

Leptin as a local inflammatory marker in chronic obstructive pulmonary disease acute exacerbation

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Background Chronic obstructive pulmonary disease (COPD) is a disease of chronic inflammation affecting the lungs. Leptin is a pleiotropic cytokine thought to play a role in host inflammatory response.

Aim This study aimed to investigate the role of leptin in sputum and serum as an inflammatory marker in acute exacerbation of COPD (AECOPD).

Patients and methods Twenty patients with stable COPD, 20 patients with AECOPD, and 12 controls were included in this study. All participants were males. BMI, routine laboratory investigations, sputum and serum leptin levels, serum tumor necrosis factor (TNF- α), and C-reactive protein (CRP) levels were measured twice in patients with AECOPD (initially and after 7 days of management) and only once in stable patients and controls.

Results In patients with patients with AECOPD, there were significant differences between sputum leptin and serum TNF- α , CRP, and leptin levels before and after treatment. Sputum leptin and serum CRP levels were significantly higher in the AECOPD group than other groups. Additionally, serum TNF- α levels were significantly higher in patients with

AECOPD than the controls. Insignificant correlation was found between AECOPD and stable groups regarding serum leptin and TNF- α levels.

Conclusion The present study highlights the role of leptin hormone as a local inflammatory marker in COPD acute exacerbation either in the sputum or the serum, together with serum TNF- α and CRP. These markers could be useful indicators of COPD acute exacerbation and its response to treatment.

Egypt J Bronchol 2019 13:139–147

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Egyptian Journal of Bronchology 2019 13:139–147

Keywords: chronic obstructive pulmonary disease, exacerbation, leptin

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Received 1 October 2018 **Accepted** 28 January 2019

Introduction

Leptin is a hormone that is synthesized and secreted from the adipose tissue. Leptin is derived from the Greek word 'leptos', which means thin or small. Discovered in 1994, leptin is a product of the *obese (ob)* gene. Adipose tissue is responsible for its synthesis and secretions. Leptin receptor (OB-R), which is one of the cytokine class I receptors, is responsible for mediating the main actions of this hormone [1]. Serum leptin levels are markedly affected by the total fat mass and fat cell volume [2]. Factors that upregulate the production of leptin by adipose tissue are obesity, insulin stimulation, glucocorticoids, acute infections, and under the influence of certain cytokines such as interleukin-1 (IL-1) [3]. Through regulating appetite at the hypothalamic appetite centers, leptin plays a fundamental role in the control of food intake and energy expenditure [4]. In patients with chronic obstructive pulmonary disease (COPD), it was hypothesized that leptin is much more expressed in the lung epithelial cells. Leptin immunoreactivity in lung tissues was observed in bronchial epithelial cells, type II pneumocytes, macrophages (tissue/alveolar), and interstitial lymphocytes [5]. Moreover, it was noticed that serum leptin values are significantly elevated in patients with COPD during acute exacerbation versus controls [6]. Severity of COPD is contributed to comorbidities and rate of exacerbations [7].

Acute exacerbation of COPD is diagnosed by worsening of the patient's baseline clinical condition necessitating change in the daily used medications [8]. Exacerbations of COPD are crucial events along the course of the disease, which have influences particularly on the patient's quality of life [9], and also have effects on symptoms and lung functions that may persist for several weeks [10]. These episodes usually accelerate the rate of lung function decline [11] and are associated with significant mortality, particularly in those requiring hospitalization [12].

Aim

The aim of this study is to evaluate the role of leptin hormone as a local inflammatory marker in patients with COPD during the periods of exacerbation.

Patients and methods

This prospective cohort study was performed in Chest Department, Kasr Al-Aini Hospital, Cairo

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University, over a period of 6 months. This work was approved by the ethical committee of the Faculty of Medicine, Cairo University. It was carried on 52 participants after obtaining their consents, who were divided into three groups: group 1 included 20 patients with acute exacerbation of COPD (AECOPD), group 2 had 20 stable patients with COPD, and group 3 contained 12 healthy volunteers as controls (smokers with normal pulmonary function test). All these participants were males.

Inclusion criteria

The following were the inclusion criteria:

- (1) Patients proved to have COPD by history of dyspnea, chronic cough, and sputum production. In addition, a history of exposure to risk factors for the disease and postbronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) less than 0.70 confirm the presence of persistent airflow limitation [7].
- (2) Patients with stable COPD were further classified according to risk stratification into low- and high-risk patients (combined COPD assessment) [7].
- (3) Patients with COPD proved to develop acute exacerbation by an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation [7].
- (4) Control group included healthy individuals, comprising smokers with normal pulmonary function test result.

Exclusion criteria included factors that affect leptin, C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α) levels in serum such as tuberculosis, ischemic heart disease, malnutrition, and malignancies, as well as BMI less than 19 and more than 29 kg/m².

All these participants were subjected to full medical history including smoking history, clinical examination, BMI calculation, and routine investigations including chest radiography. Pulmonary function testing in the form of spirometry was performed for all the study participants by using ZAN 100 spirometer (ZAN Messgeraete GmbH Company, Oberhulba, Germany), including prebronchodilator/postbronchodilator FEV1, FVC and FEV1/FVC ratio to diagnose and measure the degree of airway obstruction.

Determination of leptin level (both in sputum and serum) beside serum levels of TNF- α and CRP was performed in all these participants; these

inflammatory markers were measured using by sandwich enzyme-linked immunosorbent assay.

Sputum samples were taken at the morning before breakfast, either spontaneously expectorated or induced by hypertonic saline nebulization. For serum levels of inflammatory markers, 5 ml of venous blood sample was collected in sterile serum separator tube vacutainers. Serum and sputum samples were collected and stored in refrigerator at -20°C. Two samples were taken from the first group, which included patients with AECOPD, on day 0 (before treatment) and on day 7 after treatment, whereas only one sample was collected from stable patients with COPD and the control groups.

Statistical analysis

Results are presented as mean \pm SD for normally distributed variables. Differences between the groups were analyzed using the Mann-Whitney *U*-test. Correlations between parameters were calculated with Pearson's rank correlation analysis using SPSS, version 10.1 for Windows (SPSS Inc., Chicago, Illinois, USA). Significance was assessed at a *P* value of 0.05.

Results

Fifty-two participants formed the whole study population. They were divided into three groups: group 1 included 20 patients with COPD with acute exacerbation, group 2 included 20 stable patients with COPD, and group 3 contained 12 controls.

Table 1 shows the demographic data of all the participants. All of them were males and above the age of 40 years. The mean age for group 1 was 58.8 years, for the second group was 59.1 years, and for the controls was 52.5 years. There were no significant statistical differences among all the study participants regarding their smoking indices and BMI.

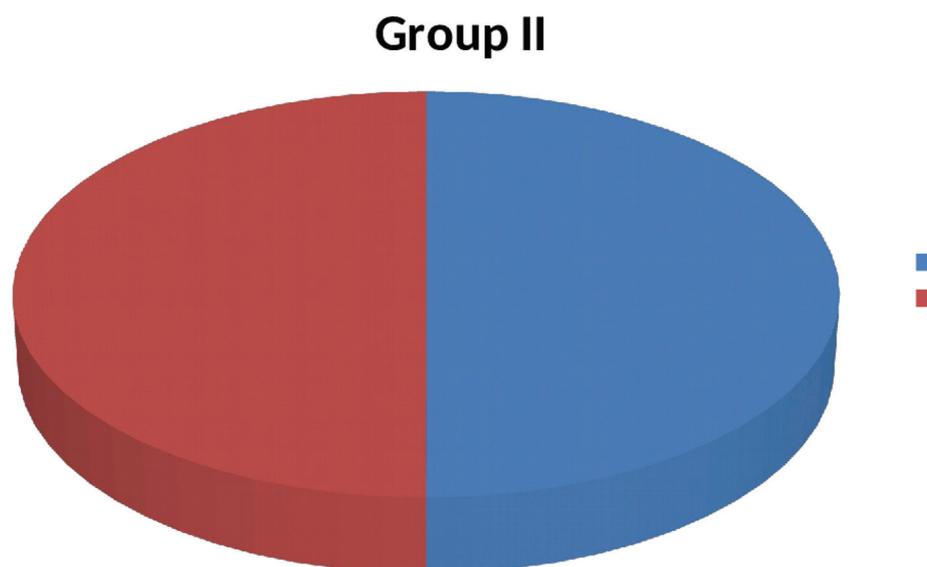
In Fig. 1, patients of group 2 (stable COPD) were further classified according to the risk stratification by

Table 1 Demographic data of the study population

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	Group 3 (mean \pm SD)	<i>P</i> value
Age (years)	58.8 \pm 9.56	59.1 \pm 9.22	52.5 \pm 9.8	0.146
BMI (kg/m ²)	23.85 \pm 2.94	24.8 \pm 2.67	24.17 \pm 2.76	0.518
Smoking index (pack year)	56.45 \pm 23.28	57.65 \pm 23.34	44 \pm 20.76	0.188

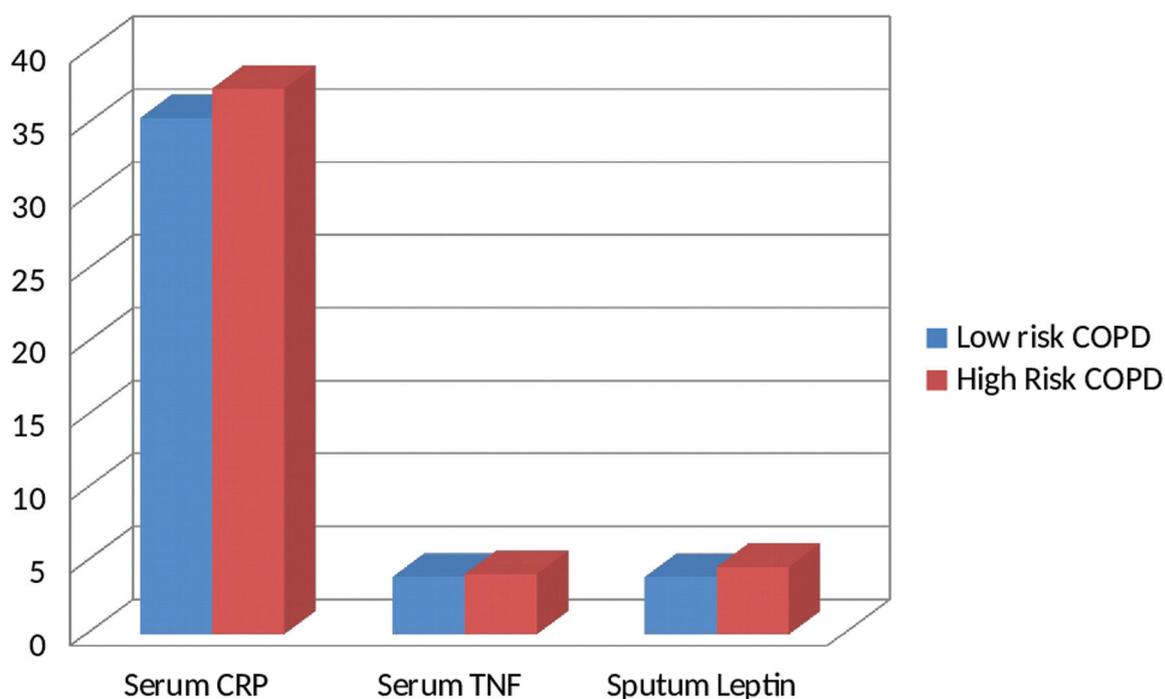
Smoking index pack year: number of packs (20 cigarettes) smoked daily for a year.

Figure 1



Risk stratification according to GOLD classification [7].

Figure 2



Correlation between serum CRP, TNF- α , sputum leptin in low- and high-risk patients. COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; TNF- α , tumor necrosis factor.

GOLD 2015 into low-risk and high-risk patients [7]. Half of them ($n=10$) were of low risk, and the rest were considered as high-risk patients with COPD.

Figure 2 shows that sputum leptin, serum TNF- α , and serum CRP levels were higher in the high-risk patients with COPD in comparison with the low-risk patients, but these correlations were not statistically significant.

In Table 2, regarding the sputum leptin level, it was found to be higher in COPD exacerbation group (group 1) as compared with the COPD stable group (group 2) and also when compared with the controls (group 3). These differences were found to be statistically significant, with P value less than 0.001. Nonsignificant higher value of mean serum TNF- α level was found within the COPD exacerbation group when compared with the stable COPD group and the

controls. Regarding serum CRP level, it was found to be higher in COPD exacerbation group followed by the stable COPD group and then the control group. It was observed that the differences among all groups regarding serum CPR levels were statistically significant, showing a *P* value less than 0.001. Statistical comparison regarding serum leptin levels among the three groups was not significant; however, it showed a higher value in group 2 compared with groups 1 and 3.

In Fig. 3, mean level of sputum leptin was higher in group 1 patients than in group 2 patients, and this correlation was statistically significant (*P*<0.001). It was also found that CRP levels in serum samples were higher in group 1 compared with group 2, with

Table 2 Statistical comparison among the study groups regarding mean values of sputum leptin, serum tumor necrosis factor- α , C-reactive protein, and leptin level

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	Group 3 (mean \pm SD)	<i>P</i> value
Sputum leptin (mg/l)	5.37 \pm 2.05	3.27 \pm 1.22	2.80 \pm 1.96	<0.001
Serum TNF- α (mg/l)	4.24 \pm 1.55	3.84 \pm 1.40	2.91 \pm 1.32	0.066
Serum CRP (mg/l)	62.75 \pm 49.23	10.4 \pm 16.70	4.08 \pm 2.57	<0.001
Serum leptin (mg/l)	2.37 \pm 2.46	2.48 \pm 2.10	1.35 \pm 1.40	0.205

CRP, C-reactive protein; TNF- α , tumor necrosis factor- α .

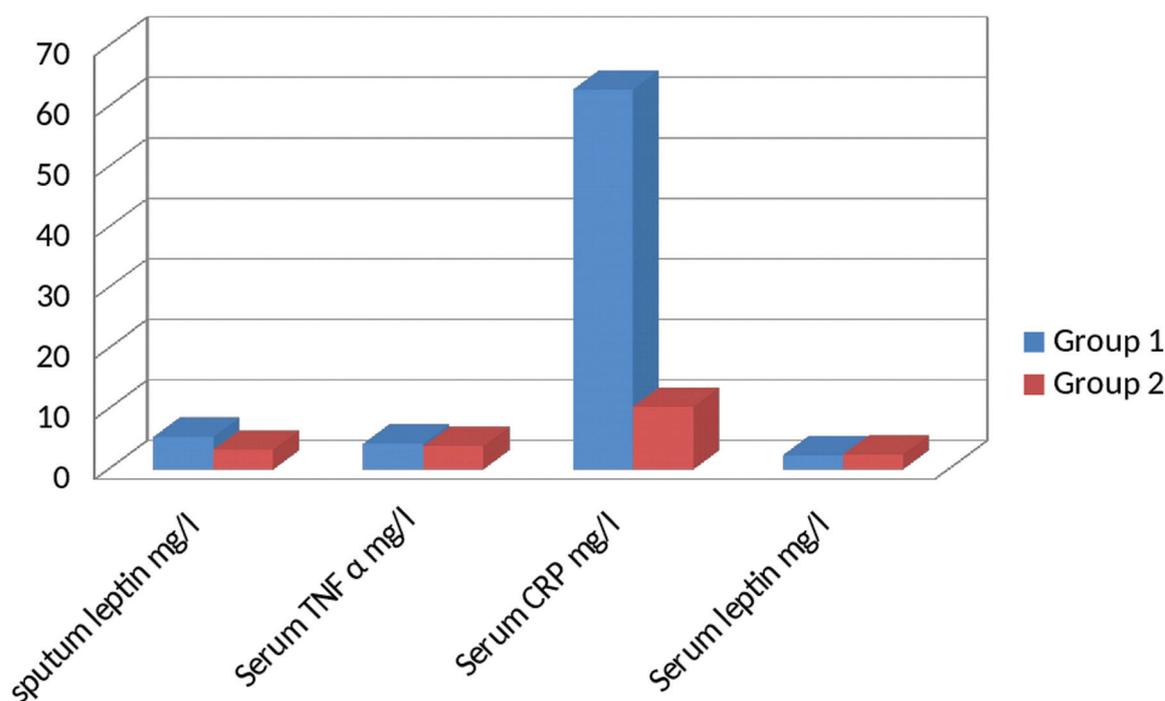
significant statistical difference. Differences between these two groups regarding serum TNF- α did not show any significant statistical value. Although it was found that mean value of serum leptin level was higher in stable COPD group than in AECOPD group, it did not show any significant statistical difference.

In Fig. 4, significant statistical differences were found in sputum leptin levels between group 1 (AECOPD) patients and group 3 (controls), where it was higher in group 1 than in the latter. Moreover, serum CRP levels were higher in group 1 as compared with group 3, and these correlations showed significant statistical differences. Higher mean value of serum TNF- α level was shown in group 1 as compared with group 3 (controls), with a significant difference. The difference between these two groups regarding serum leptin was not considered statically significant.

In Fig. 5, it was found that the mean values of sputum leptin, serum TNF- α , CRP, and leptin levels were higher in group 2 (stable COPD) patients than in group 3 (controls), but these correlations did not show any significant statistical differences.

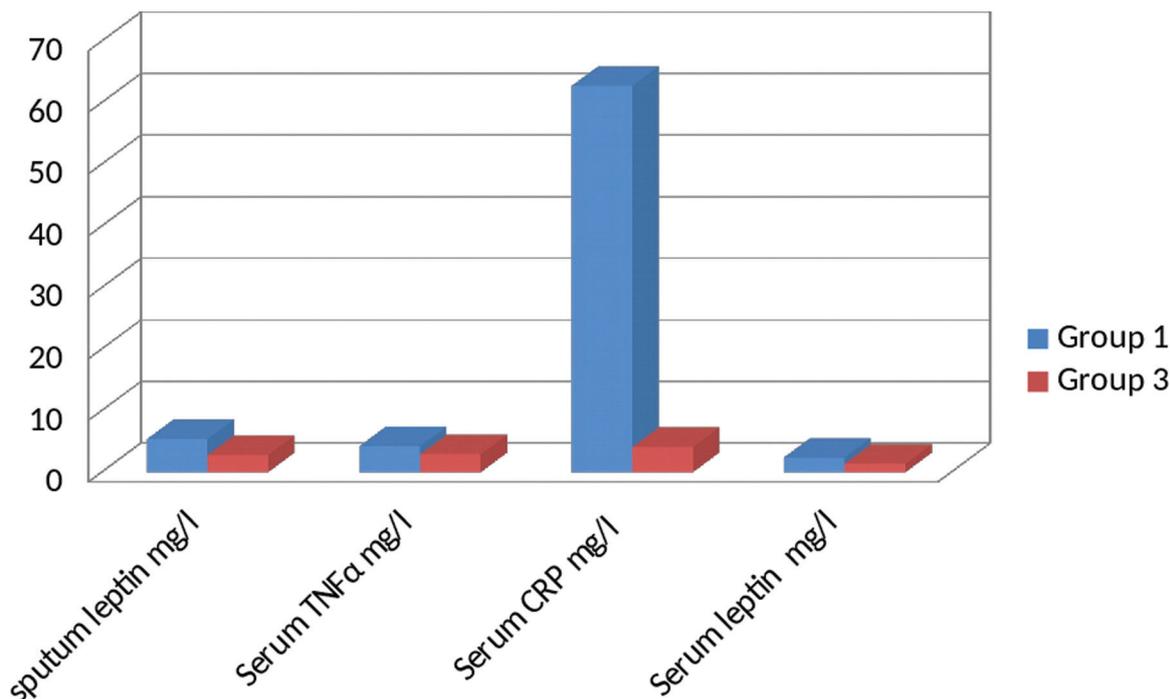
Figure 6 shows that all the inflammatory markers included in our study showed a significant reduction in their levels when repeated 7 days after initiation of treatment within group 1, which included patients with

Figure 3



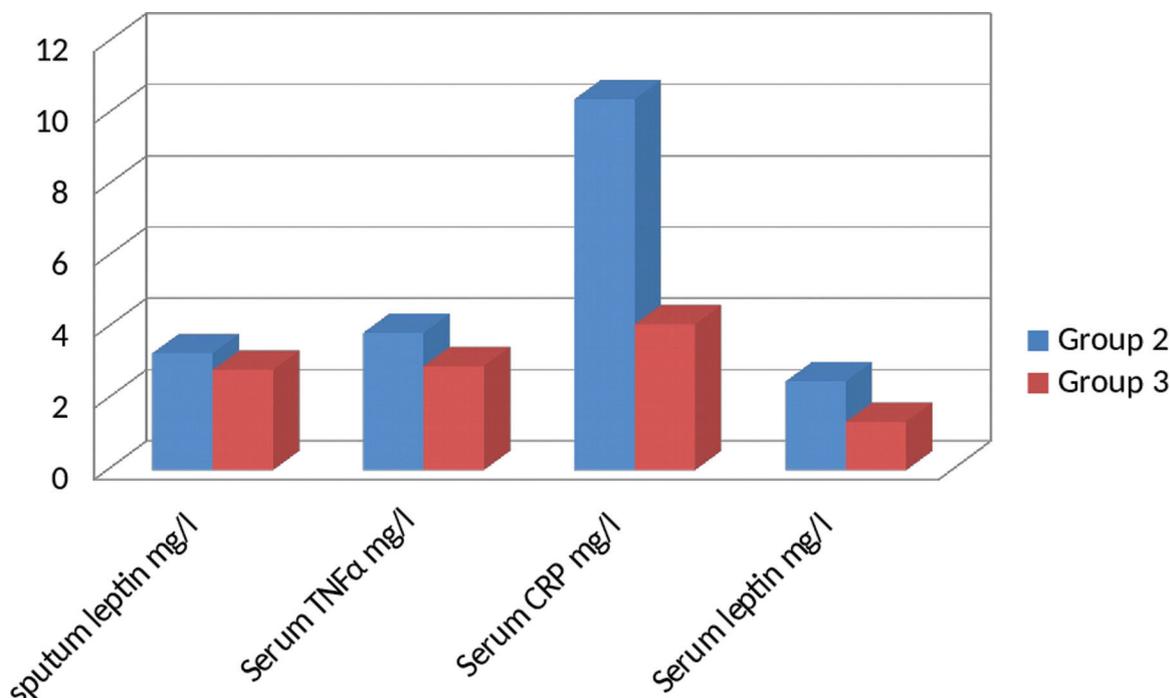
Correlation between mean sputum leptin, serum TNF- α , CRP, and leptin levels in group 1 and group 2. CRP, C-reactive protein; TNF- α , tumor necrosis factor.

Figure 4



Correlation between sputum leptin, serum TNF- α , CRP, and serum leptin levels in group 1 and group 3. CRP, C-reactive protein; TNF- α , tumor necrosis factor.

Figure 5

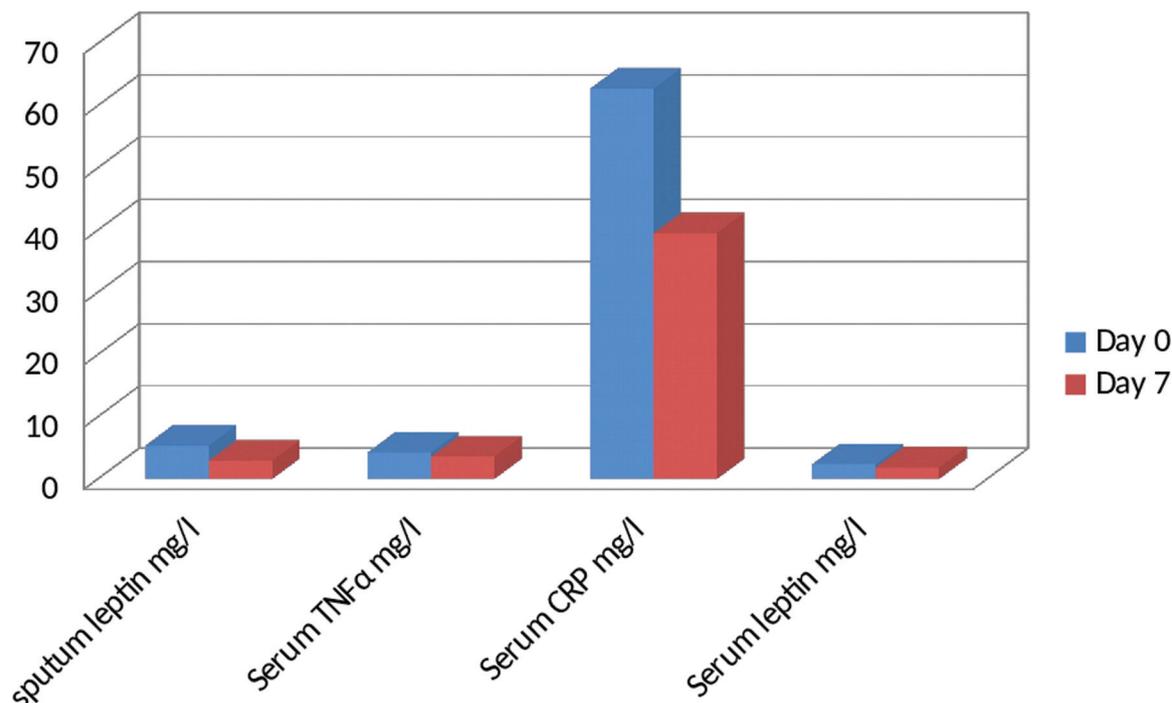


Correlation between sputum leptin, serum TNF- α , CRP, and leptin levels within group 2 and group 3. CRP, C-reactive protein; TNF- α , tumor necrosis factor.

COPD acute exacerbation. The mean level of sputum leptin on day 0 was 5.37 mg/l and became 2.95 mg/l on day 7. Regarding serum TNF- α level, the mean value at day 0 was 4.24 mg/l followed by a mean of 3.59 mg/l on

day 7. Regarding serum CRP level, the mean at day 0 was 62.75 mg/l and on day 7 was 39.5 mg/l. Moreover, serum leptin levels showed significant differences when repeated 7 days after treatment (the mean at day 0 was

Figure 6



Correlation between sputum leptin, serum TNF- α , CRP, and leptin levels in group 1 patients with AECOPD on day 0 and day 7 after treatment. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C-reactive protein; TNF- α , tumor necrosis factor.

2.37 mg/l and at day 7 was 1.82 mg/l). All these correlations showed significant statistical values ($P < 0.001$).

Discussion

In our study, all the participants were males, and this was intended to alleviate the sex differences, which could affect levels of leptin [13]. They were above the age of 40 years, and this was consistent with many authors who declared that COPD is more prevalent among the elderly [14,15], which may be related to the structural and functional changes affecting the lungs by age and also the cumulative effects of exposure to risk factors especially tobacco smoking [16]. Hence, it was found that leptin level is affected by the BMI [17]. BMI was limited in our study to be between 19 and 29 kg/m² to overcome this effect (Table 1). As per our study methodology, controls were selectively smokers to adjust the systemic inflammatory response attributed to smoking itself [16]. There was no significant statistical difference between all the study participants regarding smoking index, which was calculated using the pack-year method (Table 1).

We found that, however, levels of sputum leptin, serum TNF- α , and CRP were higher in the high-risk stable patients with COPD than in the low-risk patients, and these differences did not show any significant values

(Fig. 2). These results were consistent with Calikoglu *et al.* [18], where they found inappropriately increased levels of leptin and TNF- α noted during recurrent acute exacerbations in patients with COPD, and elevated plasma TNF- α levels was related mainly to weight losing or hypoxemic patients. This may support our findings and postulation that levels of serum TNF- α correlate more with weight loss and muscle depletion in stable COPD regardless of its functional severity [19]. We agree in our results with some authors who found negative correlation between CRP serum levels and severity of COPD [20]. In contrast to our results, Liang *et al.* [21], concluded that leptin levels were demonstrated to be associated with the severity of COPD. Moreover, our results were different from the results obtained by Huang *et al.* [22], who found that plasma levels of TNF- α were related with severity of airway diseases and could be potential markers for the evaluation of COPD.

Sputum level of leptin was measured in all the study participants, which was found to be significantly higher in the COPD exacerbation group when compared with the stable COPD group and the controls (Table 2). These findings suggested that leptin could be detected in sputum and its level increases with increase in the degree of inflammation in airways, which is the case during periods of acute exacerbation, as a local inflammatory marker. This was agreed with the

results obtained by Liang *et al.* [21], who revealed that serum and sputum leptin levels were higher in patients with acute exacerbation of COPD than the stable patients with COPD and the controls. Other authors found that leptin was detectable in induced sputum of patients with moderate COPD, and it was correlated with other inflammatory markers [23].

Serum TNF- α levels were found to be higher in AECOPD group than the stable COPD and the control groups, but without any significance (Table 2). Our results agreed with few authors who found that there were no significant differences between serum levels of TNF- α in patients with COPD and controls [24–26]. Moreover, El-Adl *et al.* [27] declared that there was no significant difference in serum TNF- α levels between patients with COPD whether in stable or acute exacerbation state and the controls. This finding may support the hypothesis that the release of the inflammatory cytokine TNF- α is mainly influenced by the smoking state rather than the disease severity, where higher levels of TNF- α were found higher in smoker controls than in COPD ex-smokers [28]. On the contrary, our study finding was against the results obtained by Prokopis *et al.* [29] who found that COPD exacerbations are characterized by increased levels of TNF- α . Moreover, other authors found that the concentrations of circulating TNF- α were significantly higher in patients with COPD in comparison with the control group, and their levels increased according to the stage of the disease [30–33].

We found that serum CRP levels were higher in group 1 (AECOPD) than group 2 (stable COPD) and group 3 (controls). These results had a statistical significance (Table 2). CRP is an inflammatory mediator which involves in the acute inflammatory response in several diseases including COPD exacerbation [34]. This finding was consistent with what was found by Chen *et al.* [35], where CRP levels in serum were in consistent elevations in AECOPD compared with controls. Moreover, Duran *et al.* [36] found that serum CRP is elevated in patients with COPD with acute exacerbations and correlates with the severity of the disease. The present study finding emphasizes the role of serum CRP levels in COPD exacerbation assessment.

Nonsignificant differences were found in serum leptin levels among the three study groups (Table 2). This may point to the postulation that leptin secretion is mainly localized in the airways by the local inflammatory and the alveolar cells, and this was

also the conclusion of some authors who found inverse correlation between sputum and plasma leptin during COPD exacerbation, suggesting that the presence of leptin in sputum is not attributable to microvascular leakage from the plasma leptin pool [23]. These findings were consistent with those of Yang *et al.* [37] who studied 72 patients with COPD, and found that there was no significant difference in serum leptin levels between patients with COPD during stable and acute exacerbation periods. However, in contrast to our results, Krommidas *et al.* [38] suggested that serum leptin is associated with the systemic inflammatory process during exacerbations of COPD.

In the present study (Fig. 3), sputum leptin and serum CRP levels were significantly higher in group 1 (COPD exacerbation) than within group 2 (stable COPD). This was agreed by many authors' research [21,35,36], and this may emphasize the role of sputum leptin together with other well-studied inflammatory markers like CRP in the diagnosis and prognosis of AECOPD.

When we analyze the results of serum TNF- α and leptin levels between the various patients with COPD (stable and exacerbation stages), we did not find any significant differences supporting that these inflammatory markers could play a role in the systemic inflammatory burst during periods of COPD acute exacerbation.

We find significant differences between the patients with AECOPD and the controls regarding sputum leptin, serum TNF- α , and CRP, but results were not significant regarding serum leptin (Fig. 4). These findings go through with ensuring the local functions of leptin in the airways, possibly being a part of the underlying pathogenesis of COPD acute exacerbation.

Increase in leptin levels in both sputum and serum was observed in group 1 (patients with AECOPD). This initial increase was followed by significant reduction in leptin levels when repeated 7 days after initiation of treatment (Fig. 6). This also was found regarding the other inflammatory markers, TNF- α and CRP, where treatment of exacerbation was associated with significant declining of their serum levels in our results (Fig. 6).

This may point to the role of leptin in the evaluation of the inflammatory responses in patients with COPD during exacerbation [39]. Our results agreed with those

published in 2017, where a study conducted on 82 patients with COPD with acute exacerbation, indicated that plasma levels of leptin and TNF- α were initially abnormal, which showed improvement when repeated before the time of discharge, giving a conclusion that serum TNF- α and leptin contribute in AECOPD inflammatory responses [40]. In another analysis of 52 patients with AECOPD, higher serum leptin and TNF- α levels were observed on day 1 compared with day 15 of hospitalization, along with a positive correlation between both biomarkers [29]. However, we did not investigate that, but current results suggest that leptin may be involved in the innate immune system of the lungs in COPD.

On the contrary, other authors also did not find significant differences between serum leptin and TNF- α levels in patients with COPD during stable or exacerbation periods [37,41]. In contrast to our results, Pinto-Plata *et al.* [42] studied the inflammatory response cytokine changes in 20 patients admitted with AECOPD and found that there was a significant increase in the mean hospital admission plasma levels of IL-6 and IL-8 with no changes in levels of TNF- α .

It has been known that COPD is a chronic inflammatory disease associated with low-grade systemic inflammation besides marked airway inflammation during stable states and is associated with more increase in systemic inflammation during the episodes of acute exacerbation. This had been demonstrated by an increase in many inflammatory cytokines [43].

Few and conflicting results have been reported regarding the levels of sputum leptin in patients with AECOPD. Further research in this field may be needed to emphasize the role of leptin as a local inflammatory marker in COPD especially during exacerbation periods.

This study had limitations of small patient volume and being a single-center experience.

Conclusion

The present study shows that leptin is detectable in induced sputum of patients with COPD and can be contributed to the inflammatory response in patients with COPD during periods of exacerbation. This was evident by the high levels of leptin found in both serum and sputum of patients with AECOPD, which was significantly reduced after a period of treatment. This

rise in leptin levels was associated with the rise in other well-established inflammatory mediators such as CRP and TNF- α . This raises the possibility of using leptin, in either serum or sputum, as a marker of COPD acute exacerbation and an indicator of good response to treatment. It is well established that COPD is a chronic inflammatory disease characterized by persistent airflow limitation, and researches are still ongoing aiming to find out the complete picture of the underlying pathogenesis, hoping to find more systemic and local inflammatory mediators and markers that can be used easily and noninvasively in the future for diagnosis, prognosis, and follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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