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Serum C Reactive Protein levels in Stable COPD Patients Attending a Tertiary Care Centre – A Prospective Study

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Abstract
Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality throughout the world. C-Reactive protein (CRP) is found in blood plasma, which rises in response to inflammation. A prospective study was conducted in a tertiary care teaching hospital to assess the levels of CRP in stable COPD patients. 100 patients with stable COPD without co-morbidities attending the respiratory OPD were recruited. CRP levels were estimated and patients were followed up for a period of 6 months to check CRP levels serially every 2 months. During exacerbation, CRP was estimated and repeated after 2 weeks of remission, if still positive, again repeated after 2 weeks. Average CRP level was high in a significant number of COPD patients. As the stage of COPD advanced CRP levels were also significantly raised. By applying ANOVA test, average CRP between different stages of COPD was found to be significantly high. Even though current smokers and reformed smokers had high average CRP, statistical significance in mean CRP between them and non smokers were not found. There was a negative correlation between CRP & BMI, but was not statistically significant. There was no significant relationship of CRP with age of the patients. There was negative correlation seen with oxygen saturation, with a significant p value. It was concluded that systemic inflammation is inherent to COPD, independent of smoking status, age & BMI but correlates with disease severity.
Keywords: *Stable COPD, CRP, Exacerbation of COPD , systemic Inflammation.*

Introduction

Chronic Obstructive pulmonary disease (COPD) is a major worldwide health problem with increasing prevalence & incidence. Although cigarette smoking is the most commonly encountered risk factor for COPD worldwide, some genetic & environmental risk factors are also well identified in the disease pathogenesis. It is well known that non smokers may also develop chronic airflow obstruction.

The indoor air pollution resulting from biomass cooking or heating is an important risk factor for COPD, especially in developing countries.[1]

COPD is a major cause of chronic morbidity and mortality throughout the world, accounting for more than 3 million deaths annually.[2]

The chronic inflammation in COPD, orchestrated by multiple inflammatory cells and mediators in the airways & the lung tissue is induced by inhalation of noxious gasses & particulate matter.[3]

Systemic inflammation & oxidative stress are the most important features of COPD.[4]

Although the origin of systemic inflammation present in COPD remains poorly understood & correlations in the regulation of inflammation in the pulmonary & systemic compartments are not well documented yet, it is clearly established that some inflammatory markers are risen in systemic circulation[3] ,[4],[5] of the blood based bio markers, C-Reactive Protein has shown the greatest promise.[6] In COPD patients increased CRP levels are associated with poor lung function, reduced exercise capacity & worsened quality of life as well as being a significant predictor of all cause mortality [7],[8],[9],[10]

C Reactive protein is a potential biomarker of systemic inflammation that is synthesized predominantly by the hepatocytes in response to tissue damage or inflammation[11]

Several previous studies have documented that CRP levels are increased in stable COPD patients [12].

However in most studies patients with co-morbidities like Diabetes mellitus & cardio-vascular disease, known to be associated with higher CRP levels were not excluded [12],[13],[14].

On the other hand, another study demonstrated that CRP had a weak correlation with COPD severity in elderly stable patients [15].

Many studies have shown a raised CRP in COPD patients.[16],[17],[18],[19], but these studies have not excluded diabetics, patients with hypertension or cardiovascular diseases.

So, this study was done with a primary objective of estimating the level of average CRP in stable COPD patients without any co-morbidities & also to find any association between BMI, Oxygen Saturation, Smoking Status & Age of the patients

Materials and Methods

This prospective study was conducted on 100 stable COPD patients in a tertiary care teaching hospital. Study duration was for a period of 1 year after obtaining clearance from Ethical committee. Male & female patients between the age of 40-60 years who were diagnosed with COPD after detailed history, physical examination & spirometry were classified as per GOLD staging.

Patients with a history of Pulmonary Tuberculosis, Diabetes Mellitus, Systemic Hypertension, Cardiovascular diseases, Bronchiectasis, Interstitial lung disease, Malignancies, Obstructive sleep apnea & asthma overlap were excluded from the study.

Patients who were stable symptomatically, i.e. no exacerbation during last 3 months were included. Data was collected using a proforma with a structured questionnaire, after obtaining informed consent .Detailed history, physical examination & necessary investigations were done as per department protocol.

3 ml of blood was drawn for CRP testing by Turbidometry method. Patients were followed up every 2 months for a period of 6 months. They were subjected to CRP testing serially every 2 months. In case of exacerbation which occurred in a few patients their CRP was estimated and repeated again after 2 weeks of remission. Patients who still had a raised CRP were subjected again to the testing after 2 weeks. Thus all patients were tested for CRP atleast 3 times and average CRP level for each patient was calculated. Normal cut off for CRP was taken as 6.

Statistical Analysis

Data was coded & entered in Microsoft Excel & statistical analysis was done, using SPSS version 21.0. Quantitative variables were summarized as Mean & Standard deviation. 95% Confidence Interval was estimated

Qualitative variables were summarized as frequency & Percentage. Since there were more than 2 groups, ANNOVA test was used to find out

the significant difference between mean of CRP in different stages of COPD.

Pearson correlation coefficient was used to find out the association between CRP with BMI, age and SPO2.

Kendall's tau_b was used to find out the correlation between stages of COPD & CRP.

100 patients were recruited of which 92 (92%) were males & 8 (8%) females. One patient lost follow up & 1 died during the study period. Mean age of the study population was 56.2 years with a standard deviation of 4.7. Body mass index of the study population ranged from 12.82 to 28.0, average being 20.02. (Table 1).

Out of these 100 patients 16 (16%) were non smokers , 62 (62%)patients had quit smoking at least 2 yrs before & 22 (22%) patients were still smoking. The mean oxygen saturation of these patients at stable period was 94.9 %. The mean of average CRP, was 9.37 with a standard deviation of 9.58 , with 95 % confidence interval 7.46 - 11.28. (Table 2)

All patients were staged into 4 groups- Mild, Moderate, Severe & Very severe. This study showed that the average CRP levels in each of the 4 groups were high. The normal CRP level by Turbidometry method was 0 to 6.

By applying ANOVA test the average CRP was higher than normal in all stages of COPD patients & the rise in CRP between different stages of COPD was statistically significant. Mean of average CRP for stage 1 COPD was 3.66, stage 2 was 4.64, stage 3 was 15.84 & stage 4 was 23.27. (Table 3).

By applying Kendall's tau _ b correlation, positive correlation was found between average CRP & stages of COPD. (P value 0.001)

Smoking Status

All patients were categorized as per their smoking status like non smokers, current smokers & reformed smokers. Reformed smokers are the ones who have stopped smoking for at least 2 yrs. Out of the hundred patients 16 patients were non smokers, 20 patients were current smokers & 64 were reformed smokers (Table 4).

The non smokers with COPD were exposed to dust or smoke as part of their occupation. The female COPD patients were exposed to biomass fuel used for cooking.

Average CRP was high in all the three categories of, patients irrespective of their smoking habits. Mean of average CRP in non smokers were 3.19, current smokers were 13.7 & that of reformed smokers were 11.6. Highest mean CRP was seen in current smokers, followed by reformed smokers. Even though mean of average CRP in current & former smokers were high statistical difference between non smokers was not seen, which suggests that irrespective of the smoking habits COPD patients have a raised CRP, implying the fact that COPD causes systemic inflammation.

Body Mass Index

BMI in the study population ranged from 12.82 t o28.0, the mean being 20.029 with a standard deviation of 3.35.There was a negative correlation between CRP & BMI, (Pearson Correlation coefficient -0.185, p value =0.13) which was statistically insignificant.

Average CRP & Age of patients

There was a positive correlation between age of the patients & average CRP. (r= 0.113, p value 0.267) but was not found to be statistically significant.

Average CRP & Age group of patients

Average CRP when compared between different age groups of patient, with T test, p value was 0.052. (Table 5)

Oxygen saturation (SpO2) & Average CRP

There was a significant negative correlation between SpO2 & average CRP. (r = 0.332) with p value of 0.001.

Table 1.Descriptives of the study population

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	100	40.0	60.0	56.230	4.6533
HEIGHT (Mt)	100	1.440	1.780	1.61822	.069642
WT (KG)	100	30.0	75.0	52.640	10.4306
BMI	100	12.81	28.0	20.02	3.35

Table 2 Descriptives of CRP

N		99
Mean		9.37
Median		4.66
Mode		2.67
Std. Deviation		9.58
Minimum		1.33
Maximum		43.25
Percentiles	25	2.66
	50	4.66
	75	11.33

Table 3 Association between Stages of COPD with CRP

Stages of COPD	**N**	**Mean**	**Std Deviation**	**C.I**		**F value**	**P value**
				L	**U**		
I Mild	21	3.66	2.88	2.35	4.98	34.045	.001
II Moderate	41	4.64	2.74	3.78	5.51		
III Severe	27	15.84	9.84	11.94	19.73		
IV Severe	11	23.27	12.24	14.51	32.03		

Table 4 : Association of Smoking status with CRP

Smoking Status	**N**	**Mean**	**Std Deviation**	**Confidence Interval**		**F-Value**	**P-Value**
				LB	**UB**		
Non Smokers	16	3.19	1.664	2.30	4.07	6.042	0.003
Current Smokers	22	13.70	13.30	7.64	19.75		
Reformed Smokers	62	9.50	8.50	7.34	11.66		

Table: 5: Significance of Age Gp with CRP

	AGEGP	N	Mean	Std. Deviation	Std. Error Mean	P
AVERAGE CRP LEVELS	40 - 50	12	5.6250	6.12584	1.76838	0.052
	> 50	87	9.8916	9.87919	1.05916	

Discussion

The main finding of the present study is that CRP levels are high in a significant number (43%) of stable COPD patients at all stages of the disease. Mean of average CRP was also found to be raised in all stages of COPD. As the stage of COPD advanced, CRP values also showed a linear increase in values. This shows that systemic inflammation is related to the severity of the disease which relates to the fact that COPD patients have ongoing systemic inflammation, which worsens as the disease progresses & may lead to disorders of other systems.

Elevated S.CRP levels indicating a low grade persistant systemic inflammation in COPD patients was 1st described in early 2000's [20],[21]. One previous study demonstrated that CRP level has strong association with physiological parameters of COPD like Dyspnoea score. [16]

So as the airflow limitation in COPD increases & the stage advances, the inflammatory marker level also rises which can lead to complications like

Pulmonary artery hypertension, cardiovascular events etc. Previously a significant linear relationship between S.CRP levels Pulmonary Artery pressure levels was reported in a group of moderate to severe COPD patients [22]. High CRP levels have been shown to be associated with all – cause cardiovascular & cancer specific causes of mortality [10] thus reflecting poor prognosis in COPD patients.

This study also shows that patients with > 50 yrs had significant higher average CRP than those with age <50 yrs, emphasizing the fact that COPD is a progressive disease & patient with higher age has more severe disease .

This study also showed that average CRP was raised in stable COPD patients, independent of their smoking status. Even though the current & reformed smokers had high average CRP, statistical significance was not seen when compared to non-smoker. Another study [16] also had similar finding about the smoking status. This establishes the fact that the inflammatory markers are raised due to the disease per se which is due to the ongoing inflammatory status & not much significance is seen regarding the smoking habit i.e it is independent of the smoking behaviour. We found a negative correlation between CRP & BMI, but was not found to be statistically significant.

Elevated levels of CRP have been reported in overweight adults.[23], Obese COPD patients (BMI >30kg/m^2) were 3.3 times more likely to have highly elevated CRP levels compared to those of normal weight (BMI 21-24.9kg/m^2) patients .

In other studies higher average CRP was seen in severe disease stages of COPD, where patients become cachectic & thin. Schols et al [12] observed that high CRP level was seen in patients with low fat mass. More studies are needed to help resolve these controversial findings

Conclusion

This study emphasis that there is a significant increase in blood CRP levels in COPD patients even during the stable period & the level progressively increases as the stage advances.

Finally we conclude that systemic inflammation is present in COPD patients & CRP is an important biomarker in COPD in means of reflecting disease severity & prognosis of patients. Since this study was undertaken in patients without other co-morbidities the increased level of CRP can be attributed solely due to the inflammatory nature of disease itself. This chronic inflammation can lead to systemic effects & worse prognosis leading to malignancies, cardiac diseases, pulmonary artery hypertension etc.

This warrants constant follow up in COPD patients to check the CRP levels periodically & monitor for development of complications.

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