A study of IL-6, IL-8, and TNF-α as inflammatory markers in COPD patients

Wafaa S. El-Shimy, Ayman S. El-Dib, Hala M. Nagy, Wael Sabry

Aim To assess the diagnostic value of interleukin 6 (IL-6), IL-8 and tumor necrosis factor-α (TNF-α) as inflammatory markers in chronic obstructive pulmonary disease (COPD) patients.

Methods and results IL-6, IL-8 and TNF-α levels were measured by ELISA in the serum and the bronchoalveolar lavage (BAL) in 10 control participants and 25 mild and moderate COPD patients, whereas 25 patients with severe COPD were studied for the serum level of these inflammatory biomarkers.

The mean value and SD of BAL and serum IL-6, IL-8 and TNF-α levels were significantly higher in COPD patients when compared with control participants; the serum level of these biomarkers were also significantly higher in severe compared with mild and moderate COPD patients.

Conclusion Increased srum and/or BAL IL-6, IL-8 and TNF-α can be used as biomarkers of the systemic inflammatory response in COPD patients, and their levels are correlated with the severity of COPD. *Egypt J Broncho* 2014 8:91–99

Egyptian Journal of Bronchology 2014 8:91–99

Keywords: chronic obstructive pulmonary disease, IL-6, IL-8, TNF-α

Chest and Clinical Pathology Department, Kafr EL-Shek Chest Hospital, Tanta University, Tanta, Egypt

Correspondence to Ayman Shehata El-Dib, Villa ElKhoalka, Foad Yousef Awess St, Bolkaly, Alexandria, Egypt
Tel: 01007473956; fax: 035436910-0453440990-0459168915;
e-mail: adalex1970@yahoo.com

Received 04 July 2014 **Accepted** 16 August 2014

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible, usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases [1].

Symptoms of COPD range from chronic cough, sputum production and wheezing to more severe symptoms, such as dyspnea, poor exercise tolerance and signs or symptoms of right-sided heart failure [2].

There has been increasing interest in using pulmonary biomarkers to understand and monitor the inflammation in the respiratory tract of patients with COPD; a biomarker refers to any molecule or material (cells, tissue), the measurement of which reflects the disease process. In COPD, several types of biomarkers have been measured and are related to the disease pathophysiology and the inflammatory or destructive process in the lung [3].

Interleukin-6 (IL-6) is synthesized by the airway epithelium, macrophages and other cells at the site of inflammation in response to environmental stress such as smoking; IL-6 has both pro inflammatory and anti-inflammatory properties. Serum IL-6 levels were significantly higher in individuals with COPD when compared with controls [4]. Serum and bronchoalveolar lavage (BAL) levels of IL-6 were more likely to increase during exacerbations of COPD [5,6].

IL-8 is a multifunctional chemokine involved in inflammation-mediated neutrophil infiltration and chemotaxis. [7] IL-8, also known as CXCL8, is a CXC chemokine that is a potent chemoattractant for neutrophils. In general, monocytes, tissue and alveolar macrophages, pulmonary epithelium, smooth muscles cells of the airway, eosinophils, fibroblasts and endothelial cells are its important sources [8]. IL-8 is frequently increased in patients with COPD; analysis of BAL and sputum samples has also shown increased levels of IL-8 in patients with mild-to-moderate COPD [9].

Tumor necrosis factor-α (TNF-α) is a powerful proinflammatory cytokine primarily produced by activated macrophages; it is thought to play a critical role in the pathogenesis of COPD by promoting and maintaining the expression and the release of various proinflammatory mediators that lead to tissue damage and remodeling [10].

Aim of the work

The aim of this work was to assess the diagnostic value of IL-6, IL-8, and TNF-α as inflammatory markers in COPD patients.

Patients and methods

This study was carried out on 50 COPD patients and 10 controls at the Chest Department, Tanta University Hospital, from September 2011 to December 2012.

They were subdivided into three groups:
(1) Group I included 10 participants who were apparently healthy, nonsmoking volunteers. Their ages ranged from 18 to 68 years.
(2) Group II included 25 patients with mild and moderate COPD. Their ages ranged from 21 to 77 years.
(3) Group III included 25 patients with severe COPD. Their ages ranged from 36 to 76 years.

Inclusion criteria for COPD

(1) Mild and moderate COPD (80% ≥ forced expiratory volume in 1 s (FEV_1) ≥ 50% predicted and FEV_1 > 1.2 l)
(1) Severe COPD (FEV_1 < 50% predicted) (according to Global Initiative for Chronic Obstructive Lung Disease [1]).

COPD can be differentiated from asthma using bronchodilator reversibility testing.

Exclusion criteria

(1) Chest diseases other than COPD.
(2) COPD patients with acute exacerbation (for BAL).
(3) Patients with the following cardiac conditions:
   (a) Unstable ischemic heart disease (recent myocardial infarction < 6 weeks, unstable angina).
   (b) Congestive cardiac failure.
(1) Patients with heart failure. Mechanically ventilated patients with PaO_2 less than 70 mmHg.
(2) Thrombocytopenia with platelets less than 10 000/μl.
(3) Psychological impairment.
(4) Cancer patients and patients receiving ımmunosuppressive treatment.
(5) Hepatic cirrhosis.
(6) Chronic renal failure.
(7) Autoimmune or connective tissue disorders, taking anti-TNF-α drugs.
(8) Pregnant women.

All participants were subjected to the following:
(1) Through history taking.
(2) Full clinical examination.
(3) Plain chest radiograph.
(4) Routine laboratory investigations.
(5) BMI.
(6) Pulmonary function tests (FEV_1, forced vital capacity (FVC), FEV_1%): all parameters were matched for age, sex, and body weight
(7) Arterial blood gases.
(8) BAL was performed to groups I and II only under local anesthesia using flexible fiberoptic bronchoscopy.

Blood and BAL were examined for the following:
(a) Total and differential cells.
(b) IL-6, IL-8, and TNF-α levels by ELISA.

Results

The mean value and SD of FEV_1, FVC, and FEV_1% were significantly lower in groups III and II when compared with group I; they were also significantly lower in group III than in group II (*t*-test < 0.001).

The mean value and SD of serum TLC, neutrophil%, lymphocyte%, and monocyte% were significantly higher in group III than in groups II and I; it was also significantly higher in group II when compared with group I (*t*-test < 0.001).

The mean value and SD of the serum eosinophil% in the three studied groups showed no significant difference (*F*-test = 0.721, *P* = 0.661).

The mean value and SD of BAL TLC, macrophage, lymphocyte, and neutrophil were significantly higher in group II when compared with group I (*t*-test < 0.001). The mean value and SD of BAL eosinophil showed no significant difference between the two groups (*t*-test = 0.675, *P* = 0.504) (Figs. 1–10 and Tables 1–10).

Serum and BAL inflammatory markers

The mean value and SD of serum IL-6, IL-8, and TNF-α were significantly higher in group III when compared with groups II and I; they were also significantly higher in group II than in group I (*t*-test < 0.001).

The mean value and SD of BAL IL-6, IL-8, and TNF-α were significantly higher in group II than in group I (*t*-test = 4.85, *P* < 0.001).

Table 1 FEV_1 value/l in the three studied groups

Groups	FEV_1/l		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Control	3.11–4.78	3.935 ± 0.511	170.631	<0.001*
Mild and moderate	1.51–3.34	2.279 ± 0.459		
Severe	0.24–1.96	0.980 ± 0.383		
Tukey's test				
Control vs. mild and moderate	Control vs. severe	Mild and moderate vs. severe		
<0.001*	<0.001*	<0.001*		

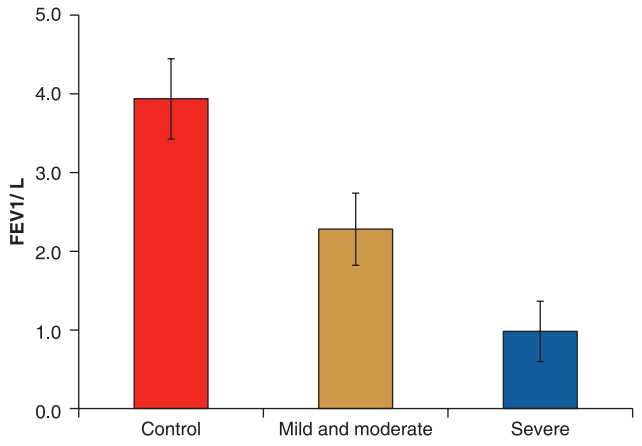
ANOVA, analysis of variance; *Significant.

Table 2 Serum IL-6 value in the three studied groups

Groups	Serum IL-6 (pg/ml)		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Control	1.9–5	3.030 ± 1.076	148.010	<0.001*
Mild and moderate	6.6–17.8	14.016 ± 3.018		
Severe	16.1–28.8	22.727 ± 3.716		
Tukey's test				
Control vs mild and moderate	Control vs. severe	Mild and moderate vs. severe		
<0.001*	<0.001*	<0.001*		

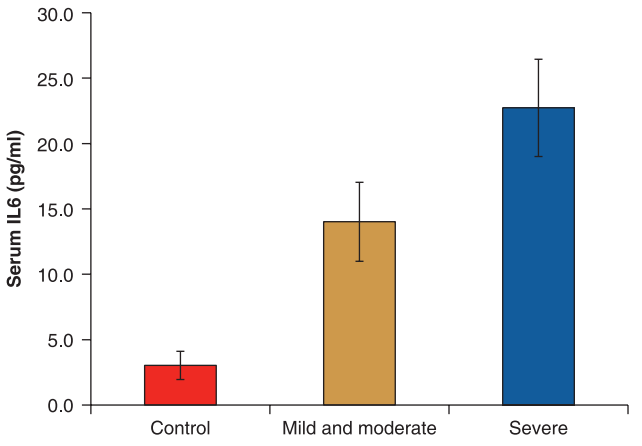
ANOVA, analysis of variance; IL, interleukin; *Significant.

Fig. 1



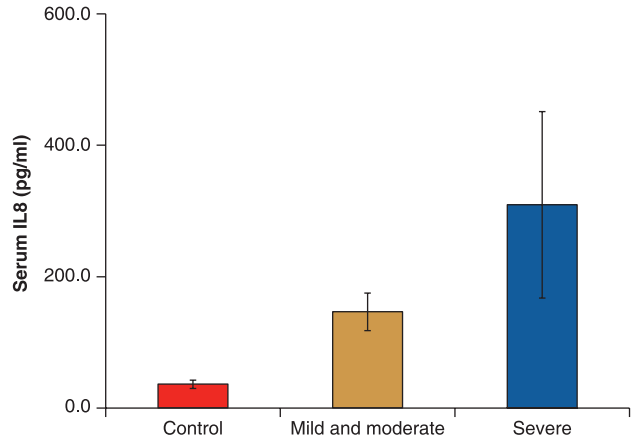
The mean value of FEV_1 in the three studied groups.

Fig. 2



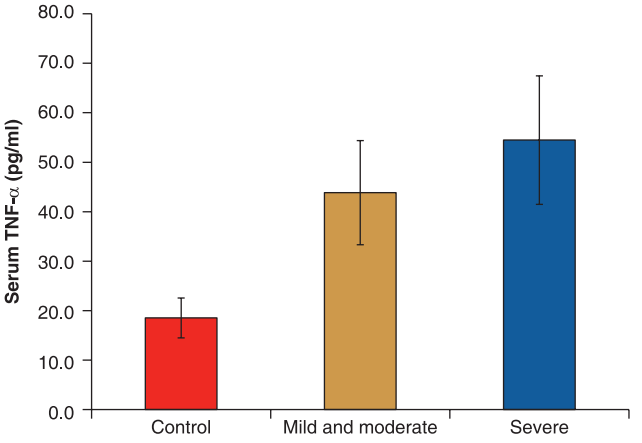
The mean value of serum interleukin-6 (IL-6) in the three studied groups.

Fig. 3



The mean value of serum interleukin-8 (IL-8) in the three studied groups.

Fig. 4



The mean value of serum tumor necrosis factor-α (TNF-α) in the three studied groups.

Table 3 Serum IL-8 value in the three studied groups

Groups	Serum IL-8 (pg/ml)		ANOVA	
	Range	Mean ± SD	F	*P*-value
Control	25–44	36.2 ± 6.334	36.112	<0.001*
Mild and moderate	64.8–188	146.432 ± 28.528		
Severe	152.8–620	309.28 ± 141.906		
Tukey's test				
Control vs. mild and moderate	Control vs. severe	Mild and moderate vs. severe		
0.008*	<0.001*	<0.001*		

ANOVA, analysis of variance; IL, interleukin; *Significant.

Table 4 Serum TNF-α value in the three studied groups

Groups	Serum TNF-α (pg/ml)		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Control	12.2–24.2	18.52 ± 4.028	38.442	<0.001*
Mild and moderate	30.22–74.4	43.833 ± 10.531		
Severe	34.6–87	54.472 ± 12.972		
Tukey's test				
Control vs. mild and moderate	Control vs. severe	Mild and moderate vs. severe		
<0.001*	<0.001*	0.003*		

ANOVA, analysis of variance; TNF-α, tumor necrosis factor-α; *Significant.

Serum correlations

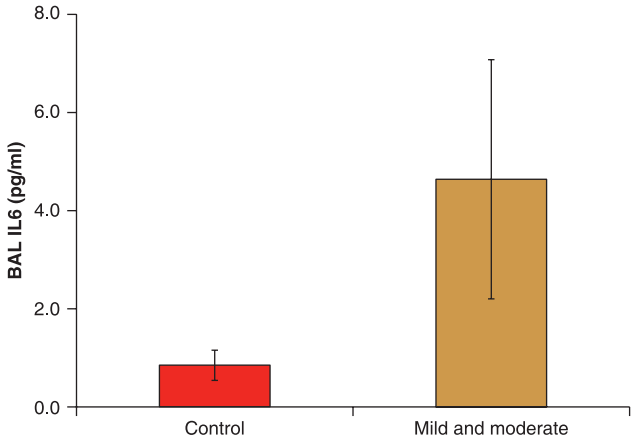
There was a significant negative correlation between serum IL-6, IL-8, TNF-α, and FEV_1%. These data denote that an increase in inflammatory markers in the serum is correlated with the severity of airway obstruction.

There was a significant positive correlation between serum IL-6, IL-8, and TNF-α and serum total leucocytic count, lymphocytic%, and neutrophilic %, which increase in association with an increase in serum inflammatory markers

BAL correlations (in group II)

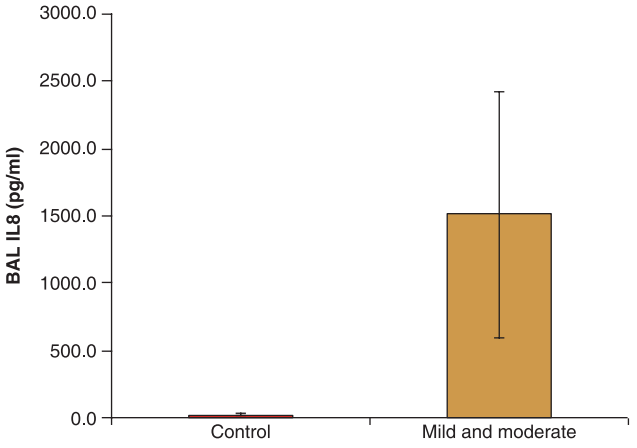
There was a significant negative correlation between BAL IL-6, IL-8, TNF-α, and FEV_1%. Hence, their levels were correlated with the severity of COPD.

Fig. 5



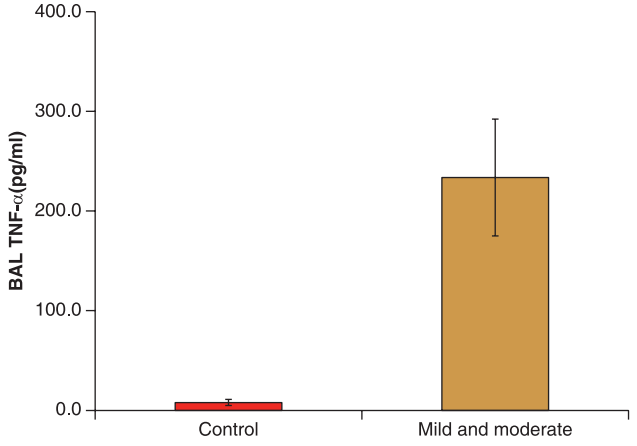
The mean value of bronchoalveolar lavage (BAL) interleukin-6 (IL-6) in groups I and II.

Fig. 6



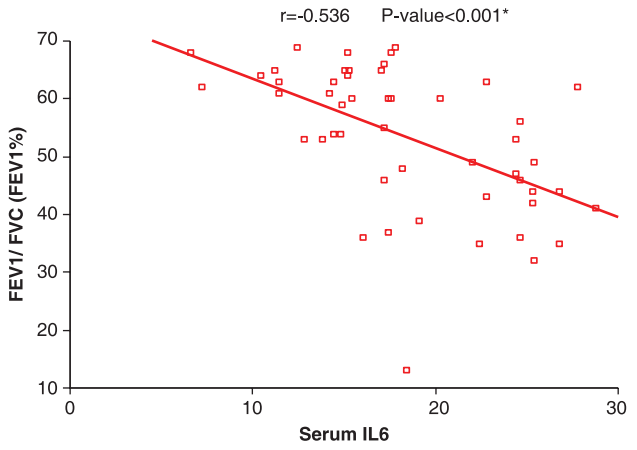
The mean value of bronchoalveolar lavage (BAL) interleukin-8 (IL-8) in groups I and II.

Fig. 7



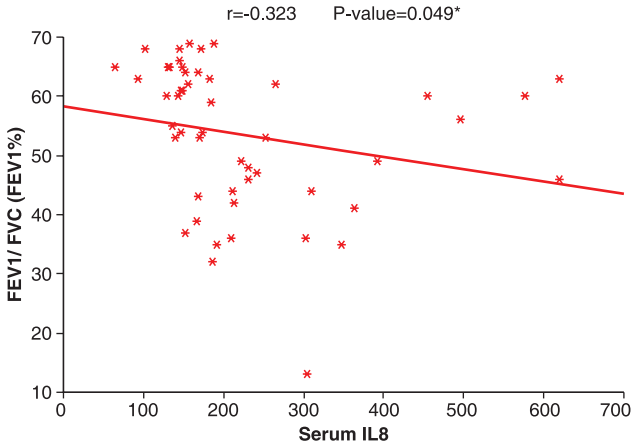
The mean value of bronchoalveolar lavage (BAL) tumor necrosis factor-α (TNF-α) in groups I and II.

Fig. 8



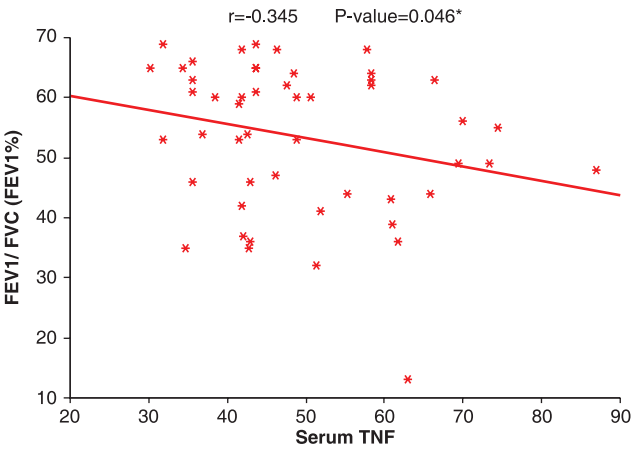
The correlation between serum interleukin-6 (IL-6) and FEV_1/FVC (FEV_1%).

Fig. 9



The correlation between serum interleukin-8 (IL-8) and FEV_1/FVC (FEV_1%).

Fig. 10



The correlation between serum tumor necrosis factor-α (TNF-α) and FEV_1/FVC (FEV_1%).

Table 5 BAL IL-6 value in groups I and II

Groups	BAL IL-6 (pg/ml)		*t*-Test	
	Range	Mean ± SD	*t*	*P*-value
Control	0.28–1.2	0.848 ± 0.307	4.855	<0.001*
Mild and moderate	2.4–13.6	4.637 ± 2.438		

BAL, bronchoalveolar lavage; IL, interleukin; *Significant.

Table 6 BAL IL-8 value in groups I and II

Groups	BAL IL-8 (pg/ml)		*t*-Test	
	Range	Mean ± SD	*t*	*P*-value
Control	16.6–32	24.34 ± 4.059	5.021	<0.001*
Mild and moderate	464.8–4300	1513.28 ± 929.35		

BAL, bronchoalveolar lavage; IL, interleukin; *Significant.

Table 7 BAL TNF-α value in groups I and II

Groups	BAL TNF-α (pg/ml)		*t*-Test	
	Range	Mean ± SD	*t*	*P*-value
Control	4.4–15.8	7.88 ± 3.103	12.079	<0.001*
Mild and moderate	110.4–344.8	233.608 ± 58.534		

BAL, bronchoalveolar lavage; TNF-α, tumor necrosis factor-α; *Significant.

Table 8 Correlation between serum IL-6, IL-8 and TNF-α and pulmonary functions

Pulmonary function parameters	Serum IL-6		Serum IL-8		Serum TNF	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
FEV_1	−0.681	<0.001*	−0.489	<0.001*	−0.422	0.002*
%Predicted FEV_1	−0.695	<0.001*	−0.521	<0.001*	−0.418	0.002*
FVC	−0.582	<0.001*	−0.488	<0.001*	−0.446	0.001*
FEV_1/FVC (FEV_1%)	−0.536	<0.001*	−0.323	0.049*	−0.345	0.046*
FEF25–75%	−0.620	<0.001*	−0.484	<0.001*	−0.434	0.002*

IL, interleukin; TNF-α, tumor necrosis factor-α; *Significant.

Table 9 Correlation between serum and BAL markers in group II

BAL markers	Serum IL-6		Serum IL-8		Serum TNF	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
BAL IL-6	0.221	0.288	0.196	0.348	0.211	0.310
BAL IL-8	0.173	0.408	0.224	0.281	0.067	0.752
BAL TNF	0.205	0.326	0.026	0.902	0.095	0.650

BAL, bronchoalveolar lavage; IL, interleukin; TNF-α, tumor necrosis factor-α; *Significant.

Table 10 Correlation between BAL markers and pulmonary functions in group II

Some pulmonary function parameters	BAL IL-6		BAL IL-8		BAL TNF-α	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
FEV_1/FVC (FEV_1%)	−0.784	<0.001*	−0.821	<0.001*	−0.798	<0.001*
FEF25–75%	−0.477	0.016*	−0.506	0.010*	−0.454	0.023*

BAL, bronchoalveolar lavage; IL, interleukin; TNF-α, tumor necrosis factor-α; *Significant.

There was a significant positive correlation between BAL IL-6, IL-8, TNF-α, and both neutrophilic% and macrophage%, which increase with an increase in BAL inflammatory markers.

Discussion

Pulmonary function studies

In the present study, a significant decrease was found in the pulmonary functions of severe COPD patients when compared with mild and moderate COPD patients and controls; the findings of the present work are consistent with those of many authors who found that pulmonary function data (FEV_1, FVC, FEV_1% and PEFR) were significantly lower in COPD patients when compared with controls [11–14].

The extent of inflammation, fibrosis and luminal exudates in the small airways is correlated with the reduction in FEV_1 and FEV_1% [15]. The airflow limitation in COPD patients is due to the increase in the resistance to airflow, which is caused by smooth muscle hypertrophy, goblet cell metaplasia, degeneration of the airway cartilage and mucous hypersecretion [16].

Serum IL-6

In the present study, serum IL-6 was significantly higher in severe than in mild and moderate COPD patients and Control participants. The results of this work are consistent with the study of Seemungal *et al.* [17], Arschang *et al.* [18], and Eickhoff *et al.* [19], who found that serum IL-6 increases during COPD exacerbation compared with stable COPD patients and healthy controls.

Also, the results of this study agree with Attaran *et al.* [20], Abd El-Maksoud *et al.* [21], and Garcia-Rio *et al.* [22], who found that the concentrations of circulating serum IL-6 were significantly higher in patients with COPD in comparison with control participants, and their levels increased according to the stage of the disease

Our results also agree with the study of Celli *et al.* [23], which included 2164 COPD patients and 245 healthy controls who had been followed for 3 years, and they found that the circulating IL-6 levels were significantly higher in individuals with COPD when compared with controls.

BAL IL-6

In the present study, it was significantly higher in mild and moderate COPD patients than in control participants. The results of the present work are consistent with the study of Soler *et al.* [24], who found that BAL IL-6 levels increased virtually linearly from nonsmoking controls through smoking controls and mild and moderate COPD to severe COPD patients.

Also, Weidong *et al.* [25] studied seven nonsmoking apparently healthy individuals and 21 patients with

COPD, and they found higher concentrations of IL-6 in BAL of the COPD group than in control individuals.

It has been established that stable COPD is associated with low-grade systemic inflammation, besides an increase in airway inflammation; COPD exacerbations are associated with more increase in systemic inflammation as demonstrated by an increase in blood leukocytes, acute-phase proteins, C-reactive protein and fibrinogen, and inflammatory cytokines. During acute exacerbations of COPD, higher levels of IL-6 have been demonstrated, which decrease again during recovery [26].

Biologically, IL-6 is the primary cytokine regulator of both C-reactive protein and fibrinogen in the liver. It also plays a critical role in hematopoiesis, causing thrombocytosis and leukocytosis with its overexpression [27].

Serum IL-8

In the present study, it was significantly higher in severe COPD patients than in mild and moderate COPD patients and control participants.

The results of the present work are consistent with the study of Daldegan *et al*. [28] who found that serum IL-8 concentrations were higher in COPD patients than in patients with asthma or in healthy control individuals.

Also, our results agree with Xie *et al*. [29], who found that serum IL-8 was statistically higher during COPD exacerbation compared with patients with stable COPD and healthy controls.

Also, Garcia-Rio *et al*. [22] found that COPD patients showed higher levels of IL-8 compared with controls, and serum concentrations were related to the severity of COPD.

Also, Demirci *et al.* (2013), studied 23 COPD patients (Stage I), 15 (Stage II) and 12 (Stage III–IV). Ten healthy nonsmoking as control group. They found that as the stage of COPD increased, the levels of IL-8 increased [30].

BAL IL-8

In the present study, it was significantly higher in mild and moderate COPD patients than in control participants.

The present findings are consistence with Riise *et al*. [31], who studied 42 patients with chronic bronchitis and 13 healthy controls. They found that BAL IL-8 levels were higher in patient with COPD compared with control participants [31].

Pesci *et al*. [32] studied 20 COPD patients and 10 normal control participants. They found that levels of IL-8 were higher in COPD patients compared with control participants [32].

Also, Soler *et al*. [24] and Rutgers *et al*. [33] found that there was a trend for BAL IL-8 to be higher in smoking controls and COPD patients as compared with controls.

Drost *et al*. [34] and Cheng *et al*. [35] found that IL-8 levels in the BAL fluid were significantly higher in patients with COPD than in controls.

Serum TNF-α

In the present study, serum TNF-α was significantly higher in severe than in mild and moderate COPD patients and control participants.

The results of this work are consistent with those of Takabatake *et al*. [36], Bolton *et al*. [37], and Itoh *et al*. [38], who found that the serum level of TNF-α was higher in COPD patients than in control participants.

Our results agree with Abd El-Maksoud *et al*. [21], Garcia-Rio *et al*. [22], Xie *et al*. [29], Ibrahim *et al*. [39], and Abd El Aziz *et al*. [40], who 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.

In contrast to our results, Yende *et al*. [41], Shin *et al*. [42], and Piehl-Aulin *et al*. [43] found that there were no significant difference between serum levels of TNF-α in COPD patients and controls.

El-Adl *et al*. [44] studied 60 COPD patients (divided into three groups: group I: 20 AECOPD patients without malnutrition; group II: 20 stable patients without malnutrition; and group III: 20 stable patients with malnutrition) and 10 healthy control individuals; they found that there was no statistically significant difference in serum TNF-α levels between the groups.

Also, Amer *et al*. [45] and Bruno *et al*. [46] studied 90 individuals [subdivided into three equal groups: group I (control), group II (patients with COPD), and group III (patients with COPD and cardiovascular complications)], and they found no significant difference between the groups.

Yende *et al*. [41] and Amer *et al*. [45] explain the decrease in serum TNF-α in COPD patients by the relatively short serum half-life of TNF-α and by the wide range of disease progression in each group.

BAL TNF-α

In the present study, it was significantly higher in mild and moderate COPD patients than in control participants.

The present findings are consistent those of with Soler *et al*. [24] , who found that the BAL concentration of TNF-α was higher in smoking controls and COPD patients than in healthy nonsmoking control individuals.

Cheng *et al*. [35] found that the levels of BAL TNF-α were also significantly higher in patients with COPD than in controls.

Abd El Aziz *et al*. [40] found that BAL TNF-α was highly significantly elevated in COPD patients than in the control group.

In contrast to our results, Drost *et al*. [34] found that TNF-α levels detected in airway secretions and the BAL fluid were generally low and were not significantly different between COPD patients and control participants; they explain the decrease in TNF-α in BAL by the action of cytokines mainly in peripheral lung tissues.

Correlation

Serum IL-6, IL-8, and TNF-α in comparison with pulmonary functions

In the present study, there were a significant negative correlation between serum IL-6, IL-8, and TNF-α and FEV_1, FEV_1/FVC (FEV_1%), and FEF25–75%.

The data of our work are consistent with those of Soler *et al*., [24] Pinto-Plata *et al*. [47], Abd El-Maksoud *et al*. [21], Attaran *et al*. [20], and Ramadan *et al*. [48], who found a significant negative correlation between IL-6 levels and FEV_1.

In contrast to our results, Akbulut *et al*.[7] found no correlation between the IL-6 value and FEV_1 and FEV_1/FVC values.

Also, Kanazawa *et al*. [49], Soler *et al.* [24], Zhang *et al*. [50], and Demirci *et al*. [30] found a negative correlation between IL-8 and FEV_1.

In contrast to our results, Pinto-Plata *et al*. [51] and Akbulut *et al*. [7] found no correlation between the IL-8 value and FEV_1 and FEV_1/FVC values.

In contrast, Pinto-Plata *et al*. [47] and Amer *et al*. [46] found a significant negative correlation between TNF-α levels and FEV_1. In contrast to our results, Abd El-Maksoud *et al*. [21]found no significant correlation between TNF-α and FEV_1.

From the previous correlations, it is clear that the increase in serum inflammatory markers has a direct correlation with the severity of COPD.

Serum IL-6, serum IL-8, and TNF-α in comparison with the total and the differential cell count%

There were a significant positive correlation between serum IL-6, IL-8, and TNF-α and the serum total leucocytic count, lymphocyte%, and neutrophil%.

Our results are consistent with the study of Bathoorn *et al*. [51] and Moermans *et al*. [52], who found a significant positive correlation between serum IL-6 and neutrophil%.

Also, Daldegan *et al*. [28] and Demirci *et al*. [30] found a positive correlation between the number of neutrophils and serum IL-8 and TNF-α.

Our data denote that the increase in the serum total cell count, lymphocyte%, and neutrophil % is associated with an increase in inflammatory markers IL-6, IL-8, and TNF-α.

BAL IL-6, IL-8, and TNF-α in comparison with pulmonary functions

There were a significant negative correlation between BAL IL-6, IL-8, and TNF-α and both FEV_1/FVC and FEF25–75%.

The present results match with the study of Soler *et al*. [24] and Weidong *et al*. [25], who found a significant negative correlation between BAL IL-6 and IL-8 and FEV_1%.

Also, Drost *et al*. [34] found a significant negative correlation between BAL IL-8 and the FEV_1/FVC ratio.

The present results matched with the study of Cheng *et al*. [35], who found a significant negative correlation between BAL TNF-α and FEV_1%.

BAL IL-6, IL-8, and TNF-α in comparison with the BAL total and differential cell count %

There was a significant positive correlation between BAL IL-6, IL-8, and TNF-α and both neutrophil % and macrophage %.

Our results are consistent with the study of Rouhani *et al*. [53] and Moermans *et al*. [52], who found a significant positive correlation between BAL IL-6 and IL-8 and both neutrophil and macrophage %

In contrast to our results, Drost *et al*. [34] found no correlation between BAL IL-8 and neutrophil%.

Also Kwon *et al*. [54] and Soler *et al*. [24] found a significant positive correlation between BAL TNF-α and both neutrophil and macrophage%.

COPD is characterized by progressive expiratory airflow limitation resulting from an abnormal inflammatory response to noxious particles or gases [55]. The initial inflammatory response to damage from noxious particles or gases is characterized by increased neutrophils, macrophages, T-lymphocytes, and increased cytokines including IL-6, IL-8, and TNF-α. The inflammation that develops is not limited to the lungs. Studies have shown increased systemic levels of IL-6, IL-8, and TNF-α in patients with COPD. This may be due to an 'overspill' of mediators from the lungs. The increase in these proinflammatory cytokines is correlated to the severity of COPD and is believed to contribute to the systemic comorbidities associated with COPD, Hacievliyagil *et al*. [56] observed that higher concentrations of inflammatory cytokines, including IL-6, IL-8 and TNF-α, are reported in patients with more severe COPD compared with those with less severe COPD.

Because of the previous association, cytokine inhibitors are tried in the treatment of COPD; TNF-α-blocking antibodies, such as infliximab, have been studied as a treatment for COPD. Unfortunately, they have not been able to show any differences in inflammatory markers. There is evidence, however, that etanercept, another TNF-α antagonist, decreases COPD hospitalizations [57].

Tocilizumab, a potent inhibitor of IL-6, is yet to be tested in COPD patients. These drugs are still in the development phase [58].

Acknowledgements

Conflicts of interest

None declared.

References

1 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global strategy for diagnosis, management and prevention of chronic obstructive lung disease* 2010 Global Initiative for Chronic Obstructive Lung Disease [GOLD]

2 Dalal AA, Liu F, Riedel AA. Diseases and conditions index. What is COPD? 2007 National Heart Lung Blood Institute [NHLBI]. *Int J Chron Obstruct Pulmon Dis* 2011;6:533–542. Published online 2011 October 14. doi: 10.2147/COPD.S24591.

3 Barnes PJ, Chowdhury B, Kharitonov SA, *et al.* Pulmonary biomarkers in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; **174**:6–14.

4 Wedzicha JA, Seemungal TA, MacCallum PK, *et al.* Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; **84**:210–215.

5 Higashimoto Y, Iwata T, Okada M. Serum biomarkers as predictors of lung function decline in chronic obstructive pulmonary disease. *Respir Med* 2009; **103**:1231–1238.

6 Ferrari R, Tanni SE, Caram LM, Corrêa C, *et al.* Three-year follow-up of interleukin 6 and C-reactive protein in chronic obstructive pulmonary disease. *Respir Res* 2010; **14**:24.

7 Akublut HH, Ozden M, Deveci F, Muz MH. IL-6 and IL-8 Levels in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *J Clin Diag Res* 2009;3;1285–1288.

8 Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J* 2001; **18**:50–59.

9 Di Stefano A, Capelli A, Donner CF. Role of interleukin-8 in the pathogenesis and treatment of COPD. *Chest* 2004; **126**:676–678.

10 Mukhopadhyay S, Hoidal JR, Mukherjee TK. Role of TNF-alpha in pulmonary pathophysiology. *Respir Res* 2006; **7**:125.

11 Peat JK, Woolcock AJ, Culle K. Decline of lung function and development of chronic airflow limitation: a longitudinal study of nonsmokers and smokers in Busselton, Western Australia. *Thorax* 1990; **45**:32–37.

12 Anthonisen NR, Connett JE, Kiley JP, Altose MD, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. *JAMA* 1994; **272**:1497–1505.

13 Gold D, Wang X, Wypij D, Speizer F, *et al.* Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; **335**:931–937.

14 James A, Palmer L, Kicic E. Decline in lung function in the Busselton Health Study. *Am J Respir Crit Care Med* 2005; **171**:109–114.

15 Ward PA. The dark side of C5a in sepsis. *Nat Rev Immunol* 2004; **4**:133–142.

16 Haraguchi M, Shimura S, Shirato K. Morphometric analysis of bronchial cartilage in chronic obstructive pulmonary disease and bronchial asthema. *Am J Respir Crit Care Med* 1999; **159**:1005–1013.

17 Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164**:1618–1623.

18 Arschang V, Martin S, Michael W, *et al.* Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. *Clin Sci* 2008; **115**:225–232.

19 Eickhoff P, Arschang V, Kiss D, Martin S, *et al.* Determinants of systemic vascular function in patients with stable COPD. *Am J Respir Crit Care Med* 2008; **178**:1211–1218.

20 Attaran D, Lari SM, Towhid M, *et al.* Interleukin-6 and airflow limitation in chemical warfare patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2010; **5**:1–6

21 Abd El-Maksoud MD, Samy N, EL Khayyal A. Clinical utility of biomarkers as predictors of lung function in chronic obstructive pulmonary disease. *N Y Sci J* 2010; **3**:25–32.

22 Garcia-Rio F, Miravitlles M, Soriano J, *et al.* Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. *Respir Res* 2010;11–63. doi:10.1186/1465-9921-11-63.

23 Celli BR, Locantore N, Duvoix A, Yates J, *et al.* Inflammatory biomarkers ımprove clinical prediction of mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; **185**:1065–1072.

24 Soler N, Ewig S, Torres A, *et al.* Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur Respir J* 1999; **14**:1015–1022.

25 Weidong S, Jiangyun Z, Zhengang L. Interleukin-6 in bronchoalveolar lavage fluid from patient with COPD. *Chlin Med J* 2001; **114**:1140–1142.

26 Dentener MA, Creutzberg EC, Schols AM, *et al.* Systemic anti-inflammatory mediators in COPD: increase in soluble interleukin 1 receptor II during treatment of exacerbations. *Thorax* 2001; **56**:721–726.

27 Kishimoto T. Interleukin-6: from basic science to medicine – 40 years in immunology. *Annual Review of Immunology* 2005; **23**:1–21.

28 Daldegan MB, Teixeira MM, Talvani A. Concentration of CCL11, CXCL8 and TNF-alpha in sputum and plasma of patients undergoing asthma or chronic obstructive pulmonary disease exacerbation. *Braz J Med Biol Res* 2005; **38**:1359–1365.

29 Xie J, Yang X, Shi J, Deng X, *et al.* A new inflammation marker of chronic obstructive pulmonary disease-adiponectin. *World J Emerg Med* 2010; **1**:190–195.

30 Demirci N, Atasever M, Ertürk H, *et al.* Correlation between high-resolution computed tomography, neutrophilic ınflammation, air-way obstruction and serum ınterleukin-8 levels in chronic obstructive pulmonary disease. *J Clin Anal Med* 2013; **4**:286–290.

31 Riise G, Ahlstedt S, Larsson S, *et al.* Bronchial inflammation in chronic bronchitis assessed by measurement of cell products in bronchial lavage fluid. *Thorax* 1995; **50**:360–365.

32 Pesci A, Balbi B, Majori M, *et al.* Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary diseases. *Eur Respir J* 1998; **12**:380–386.

33 Rutgers SR, Timens W, Kaufmann HF, *et al.* Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD. *Eur Respir J* 2000; **15**:109–115.

34 Drost EM, Skwarski KM, Sauleda J, *et al.* Oxidative stress and airway inflammation in severe exacerbations of COPD. *Thorax* 2005; **60**:293–300.

35 Cheng SL, Wang HC, Yu CJ, *et al.* Increased expression of placenta growth factor in COPD. *Thorax* 2008; **63**:500–506.

36 Takabatake N, Nakamura H, Abe S, Hino T, *et al.* Circulating leptin in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159**:1215–1219.

37 Bolton CE, Ionescu AA, Shiels KM, *et al.* Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **170**:1286–1293.

38 Itoh T, Nagaya N, Yoshikawa M, *et al.* Elevated plasma ghrelin level in underweight patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **170**:879–882.

39 Ibrahim EE, Zidan MH. The relation between the ınflammatory mediators, quality of life, and classification of the gold guidelines of COPD patients. *Egypt J Chest* 2011; **60**:117–125.

40 Abd El Aziz AA, Hammoudah MA, Farid W. Tumor-necrosis factor (TNF) alpha and pulmonary hypertension in patients with COPD. *Egypt J Chest* 2011; **60**:135–138.

41 Yende S, Waterer GW, Tolley EA, *et al.* Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax* 2006; **61**:10–16.

42 Shin KC, Chung JH, Lee KH. Effects of TNF-a and leptin on weight loss in patients with stable chronic obstructive pulmonary disease. *Korean J Intern Med* 2007; **22**:249–255.

43 Piehl-Aulin K, Jones I, Lindvall B, *et al.* Increased serum inflammatory markers in the absence of clinical and skeletal muscle inflammation in patients with chronic obstructive pulmonary disease. *Respiration* 2009; **78**:191–196.

44 El-Adl T, Hamza H, Hussin M, *et al.* Plasma leptin, tumor necrosis factor-α and nutritional status in choronic obstructive pulmonary disease patients. *Benha M J* 2007; **24**:21–22.

45 Amer MS, Wahba HM, Ashmawi SA, *et al.* Proinflammatory cytokines in Egyptian elderly with chronic obstructive pulmonary disease. *Lung India* 2010; **27**:225–229.

46 Bruno A, Alessi M, Soresi S, *et al.* Increased leptin/leptin receptor pathway affects systemic and airway inflammation in COPD former smokers. *J Inflamm Res* 2011; **4**:51–59.

47 Pinto-Plata VM, Livnat G, Girish M. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest* 2007; **131**:37–43.

48 Ramadan MR, Saadeldin AM, Osman AM, *et al.* Systemic inflammation ın COPD patients. *El-Minia Med Bul* 2010: **21**:255–263.

49 Kanazawa H, Kurihara N, Otsuka T, *et al.* Clinical significance of serum concentration of interleukin 8 in patients with bronchial asthma or chronic pulmonary emphysema. *Respiration* 1996; **63**:236–240.

50 Zhang J, Wu L, Qu J, Bai C, *et al.* Pro-inflammatory phenotype of COPD fibroblasts not compatible with repair in COPD lung. *J Cell Mol Med* 2011; **16**:1522–1532.

51 Bathoorn E, Liesker JW, Postma DS, *et al.* Change in inflammation in out-patient COPD patients from stable phase to a subsequent exacerbation. *Int J Chron Obstruct Pulmon Dis* 2009; **4**:101–109.

52 Moermans C, Heinen V, Nguyen M, *et al.* Local and systemic cellular inflammation and cytokine release in chronic obstructive pulmonary disease. *Cytokine* 2011; **56**:298–304.

53 Rouhani F, Paone G, Smith NK, *et al.* Lung neutrophil burden correlates with ıncreased pro-inflammatory cytokines and decreased lung function in ındividuals with a1-antitrypsin deficiency. *Chest* 2000; **117**:250S–251S

54 Kwon OJ, Au BT, Collins PD, *et al.* Tumor necrosis factor-induced IL-8 expression in cultured human airway epithelial cells. *Am J Physiol* 1994; **267**:L398–L405.

55 Bailey KL, Goraya J, Rennard SL. The role of systemic ınflammation in COPD. *Respir Med* 2012; **2**:15–30.

56 Hacievliyagil SS, Gunen H, Mutlu LC, *et al.* Association between cytokines in induced sputum and severity of chronic obstructive pulmonary disease. *Respir Med* 2006; **100**:846–854.

57 Dentener MA, Creutzberg EC, Pennings HJ, *et al.* Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration* 2008; **76**:275–282.

58 Kodgule R, Vaidya A, Salvi S. Newer therapies for chronic obstructive pulmonary disease. *JAPI* 2012; **60**:8–13.