9 | 22 ± 1.7 R:19.2–24.9 | 11.9           | < 0.005         |
COPD (15 stable and 21 in exacerbation) and 17 age and sex matched healthy subjects. They found that the serum level of adiponectin was significantly higher in COPD cases than those in control subjects ($P < 0.001$) and it was significantly higher in COPD during exacerbation as compared to stable states. This study was also in agreement with work done by Xie et al. [12] who made prospective study from October 2008 to October 2009, including 30 male AECOPD patients from the emergency department, 30 male stable COPD cases from the department of respiratory disease, and 30 healthy non smoking male controls. All cases had normal weight (BMI range 18.5–24.9 kg/m) the serum and induced sputum were collected from each case. They found that the concentration of adiponectin in the serum or induced sputum in AECOPD was significantly higher than those in stable COPD or healthy non smoking controls ($P < 0.01$). The concentration of adiponectin in stable COPD was significantly higher than that in healthy non smoking controls ($P < 0.01$). The inflammation in the airway leads to pathological process of COPD. In this process, a large number of inflammatory cells accumulate in the airway including neutrophils and macrophage. They release various inflammatory mediators, causing pulmonary damage [23]. COPD is also a kind of systemic inflammatory disease [28] and is characterized with abnormal activation of inflammatory cells and the abnormal increase of circulating cytokines, including CRP, IL-8, TNF-α, IL-6 and Leptin. Adiponectin is a newly discovered cytokines [13]. Neutrophils are the main inflammatory cells in the airway of COPD patients, especially in AECOPD patients. By the action of various inflammatory factors, neutrophils rapidly move to the airway through trans-
epithelial transport and cause degranulation [9]. Various inflammatory mediators are released in degranulation, promoting inflammatory reaction. Epithelial cells in the airway will stimulate expression of IL-8 under APN [20]. Adiponectin is able to inhibit macrophages producing TNF-α and reduce its synthesis and biological activity, suggesting that APN has some anti-inflammatory effects [18]. So adiponectin could play both pro-inflammatory and anti-inflammatory roles. APN could be a new marker of COPD inflammation. A further rise in serum adiponectin in the exacerbation period denotes that it may be a biomarker of inflammation in COPD patients during exacerbation. In this study, there was a significant difference in serum adiponectin between obese COPD cases during exacerbation and obese control (P ≤ 0.05) (Table 2). And there was a significant difference between obese stable COPD cases and obese control (P ≤ 0.05) (Table 3). But there was no significant difference between obese COPD cases during exacerbation and during stable state (Table 4). Very little researches were found discussing the role of serum adiponectin in obese COPD patients during exacerbation and during stable conditions. So, this study tried to find out if adiponectin plays a role in such patients. In healthy subjects, adiponectin carries out its roles for preventing development of vascular changes and the impairment of glucose and lipid metabolism, which may be induced by a variety of attacking factors, such as chemical subjects, mechanical stress, or nutritional loading. A large amount of adiponectin flows with the blood stream in the inside of vascular walls, it would be interesting to know whether adiponectin can enter the vascular walls. Adiponectin has potential inhibitory activities of these atherogenic cellular phenomena. Adiponectin was shown to inhibit the TNF-α-induced nuclear factor-KB activation through the inhibition of I Kb phosphorylation, which might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells [25]. Adiponectin also inhibits the expression of the scavenger receptor type A-1 of macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation [1]. In addition, adiponectin inhibits the proliferation and migration of smooth muscle cells, from these vascular cellular functions, adiponectin may have a potential antiatherogeneity. So, based on the above mentioned, serum levels of adiponectin may play a role in obese COPD patients, it is known that acute exacerbations of COPD (most often in response to bacterial infection) are associated with increased serum of CRP, IL-6, TNF-α, leptin, and adiponectin, as well as with increases in other factors associated with bacterial inflammation and infection. This suggests that the elevation of plasma adiponectin level in obese COPD may be associated with other pathophysiological findings beside body weight in COPD. Tomoda et al. [25] detected that adiponectin was approximately 2-fold higher in normal weight, stable COPD cases than in controls. Kirdar et al. [13] also detected approximately 2-fold higher adiponectin levels in COPD cases with normal BMI than controls. In addition they reported higher adiponectin levels in the exacerbation period compared to those in stable patients, indicating augmented inflammatory response. It was concluded from the above studies that serum level of antiobesity adipokine adiponectin was significantly higher even in COPD cases with normal BMI than the level in healthy subjects indicating that serum level of adiponectin rises earlier than body weight loss as a component of systemic inflammatory response. Many studies reported elevated serum of adiponectin in underweight COPD cases and in normal weight but there was no direct comparison between nonobese and obese COPD cases as in such studies. In Table 5 serum adiponectin was compared between nonobese and obese COPD cases during exacerbation and during stable states. It was found that, there was a statistically highly significant difference in serum adiponectin (mcg/ml) between nonobese COPD cases and obese COPD cases during exacerbation and also during stable states (P < 0.001). It was previously demonstrated that in obese patients, adiponectin levels significantly decreased. Adiponectin is an adipocyte-specific protein secreted by visceral fat tissue that has anti-inflammatory as well as antiobesity effects [17]. In patients with anorexia nervosa and cachexia, plasma adiponectin levels were elevated [27]. COPD is a syndrome rather than a single disease because there are two major phenotypes in COPD. One is the emphysema-dominant type, so-called “pink puffers,” who are frequently cachectic. Another is the airway disease-dominant type, so-called “blue bloaters,” who are frequently obese. It was demonstrated that BMI might be one of the determinants of COPD phenotype [11]. In the present study serum levels of adiponectin remarkably elevated in nonobese COPD cases rather than obese COPD cases. And this may be explained by hyperinflation, one of the physiologic characteristics of COPD, is caused by air trapping. Hyperinflation is known to cause diaphragm dysfunction [21] which results in an increase in respiratory effort [22]. The increase in respiratory effort correlates with overload of respiratory muscles and excess respiratory exercise [8]. Some studies reported changes in plasma adiponectin levels by exercise in different populations, these studies generally revealed that chronic exercise, but not short-time exercise, increased plasma adiponectin levels and enhanced expression adiponectin receptor I in skeletal muscles. Adiponectin receptor I promotes glucose uptake and lipid oxidation in the muscle [3,30]. Hyperinflation is associated with hypermetabolism and malnutrition in COPD [8]. The present study demonstrated that even in obese patients with COPD, plasma adiponectin levels elevated. These results suggest that persistent excess respiratory exercise causing hyperinflation elevates plasma adiponectin levels before body weight loss and that the elevated adiponectin may contribute to the development of malnutrition in COPD. In the present study, correlations of changes in ventilatory function tests with changes in serum adiponectin were done in all COPD cases (nonobese and obese) during exacerbation and during stable conditions. There were lack of correlation between changes in serum adiponectin and changes in FVC (% pred) in nonobese COPD and obese COPD cases from exacerbation to stable state.

| Table 9 Correlation between changes in serum adiponectin (mcg/ml) and changes in FEF 25–75 (% pred) in nonobese and obese COPD cases from exacerbation to stable states. |
|---------------------|-----|
| r       | p       |
| Non obese | -0.241 | > 0.05 |
| Obese    | 0.241  | > 0.05 |
There were also lack of correlation between changes in serum adiponectin and changes in FEV1 (% pred) in nonobese COPD and obese COPD cases from exacerbation to stable state (Table 7). There were also lack of correlation between changes in serum adiponectin and changes in FEV1/FVC ratio in nonobese COPD and obese COPD cases from exacerbation to stable state (Table 8). And there were also lack of correlation between changes in serum adiponectin and changes in FEF25-75 (% pred) in nonobese COPD and obese COPD cases from exacerbation to stable state (Table 9). So, no correlations were observed between changes in ventilatory function tests and changes in serum adiponectin level. These results were in agreement with the work done by Tomoda et al. [25] in which FEV1 did not correlate with plasma adiponectin levels but this study was done in nonobese. Also, this study was in agreement with the work done by Kirdar et al. [13] in which there was no correlation between FEV1 and plasma adiponectin levels during exacerbation or during stable conditions.

Conclusions

1. Serum adiponectin level is raised in nonobese COPD cases and the rising is more during exacerbation.
2. Serum adiponectin level is raised in obese COPD cases during exacerbation and during stable conditions.
3. Serum adiponectin level is raised in nonobese COPD cases more than in obese COPD cases.
4. There was lack of correlation between changes in serum adiponectin and ventilatory functions.

Conflict of interest

None declared.

References


