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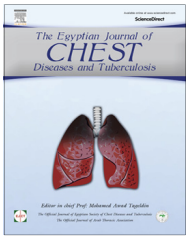

ORIGINAL ARTICLE

Evaluation of serum interleukin-1 beta as an inflammatory marker in COPD patients

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KEYWORDS

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Abstract *Background:* COPD is a chronic disease of the lungs characterized by increased obstruction to airflow that does not change markedly over periods of several months. Low-grade systemic inflammation is considered a hallmark of COPD that potentially links COPD to increased rate of systemic manifestations of the disease. Evaluation of systemic inflammation in COPD particularly when the disease is severe and during exacerbation can be measured either as increased circulating cytokines, chemokines and acute phase proteins, or as abnormalities in the circulating cells and markers. One of these inflammatory mediators is IL-1B which demonstrated recent reports in significantly high levels of IL-1β in serum of the COPD patients as compared to the healthy controls.

Aim of the study: To assess the level of serum IL-1B in chronic obstructive pulmonary disease patients during acute exacerbation and in stable conditions and also, to determine if the changes in its level correlated with changes in the ventilatory functions.

Methods: 80 cases were included in this study: 60 COPD patients and 20 healthy subjects as a control. There were 48 males and 12 females in COPD groups and 17 males and 3 females in the control group. Their age ranged from 41 to 79 years with a mean age of 59 years. The subjects were classified into 3 groups. Group I includes (30) patients with acute exacerbation of COPD. Group II includes (30) patients with stable controlled COPD. Group III includes (20) healthy persons as a control.

Results: There was a highly statistically significant difference in serum IL-1B (pg/ml) between studied groups, which indicates that IL-1B plays a role in systemic inflammatory process. There was a highly statistically significant difference in serum IL-1B concentration (pg/ml) and severity of COPD cases.

Conclusions: IL-1β correlated with clinical aspects of disease severity, suggesting that IL-1β may play a critical role in COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [7]. An exacerbation of COPD is defined as an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication. [7].

COPD is associated with a chronic inflammatory response, predominantly in small airways and lung parenchyma, which is characterized by increased numbers of macrophages, neutrophils, and T lymphocytes. The inflammatory mediators involved in COPD have not been clearly defined, in contrast to asthma, but it is now apparent that many lipid mediators, inflammatory peptides, reactive oxygen and nitrogen species, chemokines, cytokines, and growth factors are involved in orchestrating the complex inflammatory process that results in small airway fibrosis and alveolar destruction. Many proteases are also involved in the inflammatory process and are responsible for the destruction of elastin fibers in the lung parenchyma, which is the hallmark of emphysema. The identification of inflammatory mediators and understanding their interactions are important for the development of anti-inflammatory treatments for this important disease [3]. Interleukin-1beta (IL-1beta) is a proinflammatory cytokine. It is a potent activator of alveolar macrophages from COPD patients [14].

In COPD IL-1beta serum level correlates with clinical aspects of disease severity [17].

Subjects and methods

This study was created on 80 subjects, 60 COPD patients admitted in Tanta Chest Hospital in the period between August 2013 and April 2014 plus 20 apparently healthy control subjects, selected from volunteers and patients relatives. There were 48 males and 12 females in COPD groups and 17 males and 3 females in the control group. Their age ranged from 41 to 79 years with a mean age of 59 years. The subjects were classified into 3 groups:

Group I: includes (30) patients with acute exacerbation of COPD.
Group II: includes (30) patients with stable controlled COPD.
Group III: includes (20) healthy persons as a control.

The patients will be diagnosed based on the severity of COPD according to [7] using spirometry as follows:

GOLD 1: Mild	$FEV_1 \geqslant 80\%$ predicted
GOLD 2: Moderate	$50\% \leqslant FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leqslant FEV_1 < 50\%$ predicted
GOLD 4: Very severe	$FEV_1 < 30\%$ predicted

Inclusion criteria

Patients with COPD diagnosed according to GOLD [7] criteria.

Exclusion criteria

(Due to possible effects on lung function):

Patients with pneumonectomy, lung cancers.
Patients with residual extensive tuberculous lesion or active disease.
Patients with diabetes mellitus, collagen vascular disorders.
Patients with renal and hepatic disorders and those on systemic anti inflammatory therapy.

A written consent will be taken from all patients.
All subjects were submitted to the following:

1. History taking with the stress on:
   History of smoking (types and smoking index).
   History of chest symptoms (cough, expectoration, dyspnea and wheeze).
   History of any other co-morbidities as diabetes mellitus, tuberculosis, hepatic disease, renal disease, collagen vascular diseases.
2. Clinical examination both general and local.
3. Body mass index (BMI) was calculated as the weight in kg divided by height^2.
4. Complete blood count, liver function tests, kidney function tests.
5. Radiological examination: Plain X-ray chest P-A view.
6. Pulmonary function tests (spirometry) before and after broncho dilatation.
7. Serum levels of interleukin- 1 beta (IL- 1B):

Results

The results are presented in Tables 1–12.

Discussion

Table 1 shows that the mean age of COPD patients in group I was 57.5 ± 9.81 years. The mean age of COPD patients in group II was 61.4 ± 6.78 years. And the mean age of COPD patients in group III was 55.05 ± 9.25 years. There was a non-significant difference between COPD patients in group I, group II and group III as regards age.

Tables 2 and 3 show comparison between pulmonary functions before and after using bronchodilator in COPD groups.

In this study pre and post bronchodilator spirometry was done among 60 patients known to have COPD and showed partial reversibility in the FEV1% pred. (less than 12%) confirming the diagnosis of COPD cases (Tables 3 and 4).

The decline in forced expiratory volume in 1st second (FEV1%) in COPD is mainly related to thickening of the walls of small conducting airways and obstruction of these airways by mucous exudates [8]. This could be explained by the effect of smoking which induces structural changes in small and large airways, and is considered a major factor in the development of airflow obstruction in chronic obstructive pulmonary disease [4]. In the current study pre and post bronchodilator spirometry was done for group I and II, there were significant differences in spirometric data between the two groups ($p < 0.01$).

Table 1 Demographic data and statistical analysis of the studied groups as regards age.

Age/year	Group			
	Group I	Group II	Group III	Sig.
Range	41–79	48–73	38–62	
Mean ± SD	57.5 ± 9.81	61.4 ± 6.78	55.05 ± 9.25	
F test	3.566			NS
p Value	0.127			NS
	Scheffe test			
*P1 value	0.156			NS
*P2 value	0.203			NS
*P3 value	0.092			NS

*P1: comparison between group I and group II.*P2: comparison between group I and group III.*P3: comparison between group II and group III.
This table shows a non-significant difference in age between the studied groups.

The result of the current study showed a significant difference in the smoking index between the two groups of COPD patients (Table 4).

This result is in agreement with [13], who found that several studies show a significant excess decline in FEV1 in smokers over non-smokers, ex-smokers and quitters.

This result is also in agreement with [12] who found that in smokers, the risk of developing COPD is dose related.

In the current work it was found that there is a significant correlation between smoking index and IL-1B in group I and II (Tables 8 and 9).

This result is in agreement with [13], who reported that smoking results in a non-specific increase in IgE as a result of interference with IgE regulatory mechanisms and IL-1B expression may be induced in monocytes due to increased IgE levels, which may lead to their increased release in blood.

This also matched with [10] who found that subjects with lower FEV1 may have higher exposure to tobacco smoke or to environmental insults that lead to a subtle decline in lung function and, in parallel, induce a low-grade inflammatory response.

Based on the results of post bronchodilator spirometry 9 patients were classified as stage II (FEV1:50–80% predicted), 16 patients as stage III (FEV1:30–50% predicted) and 5 patients were classified as stage IV (FEV1: less than30% predicted) according to GOLD [7] in group I. And according to this study in Table 5 it was found that 6 patients who were admitted to ICU represent 20% of patients in group I.

This result agreed with [5], who found that there is a range of severity among patients hospitalized with AECOPD, with the more severely ill patients needing either non-invasive positive pressure ventilation (NIPPV) or endotracheal intubation and ventilation. As one would expect, patients admitted to the intensive care unit (ICU) have worse outcomes and increased mortality, but the use of NIPPV may provide some benefit. One study showed that ICU patients initially placed on mechanical ventilation had a much higher mortality [adjusted odds ratio (OR) 15.7; 95% confidence interval (CI)4.2,59] than patients placed on NIPPV.

In this present work it was observed that the mean range of duration of admission among COPD patients was 13.1 ± 6.3

Table 2 Comparison between pre-bronchodilator spirometry in COPD groups.

		Group		*t* Test	*p* Value	Sig.
		Group I	Group II			
FVC% pred	Pre	51 ± 10.6	55.4 ± 9.9	3.52	0.021	S
FVC L/m	Pre	2.24 ± 0.54	2.45 ± 0.54	2.96	0.036	S
FEV1% pred	Pre	40.4 ± 12.1	42.3 ± 6.9	5.326	0.005	S
FEV1 L/m	Pre	1.18 ± 0.32	1.17 ± 0.24	4.489	0.020	S
FEV1/FVC% pred	Pre	50.4 ± 8.3	54.1 ± 7.1	2.13	0.017	S
FEF 25–75% pred	Pre	23.6 ± 5.7	24.9 ± 7.16	2.35	0.024	S
FEF 25–75% L/M	Pre	0.76 ± 0.46	0.67 ± 0.32	4.518	0.005	S

This table shows a significant difference in pre-bronchodilator FVC % pred, FEV1 % pred, FEV1/FVC % pred and FEF 25–75% pred between group I and II.

Table 3 Comparison between post-bronchodilator spirometry in COPD groups.

		Group		*t* Test	*p* Value	Sig.
		Group I	Group II			
FVC% pred	Post	62.7 ± 11.2	63.8 ± 9.46	1.53	0.236	NS
FVC L/m	Post	2.29 ± 0.58	2.30 ± 0.52	0.147	0.520	NS
FEV1 pred	Post	41.8 ± 12.5	44.7 ± 5.79	4.935	0.007	S
FEV1 L/m	Post	1.27 ± 0.34	1.29 ± 0.22	2.142	0.048	S
FEV1/FVC% pred	Post	51.7 ± 9.1	54.7 ± 8.7	3.201	0.039	S
FEF 25–75% pred	Post	26.1 ± 12.2	25.1 ± 7.52	4.130	0.020	S
FEF 25–75% L/M	Post	0.81 ± 0.45	0.66 ± 0.38	3.201	0.027	S

This table shows a non-significant difference in post-bronchodilator FVC% pred between group I and II. While there was a significant difference in post-bronchodilator FEV1% pred, FEV1/FVC% pred and FEF 25–75% pred between group I and II.

Table 4 Comparison between COPD groups as regards the smoking index.

Smoking index	Group I		Group II		Total		X^2	P value
	No.	%	No.	%	No.	%		
Mild	0	0	2	7.7	2	4	4.629	0.030* S
Moderate	6	25	8	30.8	14	28		
Sever	8	33.3	9	34.6	17	34		
Very severe	10	41	7	26.9	17	34		
Total	24	100	26	100	50	100		

This table shows a significant difference between the two groups of COPD patients and the smoking index, while group III was non-smoker.

Table 5 Percentage of ICU admission among Group I COPD patients.

	ICU admission	
	N	%
Yes	6	20
No	24	80
Total	30	100

This table shows 20% of patients were admitted in ICU, while 80% of patients not admitted.

Table 6 Duration of admission among COPD patients.

	Minimum	Maximum	Mean ± SD
Duration of admission (days)	5	30	13.1 ± 6.3

This table shows the mean range of duration of admission among COPD patients 13.1 ± 6.3 with Maximum period 30 days and Minimum period 5 days.

Table 7 Levels of serum IL-1B (pg/ml) among the studied groups.

IL-1B (pg/ml)	Group			Sig.
	Group I	Group II	Group III	
Range	3.6–6.8	2.4–4	1.2–3	
Mean ± SD	5.15 ± 0.80	3.29 ± 0.43	1.52 ± 0.15	
F test	11.639			
p Value	0.001*			HS
Scheffe Test				
**P*1 value	0.006*			HS
**P*2 value	0.001*			HS
**P*3 value	0.001*			HS

P*1: comparison between group I and group II.P*2: comparison between group I and group III.**P*3: comparison between group II and group III.
This table shows a highly significant difference in levels of serum IL-1B (pg/ml) among the studied groups.

with Maximum period 30 days and Minimum period 5 days which represent a wide range (Table 6).

This is in agreement with [6] who found that lower FEV1 was associated with higher rates of COPD exacerbations and readmissions.

Table 8 Correlation between serum IL-1B (pg/ml) and the smoking index of acute exacerbation (group I) of COPD cases.

Group I	IL-1B (pg/ml)		
	r	*P* value	Sig
Smoking index	0.425	0.017	S

This table shows a positive significant correlation between serum IL-1B (pg/ml) and smoking index of group I.

Table 9 Correlation between serum IL-1B (pg/ml) and the smoking index of controlled COPD cases (group II).

Group II	IL-1B (pg/ml)		
	r	*P* value	Sig
Smoking index	0.325	0.032	S

This table shows a positive significant correlation between serum IL-1B (pg/ml) and smoking index of group II.

Table 10 Correlation between serum IL-1B (pg/ml) and ICU admission and duration of admission of group I.

Group I	IL-1B (pg/ml)		
	r	*P* value	Sig
ICU admission	−0.285	0.027	S
Duration of admission (days)	0.714	0.253	NS

This table shows a significant correlation between serum IL-1B (pg/ml) and ICU admission of group I, while there was a non-significant correlation in duration of admission between serum IL-1B (pg/ml) and the same group I.

Table 11 Correlation between serum levels of IL-1B and severity of COPD according to [7] in group I.

IL-1B (pg/ml)	GI		
	Moderate	Severe	V. severe
Range	3.6–5.8	4.18–6.8	5.7–6.1
Mean ± SD	4.30 ± 0.69	5.20 ± 0.64	5.90 ± 0.15
F test	5.325		
p Value	0.001		
Sig	HS		

This table shows a highly significant correlation between IL-1B and severity of COPD in group I.

Table 12 Correlation between serum levels of IL-1B and severity of COPD according to [7] in group II:

IL-1B (pg/ml)	GII		
	Moderate	Severe	V. severe
Range	2.4–3.2	2.7–3.9	3.5–4
Mean ± SD	2.87 ± 0.28	3.33 ± 0.36	3.82 ± 0.22
F test	6.325		
p Value	0.008		
Sig	HS		

This table shows a highly significant correlation between IL-1B and severity of COPD in group II.

In this current study it was reported that there is a highly significant difference in the level of IL-1B between the three groups. The level of (IL-1Beta) was related to the stage of the disease as there was a significant increase in (IL-1Beta) level with increasing severity of COPD; very severe COPD cases have a higher level of (IL-1Beta) than severe and moderate cases, (IL-1Beta) was also raised in severe cases than moderate cases and the difference between them was highly statistically significant ($p < 0.01$) (Table 7).

This is matched with [1], who reported that COPD results from airway inflammation involving multiple inflammatory mediators and tissue damage.

This could be explained by the nature of COPD as a complex chronic inflammatory disease of the lungs involving several types of inflammatory cells and a variety of inflammatory mediators. Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic repercussions [2].

This result is in agreement with [16], who found that there is a significantly high level of IL-1β in serum of the COPD patients as compared to the healthy controls. A few studies previously undertaken have also reported a rise in IL-1β in COPD cases.

Also this result is in agreement with [17], who reported that in the control group, the IL-1β level was 2.11 ± 0.16 pg/ml (range: 0.39–2.97 pg/ml), which was significantly lower than COPD patients (3.14 ± 0.07, range: 2.8–4.59 pg/ml, $p < 0.05$).

Sapey et al. [16], proved that there are increased levels of circulating cytokines and acute phase reactants have been seen in the peripheral circulation of patients suffering from COPD, especially during exacerbations. They also proved that IL-1β plays a critical role in COPD where it was found to correlate significantly with FEV1 suggesting its role in clinical aspects of disease severity.

All these results are in agreement with [9], who concluded that modulation of various inflammatory mediators may help in combating the clinical outcome of COPD and may have therapeutic implications whereas determination of serum IL-1β levels may help in differentiating COPD from other respiratory disorders such as asthma.

On the contrary, this result disagreed with [15], who proved that IL-1β may be related to pathophysiology in COPD, although there were no significant differences in IL-1β concentrations between their groups (Table 10).

In this current work it was found that there is a highly significant correlation between IL-1B and COPD severity in groups I and II (Table 11 and 12).

This result matched with [11], who found that IL-1β expression in COPD neutrophils correlates with disease severity. This result is also in agreement with [16], when studying the demonstration of IL-1B and TNF levels in serum and sputum, he found that IL-1B plays a critical role in COPD where it was found to correlate significantly with FEV1 suggesting its role in clinical aspects of disease severity.

Conflict of interest

We have no conflict of interest to declare.

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