Original Article

Study of inflammatory markers and BODE index in chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by progressive airflow limitation and associated with enhanced chronic inflammatory response of the airways to a variety of noxious stimuli. The current concept of COPD, however, extends beyond the respiratory system to include a variety of extrapulmonary manifestations which includes raised inflammatory markers. **Methods:** This was a single, center observational open-labeled case–controlled study which included fifty patients of diagnosed COPD and 50 age- and gender-matched controls. All patients were evaluated by detailed history taking, pulmonary function test, 6-min walk test, and calculation of BODE scores. Levels of serum inflammatory markers such as cortisol, tumor necrosis factor alpha, interleukin-6 (IL-6), lactate dehydrogenase, and C-reactive protein were estimated using standard quality equipments. **Observations:** Majority of the patients in the study and control groups were males and were aged above 40 years. Thirty-eight of the fifty COPD patients had BODE scores of more than 3. All the studied inflammatory markers were significantly higher in the COPD group as compared to the control group. Of all the studied markers, only IL-6 showed a significant correlation with BODE index, i.e., higher IL-6 values were associated with higher BODE scores. No correlation was seen between the other markers and BODE scores. **Conclusions:** Our data suggest that IL-6 is a biomarker that correlates with BODE score. IL-6 as a target for therapy in COPD needs to be further studied. Follow-up studies are needed to validate findings.

KEY WORDS: BODE, chronic obstructive pulmonary disease, inflammatory markers, interleukin-6

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) 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.[1]

In addition to causing pulmonary abnormalities, COPD is associated with systemic manifestations such as weight loss, skeletal muscle dysfunction, systemic inflammation, and cardiovascular disease. Mechanisms for these changes include persistent inflammation and oxidative stress.[2-4] A physiological variable – the forced expiratory volume in 1 s (FEV1) is often used to grade the severity of COPD. However, patients with COPD have systemic manifestations that are not reflected by FEV1 alone. Apart from FEV1 and BODE index, parameters such as 6-min walk distance, CAT score, dyspnea scores, as well as a history of infective exacerbations can be used to gauge the severity of COPD.

Biomarkers are measurable indicators of some biological state or condition. The study of biomarkers is an upcoming area of medicine which is being touted as having a good potential to not only find out the disease activity but also to navigate therapy. However, there is a dearth of information and knowledge regarding the use of biomarkers to determine the activity of COPD.

This study is an endeavor to study the various biomarkers in COPD – namely C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), serum cortisol and lactate dehydrogenase (LDH) levels as indicators of active inflammation and their association with other parameters such as BODE index. It is an attempt to open avenues toward a better understanding of the inflammation associated with COPD and may pave the way for therapies being directed at the core pathophysiology of COPD, i.e., inflammation.

SUBJECTS AND METHODS

The study was a single, center, open-labeled observational case–controlled study carried out at a tertiary health-care center in Mumbai, India. One hundred participants were enrolled in the study, of which fifty were diagnosed cases of COPD, and the remaining fifty were age- and gender-matched controls. The study was conducted after taking required permissions from the Institutional Ethics Committee. Patients were enrolled in the study over a period of 18 months. The COPD patients were included in the study after obtaining a valid consent. Patients with active pulmonary tuberculosis and unable to perform pulmonary function test (PFT) and 6-min walk test (6MWT) were not included in the study.

Hospital staff, students, and interns who were healthy, nonsmokers and willing to participate in the study were included as controls. In addition, healthy relatives of patients who did not have history of exposure to smoke or infectious diseases such as tuberculosis were included in the study as controls after taking consent. The controls were matched for gender and age. Patient details – the patient's age, height, and weight (without shoes) were recorded for the calculation of reference values. Apart from the chest X-ray, routine blood investigations, sputum acid-fast bacilli examination and PFT, 6MWT, and inflammatory markers were estimated of the patients. BODE score was calculated by analyzing all the four variables [Table 1].[5]

- BMI (B) = Weight (kg)/Height (m²)
- Airflow obstruction (O) obtained from the spirometry reading – postbronchodilator FEV1
- Dyspnea (D) - calculated by questioning the patient about the severity of breathlessness based on the Medical Research Council grading
- Exercise tolerance (E) measured by the 6MWT.

Scoring for every patient done by analyzing all the four parameters and the final BODE score (out of a maximum of 10) obtained.

Table 1: Scoring BoDE Index

Variable	Points on the BODE index			
	0	**1**	**2**	**3**
FEV$_1$ (% predicted)	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC dyspnea scale	0-1	2	3	4
BMI (kg/m²)	>21	≤21		

Total BODE index score: 0-10 units. FEV$_1$% predicted: Predicted amount as a percentage of the forced expiratory lung volume in 1 s, MMRC: Modified medical research council dyspnea scale, BMI: Body mass index, 6MWD: 6-min walking distance

Table 2: Age distribution in the chronic obstructive pulmonary disease and control group

Age groups (years)	COPD (%)	Control (%)	Total (%)
20-40	4 (4)	0	4 (4)
40-60	20 (20)	16 (16)	36 (36)
Above 60	26 (26)	34 (34)	60 (60)
Total	50 (50)	50 (50)	100 (100)

COPD: Chronic obstructive pulmonary disease

Table 3: BODE index distribution in chronic obstructive pulmonary disease group

BODE index	Number of patients in the copd group (%)
0	0
1-3	12 (24)
3-5	21 (42)
>5	17 (34)
Total	50 (100)

Serum markers of systemic inflammation were calculated in a special laboratory in the Department of Biochemistry, using standard quality equipment and well-trained technicians.

Data analysis
Data were recorded in the prescribed format of case record form and compiled in the Microsoft XL worksheet 2010. Descriptive statistics was employed to represent data.

Statistical analysis
For statistical analysis ''GraphPad InStat Software Indiago California'' was used. The quantitative data between the two groups was compared using unpaired *t*-test.

RESULTS

A total of 100 patients were enrolled in the study, out of which 86% were male, and 14% were female. Forty-six percentage of the COPD group were male, and 4% were female.

Out of the 100 patients included in the study, 4% patients (4% COPD and 0% in controls) were between 20 and 40 years, 36% patients (20% COPD and 16% controls) were between 40 and 60 years and 60% (26% of COPD and 34% of controls) were above 60 years of age [Table 2].

In the COPD group, 24% patients had a BODE index between 1 and 3, 42% patients had a BODE index between 3 and 5, and the remaining 34% had a BODE index above 5 [Table 3].

Table 4: Comparison of the mean values of inflammatory markers in the chronic obstructive pulmonary disease group and control group

Markers	COPD	Control	*P*	Significance
CRP	4.732	1.306	<0.0001	Significant
IL-6	36.282	3.732	0.007	Significant
TNF-α	87.721	15.878	<0.0001	Significant
LDH	326.26	155.41	<0.0001	Significant
Cortisol	39.496	25.302	<0.0001	Significant

CRP: C-reactive protein, IL-6: Interleukin 6, TNF-α: Tumor necrosis factor-alpha, LDH: Lactate dehydrogenase, COPD: Chronic obstructive pulmonary disease

Table 5: Association of inflammatory markers and BODE index

Markers	Mean of markers	Mean BODE index	*P*	Significance
CRP	4.732	4.7	0.6	Not significant
1L-6	36.282		0.04	Significant
TNF-α	87.721		0.1	Not significant
LDH	326.26		0.2	Not significant
Cortisol	39.496		0.9	Not significant

CRP: C-reactive protein, IL-6: Interleukin 6, TNF-α: Tumor necrosis factor-alpha, LDH: Lactate dehydrogenase, COPD: Chronic obstructive pulmonary disease

The mean BODE index of the COPD group was 4.7 whereas it was 0.4 in the control group.

In this study, five inflammatory markers were investigated, both in the COPD group and in the control group. The markers were CRP, IL-6, TNF-α, LDH, and cortisol [Table 4]. Significance between the markers in the COPD and control group was determined using the "unpaired *t*-test."

The mean CRP in the COPD group was 4.732 whereas it was 1.306 in the control. *P* value of the difference was <0.001; it was statistically significant.

The mean IL-6 in the COPD group was 36.282, whereas it was 3.732 in the control. The *P* value of the difference was 0.007; it was statistically significant. The mean TNF-α in the COPD group was 87.721 whereas it was 15.878 in the control ($P < 0.001$). The mean LDH in the COPD group was 326.26 whereas it was 155.41 in the control ($P < 0.001$).

The mean cortisol in the COPD group was 39.496 whereas it was 25.302 in the control ($P < 0.001$) [Table 5]. As the data were quantitative type of data, when an association between various inflammatory markers and BODE Index was attempted, the mean of various inflammatory markers and the mean of BODE index of the COPD group were compared using the "unpaired *t*-test."

The association between various inflammatory markers and the BODE index revealed that only association of IL-6 was significant whereas that of other markers studied was statistically insignificant [Table 5].

DISCUSSION

COPD is an obstructive airway disease, which has an amplification of the underlying inflammatory process of the airways, manifested by cardinal symptoms of productive cough, and progressive shortness of breath.

The current understanding of COPD has revealed it to be a systemic disease rather than being restricted to the respiratory system. It has various extrapulmonary manifestations such as Ischemic heart disease, metabolic syndrome, obstructive sleep apnea syndrome, and anemia.

In this study, a total of 100 patients were included, out of which 50 patients had stable COPD. The remaining 50 were healthy age- and gender-matched controls. In the study population, there were 46 males and 4 females as compared to 40 males and 10 females in the control population. There were more males in the study compared to females. This is comparable to the general prevalence of COPD in India, where the male to female ratio is 1.56:1 above the age of 35 years.[5]

In our study of the various inflammatory markers, it was found out that all the biomarkers were significantly raised in the study group as compared to the control group [Table 4]. These findings are comparable to a study conducted by Gan *et al*.[6] wherein he found that individuals with chronic airflow limitation in COPD had significantly raised levels of CRP, TNF-α, and IL-6.

Furthermore, in a study by Karadag *et al*.[7] inflammatory markers such as CRP, IL-6, and TNF-α were raised in patients with stable COPD. de Torres *et al*.[8] found that CRP levels were significantly raised and were an important factor in the outcome of stable COPD patients. This was also confirmed by a study conducted by Bhandohal *et al*.[9] who evaluated serum biomarkers of oxidative stress and airway inflammation in COPD.

BODE index was calculated using the standard parameters. As per Table 5, none of the COPD patients had a BODE score of 0. Twelve patients had a BODE index between 1 and 3, 21 patients had a BODE index between 3 and 5, and 17 patients had a BODE index more than 5. The mean BODE index of the study group was 4.7, compared to 0.4 of the control group. This difference was found to be statistically significant ($P < 0.001$).

The biomarkers of inflammation were studied for their correlation with BODE index in the study group. It was found that only IL-6 had a positive significant correlation with BODE index in the patients with COPD ($P = 0.04$), i.e., as levels of IL-6 increased the values of BODE index increased.

Various studies have attempted to find the association of biomarkers of inflammation with BODE index. In a study conducted by Garcia-Rio *et al*.,[10] IL-6 and CRP had a

significant association with BODE index. It showed that as the values of BODE index increased, the levels of IL-6 and CRP also increased. In another study carried out by Agustí *et al*.,[11] levels of CRP, IL-6, and TNF-α increased with the severity of airflow limitation and BODE index. Thus, the study corroborates with most of the Western studies which show a correlation between inflammatory markers, especially IL-6 and BODE index. Extensive search did not yield any study on inflammatory markers and BODE index in COPD in the Indian setup.

COPD is currently ranked fourth as far as global mortality is concerned. The deaths due to this disease continue to soar because of the rampant use of cigarettes and because of inadequate therapy.

The current therapeutic regimen concentrates mainly on hypoxia and bronchodilation which are mainly symptomatic in approach. This study may pave the way for a pathogenic therapeutic rationale in COPD by concentrating on the main pathophysiology of COPD, which is inflammation.

As the population of patients in this study is small, the finding of this study need to be confirmed on larger multicentric study on common protocol population. The association needs to be further confirmed with a follow-up study.

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Conflicts of interest
There are no conflicts of interest.

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