Evaluation of inflammatory markers in relation to serum level of adiponectin in obese asthmatic patients

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Context
Obesity and asthma are major public health problems affecting large numbers of population across the world. Obesity induces some physiological and metabolic changes, which are associated with the development of asthma. Inflammation in adipose tissue could lead to airway inflammation causing asthma in the setting of obesity.

Aim
The aim of this study was to compare the serum level of adiponectin and inflammatory markers [tumor necrosis factor α and C-reactive protein (CRP)] in obese asthmatic patients versus nonobese asthmatic patients compared with a third control group of healthy individuals of the same age and sex.

Settings and design
The study included two patient groups, and a third one served as a control group. The study was carried out in the Pulmonology and Internal Medicine Departments and Outpatient Clinics in Alexandria Main University Hospital.

Materials and methods
Anthropometric measurements (BMI, waist circumference, and waist to hip ratio) were obtained. Serum adiponectin, tumor necrosis factor α, and CRP levels were measured. Routine laboratory investigations, lipid profile, and blood glucose tests were performed in all studied groups.

Results
The mean serum level of CRP was more elevated in the obese patients in comparison with the control group ($P = 0.002$) and was also elevated in the normal weight asthmatic patients in comparison with the control group ($P < 0.001$). The mean adiponectin serum level was significantly lower in obese asthmatic patients than in normal weight asthmatic patients, and significantly lower in nonobese asthmatic patients in comparison with controls ($P < 0.001$ for each).

Conclusion
Prevention of obesity may be the most beneficial therapy for the obesity–asthma phenotype, and modulating adiponectin may open a unique and innovative approach toward managing asthma.

Keywords:
bronchial hyper-responsiveness, C-reactive protein, high-density lipoprotein, interleukin-6, low-density lipoprotein, plasminogen activator inhibitor-1, triglycerides, tumor necrosis factor α, waist circumference, waist to hip ratio

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Introduction

Obesity is often defined as a condition of abnormal or excessive fat accumulation in adipose tissue that is regarded as a chronic inflammatory state, gravely enough to the extent that it impairs both physical and psychosocial health and well-being. Obesity can also be defined as increase in body fat mass percent or content [1]. Obesity is caused by a complex interplay of genetic, environmental, and metabolic programming, especially early in life, and lifestyle habits [2].

The most common and accepted classification of weight is based on BMI, calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). This categorizes adults into underweight (BMI<18.5), normal (BMI: 18.5–24.9), overweight (BMI: 25–29.9, also called preobese), and obese (BMI≥30) [3].

Recently, the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) has proposed a new classification that incorporates not only assessment of body mass but also validated ethnicity-adjusted

anthropometrics to identify individuals with increased adipose tissue, placing them at risk and the presence and severity of obesity-related complications [4].

Adipocytes typically constitute the majority of adipose tissue cellular content, and they are surrounded by fibrous connective tissue, collagen, nerves, and blood vessels [5].

Adipose tissue has been termed as an endocrine organ, because it secretes adipocytokines and other vasoactive substances into the blood stream, which can influence the function and structural integrity of target tissues, including adiponectin, leptin, resistin, tumor necrosis factor α (TNF-α), plasminogen activator inhibitor-1, angiotensin II, interleukin-6 (IL-6), and soluble preadipocyte factor, together with the relatively new adipokines (apelin, eotaxin, visfatin, chemerin, and omentin) [6].

Bronchial asthma is a clinical syndrome characterized by a state of airway inflammation and increased bronchial reactivity, leading to episodic reversible airway obstruction. Asthma results from complex interactions of inflammatory cells, their mediators, airway epithelium and smooth muscle, and the nervous system. In genetically susceptible individuals, these interactions can lead the patient with asthma to symptoms of breathlessness, wheezing, cough, and chest tightness [7].

A growing body of literature suggests that asthma is more likely to occur in obese patients. There are several hypotheses, such as mechanical effects in the lungs or systemic inflammatory roles of visceral fat adipokine secretion or by other influences [8].

Inflammatory effects of obesity on bronchial asthma

In the setting of obesity, the ability of adipose tissue to elaborate inflammatory cytokines, including TNF-α and C-reactive protein (CRP), increases, whereas the synthesis of adiponectin, which possesses anti-inflammatory properties, declines. Inflammatory mediators produced in adipose tissue spill over into the peripheral circulation and contribute to a low-grade state of chronic systemic inflammation because of the relatively high level of these mediators in asthmatic visceral adipose tissue, which drains into the portal circulation and subsequently passes through the vasculature of the lung [9,10].

TNF-α was found to induce IL-13 and cytokine transforming growth factor β release from allergic eosinophils and alveolar macrophages, thereby playing crucial roles in asthmatic airway remodeling [11]. TNF-α is also expressed in increased amounts by mast cells [12] and present in increased concentrations in bronchoalveolar fluid from the airways of patients with asthma [13]. Increased CRP levels are strongly and independently associated with respiratory impairment and more frequent bronchial hyper-responsiveness. These results suggest that both respiratory impairment and bronchial hyper-responsiveness are associated with a systemic inflammatory process [14]. Moreover, adipose tissue can respond to proinflammatory stimuli initiated in the lung and exacerbate adipokine production [15,16]. Given the presence of adiponectin and its receptors in the lung, it is conceivable that the loss of the anti-inflammatory effects of adiponectin in obesity contributes to asthma prevalence or severity.

Other adipokines such as leptin and eotaxin are also involved in the pathogenesis of bronchial asthma [17].

The aim of the study was to determine the association of obesity with asthma by comparing the serum level of adiponectin and inflammatory markers (TNF-α and CRP) in obese asthmatic patients versus nonobese asthmatic patients compared with a third control group of healthy individuals of the same age and sex.

Patients and methods

The study included 60 asthmatic patients of both male and female sex with age between 17 and 79 years attending the Outpatient Clinic as well as inpatients of the Pulmonology and Internal Medicine Departments in Alexandria Main University Hospital. The patients were categorized into two groups. Group I included 30 asthmatic obese patients with a BMI of 30 or greater, and group II included 30 asthmatic nonobese patients with BMI less than 25. Individuals with diabetes mellitus, renal failure, hepatic failure, respiratory failure, other endocrinal dysfunction, or receiving systemic steroids for the past 3 months were excluded. A third group (group III) including 10 healthy age-matched individuals served as a control group.

Anthropometric measurements other than BMI were obtained, including waist circumference (WC) and waist to hip ratio (WHR). Serum adiponectin, TNF-α, and CRP levels were measured in all studied groups using enzyme-linked immunosorbent assay. Laboratory investigations included routine test such as complete blood count, liver enzymes, and renal function tests (to exclude systemic diseases), and lipid profile (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides) and blood glucose levels (fasting and 2-h postprandial) were also performed.

Statistical analysis

Data were fed into the computer and analyzed using IBM SPSS software package (version 20.0) (Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp). Qualitative data were described using number and percentage. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level.

Results

Higher levels of blood glucose, triglycerides, total cholesterol, and low-density lipoprotein and lower levels of high-density lipoprotein were detected in obese patients. Moreover, obese patients have larger WC and WHR in comparison with the normal weight asthmatics and controls.

The mean CRP of the obese asthmatic group (3.03 ± 2.34 mg/l) was found to reach higher levels compared with nonobese asthmatic patients (2.46 ± 1.30 mg/l), although it did not reach a significant statistical difference. However, it was significantly higher in both obese asthmatics and normal weight asthmatics in comparison with controls (1.37 ± 0.61 mg/l) (Table 1).

As regards TNF-α, our study showed no significant statistical difference when comparing mean TNF-α between the three groups (Table 1). A significant direct correlation was observed between CRP with TNF-α in obese and normal weight asthmatic patients, with a *P* value of 0.029 (Fig. 1).

The mean serum adiponectin was significantly low in obese asthmatic patients (2.29 ± 0.09 ng/ml) compared with nonobese asthmatic (2.50 ± 0.12 ng/ml) and normal individuals (2.69 ± 0.14 ng/ml). It was also significantly low in asthmatic normal weight persons in comparison with healthy individuals (Table 1). Serum adiponectin level was negatively correlated with BMI, WC, and WHR in the asthmatic group (obese and normal weight) ($P < 0.001$) (Figs. 2-4).

Table 1 Comparison of inflammatory markers (tumor necrosis factor α, C-reactive protein) and adiponectin serum levels in the three studied groups

Total samples	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=10)
Serum CRP (mg/dl)			
Minimum-maximum	1.05-13.40	1.09-5.70	0.80-2.80
Mean±SD	3.03±2.34	2.46±1.30	1.37±0.61
Median	2.45	2.15	1.15
Significance between groups	P_1=0.297, P_2<0.001*, P_3=0.002*		
Serum TNF-α (pg/ml)			
Minimum-maximum	0.79-225.33	1.58-193.51	2.57-75
Mean±SD	23.01±51.66	13.13±35.04	11.52±22.34
Median	4.55	4.94	4.64
Significance between groups	P_1=0.824, P_2=0.864, P_3=0.803		
Serum adiponectin (ng/ml)			
Minimum-maximum	2.14-2.50	2.33-2.85	2.50-2.98
Mean±SD	2.29±0.09	2.50±0.12	2.69±0.14
Median	2.30	2.45	2.67
Significance between groups	P_1<0.001*, P_2<0.001*, P_3<0.001*		

P value < 0.05 is statistically significant. CRP, C-reactive protein; TNF-α, tumor necrosis factor α.

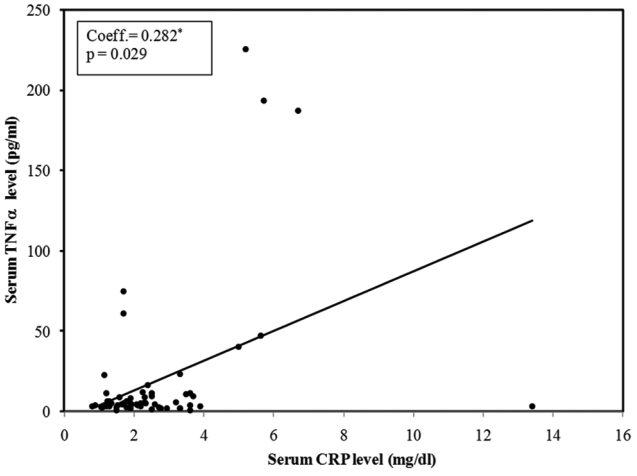
Discussion

In our study, we report that the proinflammatory CRP is increased in the obesity state, whereas the anti-inflammatory adipocytokine adiponectin is reduced.

This is supported by many studies, such as the study by Bahceci *et al.* [18], which showed that the mean TNF-α, CRP, and IL-6 levels were higher in obese patients than in controls and were positively correlated with adipocyte size. Therefore, adiposity may be an inflammatory condition. Our study is also consistent with the study by Sahoo *et al.* [19], which suggests that CRP levels may be used as a systemic biomarker for the lung inflammation in asthmatic patients as it can be easily measured compared with other biomarkers. This has led to the speculation that proinflammatory cytokines may augment airway inflammation, producing asthma in obesity.

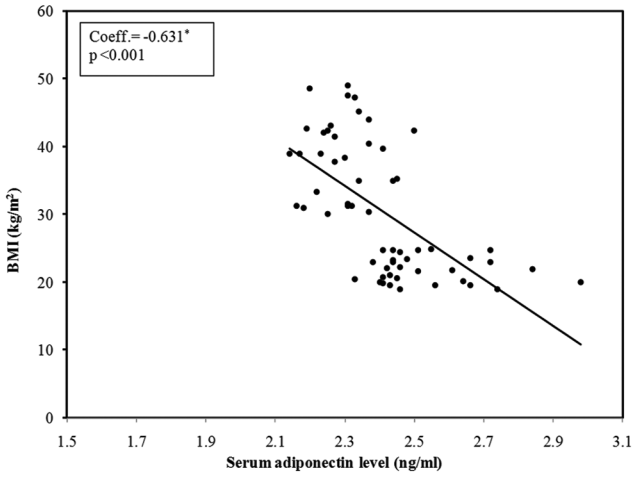
Hypoadiponectinemia observed in patients with obesity in this study is similar to those previously recorded in the literature. It is known that circulating levels of these

Figure 1



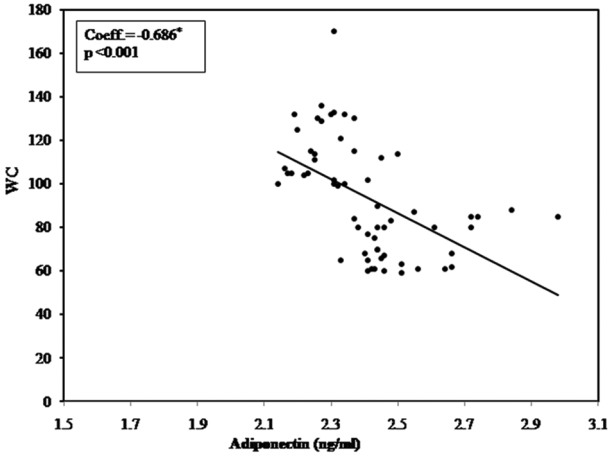
Correlation between serum tumor necrosis factor α (TNF-α) with serum C-reactive protein (CRP) levels in obese and normal weight asthmatic patients.

Figure 2



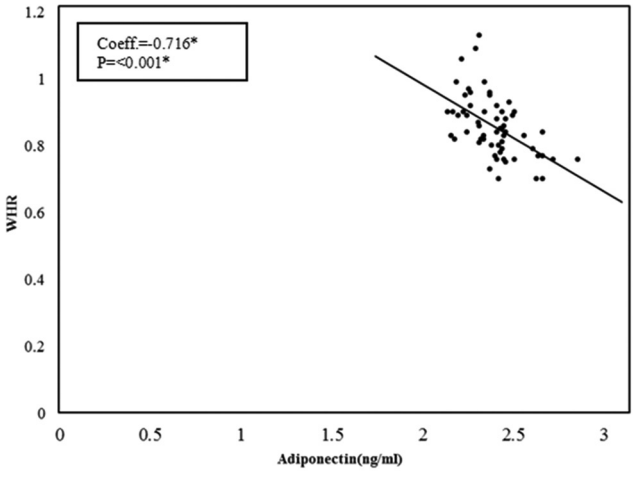
Correlation between serum adiponectin with BMI in obese and normal weight asthmatic patients.

Figure 3



Correlation between serum adiponectin with waist circumference (WC) in obese and normal weight asthmatic patients.

Figure 4



Correlation between serum adiponectin level and waist to hip ratio (WHR) in obese and normal weight asthmatic patients.

hormones are largely determined by adipose tissue mass; their biochemical and functional effects are magnified in the obese individuals. Adiponectin, however, generally acts as an anti-inflammatory hormone and is reduced by obesity. One possible explanation is that hypoxia-related necrosis of adipocytes activates macrophages in obese individuals [20]. These activated macrophages produce TNF-α and IL-6, which in turn may directly inhibit the local production of adiponectin in a paracrine manner [21].

Supporting our results, some studies demonstrated that low serum total adiponectin concentrations are associated with a greater risk for asthma [22]. Moreover, Ali Assad and Sood [23] demonstrated that serum adiponectin concentrations are protective against asthma among premenopausal women and peripubertal girls. Some other studies showed that serum adiponectin concentrations are inversely associated with asthma severity among boys but positively associated among men.

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Conflicts of interest
There are no conflicts of interest.

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