Original Article

DOI: 10.17354/ijss/2015/470

C-Reactive Protein in Chronic Obstructive Pulmonary Disease, its Correlation with Lung Function and the Role of Statin in Chronic Obstructive Pulmonary Disease

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Abstract

Background: The link between increased C-reactive protein (CRP) and the prediction of cardiovascular risk has suggested that there might be an association between chronic obstructive pulmonary disease (COPD) and the increased incidence of cardiovascular disease (CVD) among other comorbidities.

Aim: The present study was done to study the relationship between the biomarker of systemic inflammation *viz*. CRP and disease severity, functional status and outcome in COPD patients over a period of 120 days after an acute exacerbation.

Materials and Methods: An observational cross-sectional study was done on 179 patients with COPD presenting in acute exacerbation to Department of Medicine in Nehru Chikitsalay of B. R. D Medical College, Gorakhpur from January 2014 to June 2014. Forced expiratory volume, BODE index and COPD assessment test were studied. All patients underwent a detail history and clinical examination at presentation and on follow-up visits on days 15, 30, and 120.

Results: In present study out of 179 patients, 105 (58.65%) were male, and 74 (41.34%) were female. Most of the patients were in the age group of 50-70 years (60.88%). The CRP was raised (≥3 mg/l) in 136 (75.97%) patients out of that 82 (79.61%) attended day 120 follow-up and the other, 43 (24.02%) patients did not have a raised CRP at the initial visit. Out of 27 patients who expired, 26 (96.29%) had raised CRP (≥3 mg/l) at initial presentation. A total 28 patients were lost during follow-up.

Conclusion: We observed that not all COPD patients had a raised CRP but in those who had a raised CRP, its levels correlated with lung function and functional status of the individual and CRP trends could be a predictor of death. In our study, we found a definite correlation between CRP and lung function. COPD is the "cause or effect of systemic inflammation still needs to be established.

Keys words: C-reactive protein, Chronic obstructive pulmonary disease, Lung function

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable lung disorder characterized by progressive, poorly reversible airflow limitation often with systemic manifestations, in response to tobacco smoke and/or other harmful inhalational exposures.[1] Exacerbations and comorbidities contribute to the overall severity of disease and functional status in individual patients.[1]

COPD is frequently associated with comorbidities,1 the most serious and prevalent being atherosclerosis cardiovascular disease,[2] anorexia,[2,3] lung cancer,[1,4] osteoporosis,[3] muscle weakness,[1] cachexia,[3,1] normocytic normochromic anemia, increased gastro esophageal reflux and clinical depression and anxiety. These comorbidities contribute to impaired functional capacity, worsening dyspnea, reduced health-related quality of life and increased mortality.

Access this article online

www.ijss-sn.com

Month of Submission : 08-2015
Month of Peer Review : 09-2015
Month of Acceptance : 10-2015
Month of Publishing : 10-2015

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There are several biomarkers of systemic inflammation studied in COPD of which C-reactive protein (CRP) and fibrinogen are very important. The link between increased CRP and the prediction of cardiovascular risk has suggested that there might be an association between COPD and the increased incidence of cardiovascular disease (CVD) among other comorbidities.[5,6]

Statins are a group of drugs are that has shown to have pleotropic effects like anti-inflammatory and vasodilatory functions in addition to their lipid-lowering effects.[7] Statin therapy has been shown to reduce CRP levels even in those with normal lipid levels. Though proven in coronary artery disease the role of statins in COPD is emerging.[8]

The present study was done to study the relationship between the biomarker of systemic inflammation *viz.* CRP and disease severity, functional status and outcome in COPD patients over a period of 120 days after an acute exacerbation.

MATERIALS AND METHODS

An observational cross-sectional study was done on 179 patients with COPD presenting in acute exacerbation (AECOPD) to Department of Medicine in Nehru Chikitsalay of B. R. D Medical College, Gorakhpur from January 2014 to June 2014, who were diagnosed by following.

A written Informed consent and Institutional Medical Ethical Committee approval was taken before starting the study.

About 179 patients clinically diagnosed as AECOPD were included in the study. Without any history of diabetes, hypertension and chronic kidney disease, and not consent.

A record was maintained for height, weight, body mass index (BMI), and 6 min walk distance for all patients. Act of three subjected to routine blood examination hemoglobin forced expiratory volume (FEV1) was noted in all patients a spirometry following the (American thoracic guidelines). Modified Medical Research Council Dyspnea Scale was used to assess the severity of dyspnea in COPD patients as per the prescribed format by GOLD.

BODE index for COPD which includes BMI (B), degree of airflow obstruction (O), functional dyspnea (D), and exercise capacity (E) was also obtained from the patient's data. COPD assessment test (CATest) was used to assess the impact of COPD on the functional status of the patient.

All the patients underwent a detail history and clinical examination at presentation and on follow-up visits on days 15, 30, and 120.

RESULTS

In present cross-sectional study out of 179 patients, 105 (58.65%) were male and 74 (41.34%) were female. Most of the patients were in the age group of 50 to 70 years (60.88%) (mean ± 50 years).

Comparison of mean CRP levels done by Mann-Whitney test showed that mean CRP among males was 29.07 ± 42.07 mg/l and that in females were 39.05 ± 63.05 mg/l ($P = 0.93$).

The CRP was raised (≥3 mg/l) in 136 (75.97%) patients out of that 82 (79.61%) attended day 120 follow-up and the other, 43 (24.02%) patients drop out to some cause. Out of 27 patients who expired, 26 (96.29%) had raised CRP (≥3 mg/l) at initial presentation. A total contraindictory 28 patients were lost during follow-up.

The mean CRP of the patients who had raised CRP at the acute exacerbation was 34.55 ± 47.18 mg/l. At 120 days follow-up visit, COPD patients still had a high CRP (≥3 mg/l). Mean CRP was 3.96 ± 3.69 mg/l.

Comparison of percentage predicted FEV1 (day 15 follow-up visit) levels in patients with CRP ≥3 mg/l and those with CRP <3 mg/l showed that patients with serum CRP levels ≥3 mg/l had significantly less FEV1 at day 15 follow-up visit than those with CRP <3 mg/l at presentation.

Mean 6 min walk distance (at day 15 follow-up visit) in patients with CRP ≥3 mg/l was 317.92 ± 91.8 and those with CRP <3 mg/l was 276.3±102.7 which means patients with serum CRP levels ≥3 mg/l had significantly less 6 min walk distance at day 15 follow-up visit than those with CRP<3 mg/l at presentation.

Median Modified Medical Research Council (MMRC) in patients (109) with CRP ≥3 mg/l was 3 and patients (43) with CRP <3 mg/l was 2 which means patients with serum CRP levels ≥3 mg/l had significantly worse MMRC dyspnea score than those with CRP < 3 mg/l at presentation.

CATest score in patients (109) with CRP ≥3 mg/l was 24 and those with CRP <3 mg/l CATest score was 21 which means patients with serum CRP levels ≥ 3 mg/l had significantly worse CATest score dyspnea score than those with CRP < 3 mg/l at presentation.

Correlation of change in CRP with change in 6 min walk distance, FEV1, MMRC and CATest score over 120 days showed that The change of CRP was significantly correlated with improvement in 6 min walk distance, FEV1, MMRC, and CATest score over the study period of 120 days.

Out of those who had raised CRP at day 1 and attended day 120 follow-up visit, 44 patients had CRP ≥3 mg/l and 36 patients had CRP < 3 mg/l at the day 120 follow-up visit.

Expired patients (27) had mean CRP (mg/l) of 45.89 ± 48.93 and Survived (110) patients had CRP (mg/l) of 25.4 ± 3.4 which means The COPD patients who expired during the post exacerbation period had a higher CRP at the acute exacerbation than those who survived. None of the patients who expired were on statin therapy.

Mean CRP at day 1 and day 15 among patients who expired during the study was 45.89 ± 48.93 and 53.98 ± 45.65, respectively, and in those who survived was 25.32 ± 42.66 and 7.98 ± 10.35, respectively.

DISCUSSION

COPD is a life threatening disease with ever increasing incidence and prevalence. It has been called to be a "Silent epidemic" across the globe. COPD is frequently associated with comorbidities like CVD, osteoporosis, anemia, depression, lung cancer among others which make their impact on health even more alarming.[1,4]

In a study done by Gupta *et al.*, the mean age of COPD patients was 59.38 ± 11.70 years with a Male:Female ratio of 81:19. Our study has shown the similar results.[9]

We enrolled the patients as per the inclusion criteria, and follow-up was advised to them on days 15, 30 and 120 after the initial presentation. At the initial presentation, the mean CRP of all COPD patients was raised in COPD in acute exacerbation. This supports that there is evident systemic inflammation at the acute exacerbation of COPD. The rise in CRP at the exacerbation could be due to a response to infection as there was a group of 43 patients who had CRP <3 mg/l at the acute exacerbation.

The decline in CRP levels on follow-up may be a marker of recovery from the exacerbation of COPD among this subgroup of patients.

Among COPD patients who had CRP <3 mg/l at the initial presentation, there was no significant change in CRP on successive follow-up visits thereafter. This suggests that COPD is a heterogenous disease with multiple phenotypes. Gupta *et al.* did a study in Rohtak and found that that CRP was raised at acute exacerbation of COPD and there was a significant decline in CRP on a follow-up visit thereafter.[9]

We compared the pre-exacerbation functional status among those with raised CRP (≥ 3 mg/l) and those with CRP (< 3 mg/l) at the acute exacerbation. We found that the group of patients with raised CRP had a worse MMRC score and CATest score. They also had a worse FEV1 and 6 min walk distance at the first follow-up visits.

On interquartile analysis of the lung function parameters, we found that the quartile with higher CRP had a statistically worse CATest score and worse FEV1 and worse 6 min walk distance at day 15 follow-up visits (Table 1). This further supports that patients with more systemic inflammation had worse functional capacity and more severe airflow limitation. Table 2 showed correlation between CRP with lung function parameters of survivors on corresponding visits.

Table 2: Correlation analysis between CRP with lung function parameters of survivors on corresponding visits

LFP	Day 1 (*n*=109)		Day 15 (*n*=101)		Day 30 (*n*=86)		Day 120 (*n*=80)	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
6 MWD	-	-	−0.24	0.003	−0.28	0.002	−0.33	0.0006
FEV_1	-	-	−0.25	0.002	−0.24	0.01	−0.22	0.02
BODE	-	-	0.4	0.0001	0.23	0.01	0.35	0.0002
MMRC	0.41	0.0001	0.36	0.0001	0.31	0.0008	0.4	0.0001
CAT	0.42	0.0001	0.41	0.0001	0.37	0.0001	0.4	0.0001

CRP: C-reactive protein, 6 MWD (m): 6 min walk distance, MMRC: Modified Medical Research Council Dyspnea Scale, CAT: COPD assessment test, FEV1: Forced expiratory volume in 1 s, LFP: Lung Function Parameters. CRP was significantly correlated with 6 min walk distance, FEV1, MMRC and CATest score on each of the visits. (*r*=Pearson/spearman correlation coefficient)

Table 1: Inter quartile analysis of CRP with respect to various lung function parameters

Lung function parameter	CRP (mg/l)				*P* value
	I Quartile (0.2-2.6) (*n*=39)	II Quartile (2.6-9) (*n*=37)	III Quartile (9-26) (*n*=37)	IV Quartile (26-212) (*n*=37)	
6 MWD (m)	92.4±97.6	263.8±104.5	241.7±99.2	202.4±109.3	0.001
MMRC	2	3	3	3	0.56
CAT	21	22	23	25.5	0.001
FEV_1 (% predicted)	44.5±17.2	2.16±15.1	38.9±14.2	34.6±13.6	0.001

CRP: C-reactive protein, 6 MWD (m): 6 min walk distance, MMRC: Modified Medical Research Council Dyspnea Scale, CAT: COPD assessment test, FEV1: Forced expiratory volume in 1 s. With a higher CRP quartile, we observed a worse 6 min walk distance, worse FEV1 and a worse COPD assessment test score

Table 3: Comparison of lung function parameters between statin and non-statin group

LFP	Day 1			Day 30			Day 120		
	Statin (*n*=30)	Not statin (*n*=109)	*P* value	Statin (*n*=26)	Not statin (*n*=86)	*P* value	Statin (*n*=23)	Not statin (*n*=82)	*P* value
CRP	40.7±8.7	31.92±4.2	0.2	5.29±0.9	5.746±0.8	0.7	3.548±0.6577	3.973±0.4718	0.6
6 MWD	254.2±20.6	234.5±9.4	0.4	300.6±18.8	304.7±1.1	0.8	312.7±20.84	317.9±10.92	0.8
FEV_1	37.96±2.7	37.84±1.3	0.9	38.81±2.7	39.80±1.5	0.7	38.40±2.941	40.89±1.508	0.4
CAT	23	23	0.8	19	18	0.9	17	16	0.9
MMRC	3	3	0.7	2	2	0.6	2	2	0.57

CRP: C-reactive protein, 6 MWD (m): 6 min walk distance, MMRC: Modified Medical Research Council Dyspnea Scale, CAT: COPD assessment test, FEV1: Forced expiratory volume in 1 s, LFP: Lung Function Parameters

de Torres *et al.* compared the clinical parameters of COPD patients with initial CRP values >3 mg/l or ≤3 mg/l in a study, and they did not find any significant differences in FEV_1, forced vital capacity, confidence interval/conventional physiotherapy, GOLD stage, MMRC scale or BODE score between the two subgroups.[10]

In our study, on the last follow-up visit at 120 days after the initial presentation in the stable phase of the disease, COPD patients still had a raised CRP with the mean of 3.96 ± 3.67 mg/l, being higher than 3 mg/l considered as the upper limit[11] denoting a parallel low grade systemic inflammation. This suggests that systemic inflammation is an inherent part of the disease both in the acute exacerbation as well as in the stable state. The ongoing systemic inflammation in COPD may be the link between COPD and the comorbidities often observed in COPD though further studies are required in this regard.

Halvani *et al.* did a study on 45 stable COPD patients and found that CRP was raised in COPD patients without potential confounders like ischemic heart disease and cigarette smoking.[12]

Although present study did not find any benefit of statin in all patients of COPD (Table 3), the role of statins in acute exacerbation of COPD in patients with raised CRP will need to be studied in a larger prospective study.

Our study had some limitations. First, a significant number of patients did not turn up for follow-up at all the visit. Second, we used a turbidimetry method for measurement of CRP and not the enzyme-linked immunosorbent assay method which is said to be the best method.[13]

CONCLUSION

Present study showed that not all COPD patients had a raised CRP but in those who had a raised CRP, its levels correlated with lung function and functional status of the individual and CRP trends could be a predictor of death. In our study, we found a definite correlation between CRP and lung function. COPD is the "cause or effect" of systemic inflammation still needs to be established.

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How to cite this article: : Kumar R, Nigam P. C-Reactive Protein in Chronic Obstructive Pulmonary Disease, its Correlation with Lung Function and the Role of Statin in Chronic Obstructive Pulmonary Disease. Int J Sci Stud 2015;3(7):168-171.

Source of Support: Nil, **Conflict of Interest:** None declared.