To study the serum C-reactive protein level and its correlation with prognostic variables in stable COPD patients

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Abstract

Introduction: C-reactive protein is a stable and excellent biomarker of systemic inflammation which is easy to measure. COPD is an inflammatory disorder of lung with widespread Systemic manifestations and associated Systemic inflammatory response. C-reactive protein levels are increased in COPD patients. Present study investigated C-reactive protein level in stable COPD patients and its relation with clinically important outcome variable, exercise capacity.

Method: Study included 56 stable COPD patients with mild to moderate severity in age group 40-70 years and 56 nonsmoking controls in the same age group. Clinical and physiological characteristics were determined and C-reactive protein levels were measured.

Result: This study confirms the finding of higher C-reactive protein levels in smoker COPD patients (4.9 vs 4.0 mg-L\textsuperscript{-1}) as compared to nonsmoker COPD patients. It also confirms that level of C-reactive protein in ex-smoker COPD population remains significantly higher than nonsmoker control group (4.9±0.5 vs 3.1mg/l).

Conclusion: C-reactive protein level was strongly associated and correlated with 6 minute walk distance, FEV\textsubscript{1} and GOLD stages, so C-reactive protein level can indirectly reflect prognosis of COPD patient and his exercise capacity. We recommend that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients. It also provides strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

Keywords: COPD, C-reactive Protein Level, Exercise Capacity, 6MWT.
prognostic factor of COPD i.e. exercise capacity (6MWT), FEV$_1$ and GOLD stage.

Aims and Objectives

1. To know the mean serum C-reactive protein level in normal healthy individual as well as COPD patients in the same age group.
2. To find out association of serum C-reactive protein level with prognostic variables like exercise tolerance, FEV1 and GOLD disease stage in stable COPD patient.

Material and Methods

Fifty six patients of age 40-70 years with mild to moderate grade of COPD (FEV$_1$>50% predicted), with no exacerbations reported in last 6 months, were chosen from the outpatient department and were selected as cases for the study. Patients having recent abdomino-thoracic or ophthalmic surgery, recent coronary events, high blood pressure or any clinical evidence of infection, inflammation or CCF in previous three months were excluded. Simultaneously, fifty six apparently healthy nonsmoking subjects of similar age were also included as control.

After selection of patients, detailed history was taken to obtain information regarding age, education, occupation, socioeconomic status, personal habits, smoking, diabetes mellitus, hypertension etc. A thorough clinical examination was done. Routine investigations including complete blood count, erythrocyte sedimentation rate to exclude any infection, sputum for acid fast bacilli to rule out pulmonary Koch’s, serum billirubin and SGPT to exclude liver pathology (as CRP is mostly produced by liver) was done. Patients were then subjected to 6 minute walk test and spirometry.

In spirometry, best of three consecutive tests were taken into consideration. Patients were advised to stop bronchodilators and anticholinergic drugs for a period of 12 hours before spirometry. Forced vital capacity (FVC), Forced expiratory volume in 1 second(FEV1) and the ratio of FEV1/FVC, peak expiratory flow during middle half of FVC(FEF 25-75 or MMEFR) were measured. Pre and post bronchodilator study was done in all patients and there was no significant reversibility after bronchodilators in COPD patients. Participants were divided into four subgroups- mild, moderate, severe, very severe grade of COPD as per WHO GOLD criteria[6].

C-reactive protein was measured in serum, by immunoturbidimetry[7], in blood sample obtained in the morning (mean time 9.30 am) after 4hrs fasting.

Statistical Analysis: Variables were presented as a percentage, mean ± standard deviation or median depending on their distribution. As C-reactive protein values have non-normal distribution, logarithmic transformation was used to perform parametric testing. Univariate ANOVA with 95% confidence intervals(CI) for the estimation of differences were used to compare groups. Bivariate correlations between variables were evaluated by Pearson’s correlation. Statistical analysis was done using STAT PLUS® STATISTICAL ANALYSIS PROGRAMME version 2008 developed by ANALYSIS SOFT®.

Results

After analyzing the the patient population few observations were made .Mean age of patients was 58+_12 years. There were 12(21.4%) patients in the age group of 41-50 years,20(35.7%) in 51-60 years,24(42.9%) in the age group of 61-70 years. There were 51(91.1%) males and 5(8.9%) females. Out of 56 cases, 41(73.2%) cases were bidi or cigarette smokers, 5(8.9%)were having other risk factors(occupational and indoor air pollution), whereas 10 (17.9) had exposure to both. Mean body mass index (BMI) of these patients was 18+_3 Kg/m$^2$

Thirty (53.5%) patients were using inhaled $\beta_2$-agonist, four(7.2%) oral methyl-xanthines, twelve(21.4%) oral methyl-xanthines plus inhaled $\beta_2$-agonist and ten(17.9%)were taking inhaled $\beta_2$-agonist plus inhaled steroid. During the period of stability spirometry revealed 16(28.6%)of patients having mild COPD and 40(71.4%) as having moderate COPD, with overall mean FEV$_1$ 67+_17% predicted.

Comparison between cases and controls showed C-reactive protein levels were higher in chronic obstructive pulmonary disease patients than controls (4.9 vs 3.1 mg-L$^{-1}$). Moreover C-reactive protein levels were not equal between ex-smokers and current smoker COPD patients being higher in the later. In 6 minute walk test (6MWT), Mean distance
travelled by cases was 401.99 meters. Analysis of different variables to find out correlation with C-reactive protein levels was done. Comparisons of log C-reactive protein levels adjusted for 6 minute walk distance, FEV₁% and Body mass index did not reach statistical significance for sex, number of exacerbations smoking status and corticosteroids use.

Table-1: Parameters that significantly Correlated with log C-reactive protein levels

| Variable       | Correlation | p-value |
|----------------|-------------|---------|
| 6 minute walk distance | -0.28       | 0.001   |
| FEV₁%          | -0.24       | 0.029   |
| GOLD stage     | 0.19        | 0.040   |

log C-reactive protein levels showed statistically significant correlation with 6 minute walk distance, FEV₁% and GOLD stage. Then the variables showing significant correlation with log C-reactive protein levels were selected for multivariate analysis.

Table 3: Result of multivariate analysis

| Predictive parameter | Regression coefficient | p-value |
|----------------------|------------------------|---------|
| 6 minute walk distance | -0.004                 | 0.001   |
|                       | 0.001                  | -0.002-0.001 |
| FEV₁%                | 0.008                  | 0.008   |
|                       | -0.010-0.023           | 0.298   |
| GOLD stage           | -0.019                 | 0.125   |
|                       | -0.263-0.233           | -0.031  |

Result of multivariate analysis showed that 6 minute walk distance was the best explanatory factor for log C-reactive protein levels and rest others could not significantly correlated.

Table 2: Comparision of association of serum C-reactive protein with other variables in different studies

| Study                | year | 6MWD       | FEV₁%       | GOLD     | BMI        | No.of exacerbations |
|----------------------|------|------------|-------------|----------|------------|---------------------|
| Torres et al[8]      | 2008 | Negative association(c=-0.30,p=0.001) | Negative association(c=-0.20,p=0.030) | Positive association(c=0.17,p=0.040) | Positive association(c=0.17,p=0.050) | -                   |
| Kirdar S et al[9]    | 2008 | -          | -           | -        | Negative association(p=0.034) | -                   |
| Barnes P.J.et al[10] | 2006 | -          | -           | -        | Positive association(p=0.044) | -                   |
| SFP Man et al[4]     | 2006 | -          | Negative association(p=<0.001) | -        | -          | -                   |
| Celli B.R.et al[11]  | 2006 | -          | -           | -        | -          | No significant association |
| Koechlin et al[12]   | 2004 | Negative association | -          | -        | -          | -                   |
| Garrod R et al[13]   | 2007 | Negative association(r=0.50,p=<0.01) | -          | -        | -          | -                   |
| Doron Arnson et al[14]| 2006 | Negative association(c=-0.28,p=0.001) | Independent Negative association(c=-0.24,p=0.029) | Independent positive association(c=0.19,p=0.040) | Independent positive association(c=0.18,p=0.050) | No significant association |
| Present study        | 2015 | Negative association(c=-0.28,p=0.001) | Independent Negative association(c=-0.24,p=0.029) | Independent positive association(c=0.19,p=0.040) | Independent positive association(c=0.18,p=0.050) | No significant association |
Discussion

This study investigated the influence of prognostic factors on C-reactive protein levels in a well-defined population of stable COPD patients. The main finding of this study is that C-reactive protein levels are mostly associated and correlating with 6-minute walk distance. The study also found that C-reactive protein levels also correlated independently with two other important prognostic variables: FEV$_1$ and GOLD stage.

There is now sufficient evidence to support the presence of extra-pulmonary consequences of COPD that can be detected clinically. They can also be measured by the increased level of systemic bio-markers. C-reactive protein is one of these markers. It is an acute phase protein synthesized predominantly by the hepatocytes in response to tissue damage or inflammation.

Gan and co workers [15] showed that C-reactive protein is elevated in patients who actively smoked, had reduced lung function or even stable COPD. Study by Sin DD et al[16], demonstrated that in COPD patients-C-reactive protein levels predicted cardiovascular mortality. Lacy P et al[17] 2004, demonstrated that cardiovascular mortality and inflammation decreased with treatment with inhaled fluticasone. Pinto Plata et al[18], have shown that patients with COPD have higher levels of C-reactive protein independent of cardiovascular risk factors. Higher C-reactive protein level in stable COPD patients was also noted by Karadag F.et al[9].

Our study also confirms the previous finding of higher C-reactive protein levels in smoking COPD patients (4.9 vs 4.0 mg-L$^{-1}$) as compared to nonsmoking COPD patients, as also had been demonstrated by Gan WQ et al[4]. The level of C-reactive protein in ex-smoking COPD population remained significantly higher than nonsmoking control group ( 4.0 vs 3.1 mg-L$^{-1}$). Similar findings were also observed in study done by Casanova C.et al[8] and SFP Man et al.[4]. Then Pinto plata et al[18] also found similar results.

In present study using pearsons bivariate linear correlation coefficient correlation of serum C-reactive protein levels was found with FEV$_1$%, 6 minute walk distance, GOLD stage but result of multivariate analysis showed that only 6 minute walk distance significantly correlated with C-reactive protein levels. Similar results were found in some previous studies.

It was also observed that C-reactive protein levels inversely correlated with 6 minute walk distance. Broekhuizen et al 2006[19] found that C-reactive protein increases with poor exercise capacity. This indicates measuring C-reactive protein levels in stable conditions could indirectly reflect the exercise capacity of these patients, which is an important prognostic factor of the disease.

This study confirms the previous finding of higher C-reactive protein levels in smoking COPD patients as compared with nonsmoking COPD patients, as demonstrated by Gan WQ 2005[15]. The level of C-reactive protein in ex-smoking COPD population remained significantly higher than nonsmoking control group. This suggest that once initiated the inflammatory state seems to persist, albeit at a seemingly lower level. It provides us strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

Conclusion

Our study confirms that C-reactive protein levels are higher in COPD patients. This biomarker levels are associated with important clinical variables like FEV$_1$%, GOLD stage and 6 minute walk distance, which help to predict prognosis and patient outcome. Of these 6 minute walk distance is most strongly associated with C-reactive protein levels. So C-reactive protein levels indirectly reflects exercise capacity of stable COPD patients. Thus we conclude that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients.

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References

1. Vijayan VK. Chronic obstructive pulmonary disease.Indian J Med Res. 2013 Feb;137(2):251-69.

2. Agustí AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J. 2003 Feb;21(2):347-60.

3. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and
smokers. Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 1):1055-60.

4. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic reviewand a meta-analysis. Thorax. 2004 Jul;59(7):574-80.

5. Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. Chest. 2006 Aug;130(2):326-33.

6. Global strategy for the diagnosis, management and prevention of COPD 2014: Diagnosis and assessment, chapter 3:14.

7. Price CP, Trull AK, Berry D, Gorman EG. Development and validation of a particle-enhanced turbidimetric immunoassay for C-reactive protein. J Immunol Methods. 1987 May 20;99(2):205-11.

8. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005 Mar 15;171(6):591-7. Epub 2004 Dec 10.

9. Karadag F, Kirdar S, Karul AB, Ceylan E. The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease Eur J Intern Med. 2008 Mar;19(2):104-8. doi: 10.1016/j.ejim.2007.04.026.

10. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003 Oct;22(4):672-88.

11. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005-12.

12. Koechlin C, Couillard A, Cristol JP, Chaney P, Hayot M, Le Gallais D, Préfaut C. Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? Eur Respir J. 2004 Apr;23(4):538-44.

13. Garrod R, Marshall J, Barley E, Fredericks S, Hagan G. The relationship between inflammatory markers and disability in chronic obstructive pulmonary disease (COPD). Prim Care Respir J. 2007 Aug;16(4):236-40.

14. Aronson D, Roterman I, Yigla M, Kerner A, Avizohar O, Sella R, Bartha P, Levy Y, Markiewicz W. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. Am J Respir Crit Care Med. 2006 Sep 15;174(6):626-32. Epub 2006 Jun 15.

15. Gan WQ Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest. 2005 Feb;127(2):558-64.

16. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation. 2003 Mar 25;107(11):1514-9.

17. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004 Oct 1;170(7):760-5. Epub 2004 Jun 30.

18. Pinto-Plata VM, Müllerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax. 2006 Jan;61(1):23-8. Epub 2005 Sep 2.

19. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. Thorax. 2006 Jan;61(1):17-22. Epub 2005 Jul 29.
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