Study of Inflammatory Biomarker (PARC/CCL 18) in Chronic Obstructive Pulmonary Disease and its Correlation with Disease Severity in South Indian Population

Ganesan. R1, Varadharaju2, Vishnukanth3, Karthik3, Gaur. G.S4

1Assistant Professor, Department of Physiology, Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, Melmaruvathur, Tamil nadu, India, 2Assistant Professor, 3Associate Professor, 4Professor & Head, Department of Physiology, JIPMER, Pondicherry, India

Abstract

Aim: Our recent studies have shown that inflammatory biomarker (PARC/CCL 18) in chronic pulmonary disease and its correlation with disease severity in south Indian population. Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by chronic obstruction of lung airways which is not entirely reversible. Pulmonary and activation-regulated chemokine ligand-18(PARC/CCL18) is a 7-kD protein that is constitutively expressed by monocytes/macrophages and dendritic cells and is secreted predominantly in the lung. It is a promising inflammatory marker in COPD.

Material and Method: This was a Descriptive study conducted in 130 male COPD patients. It was designed to assess the specific inflammatory marker and study their relationship with disease severity levels in male COPD patients.

Results: inflammatory biomarkers of Pulmonary and activation regulated chemokine ligand-18 levels were significantly (P<0.003) increased in very severe COPD patients when compared with mild, moderate and severe COPD patients.

Conclusion: From the present study, we conclude that in COPD specific biomarker serum PARC/CCL18 associated with disease severity

Keywords: Chronic obstructive pulmonary disease, Pulmonary and activation regulated chemokine ligand-18, lung

Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by chronic obstruction of lung airways which is not entirely reversible.1 According to WHO, the burden of COPD is 65 million around the world.2 COPD was predicted to be the third most common cause of death by 2020.3 In India, burden of COPD -14.84 million, out of which 2 to 22% are men and 1.2 to 19% are women.4,5

The gold standard investigation for diagnosis of COPD is Spirometry.5-7 But, in India, most of the epidemiological studies use symptoms and self-reported questionnaires for the screening of COPD patients.4 These are subjective and nonspecific methods having large failure rates and will lead to under diagnosis of COPD.8,9

Cigarette smoking is considered as a significant risk factor of COPD in 50-70% of patients.10 Studies proved that non-smokers also develop COPD & may account for one third of all COPD cases.11-13 In India 68.6% COPD patients are Non-smokers.13 Secondhand smoke exposure (SHS) believed to be the essential cause for COPD in nonsmokers.14 In India, Smoking index & Questionnaires were commonly used to assess smoking status of COPD patients but these can’t measure SHS and Passive smoking which cause COPD in nonsmokers.15,16 So COPD in non-smokers go often undiagnosed in India which make them vulnerable to COPD induced morbidity and mortality.

DOI Number: 10.5958/2320-608X.2019.00120.3
Most of the studies used inflammatory biomarkers such as C-reactive protein (CRP), Fibrinogen, Interleukin-6 (IL-6) & TNFα to assess cardiovascular risk in COPD.\(^3\) The use of these inflammatory biomarkers may be limited in COPD because they are secreted also by non-pulmonary organs such as the liver and the bone marrow. Hence these inflammatory markers are not specific to COPD.

Pulmonary and activation-regulated chemokine ligand-18 (PARC/CCL18) "is a 7-kD protein that is constitutively expressed by monocytes/macrophages and dendritic cells and is secreted predominantly in the lungs". It is a promising inflammatory marker in COPD.\(^5\) In COPD, PARC levels found to be increased, in association with reduced FEV1 and was also found to be associated with acute exacerbations. PARC was found to be independently associated with lung function, cardiovascular morbidity and mortality associated with COPD.\(^1\)

Hence in the present study, specific inflammatory markers of PARC/CCL18 levels were assessed, and their relation with disease severity was studied.

**Materials & Method**

**Study Design:** This was a Descriptive study conducted in 130 male COPD patients. It was designed to assess the cardiac autonomic functions, specific inflammatory marker and serum cotinine levels and study their relationship with disease severity and also to find the association of cardiac autonomic function, the specific inflammatory marker with serum cotinine levels in male COPD patients. The study was conducted in Department of Physiology, JIPMER in Collaboration with Department of Pulmonary Medicine, JIPMER. Before the start of the study, approval from JIPMER scientific advisory committee and Institute ethics committee for human studies were obtained. In the study group, biochemical parameters of PARC/CCL18 were studied. Later they were classified into four subgroups based on GOLD stage criteria into mild, moderate, severe and very severe COPD.

**Selection of Subjects:**

Male COPD patients attending JIPMER Pulmonology OPD who come under Inclusion and exclusion criteria were included in the study. Subjects were health educated about the disease and are motivated to know their Disease severity & Cardiovascular risk associated with their Disease.

**Experimental Design:**

The study was carried out in pulmonary function testing laboratory, and autonomic function testing laboratory in Department of Physiology, JIPMER between 9 am to 1 pm. The laboratory conditions were quiet, the temperature of 25-27°C and adequate lightening provided. The study involved minimal invasive procedure of collecting 5 ml blood. The subjects were explained clearly about study protocol in their native language and written informed consent was obtained from them. The participants were asked to have light Breakfast around 7 am and come for tests around 9 am as the subjects will have difficulty in performing PFT and CAFT with the full stomach. The subjects were told to refrain from smoking, drinking caffeinated beverages and the morning dose medications for COPD at least 12 hours before the recording. In case of any adversity in health, such as fever, exacerbation of COPD, poor sleep or physical discomfort, tests were postponed, and the subjects were asked to report on another convenient day. Subjects were also asked to stop taking medications affecting their attention like psychotropic drugs (sedatives & antihistaminics).

**Statistical Analysis of Data**

SPSS version 19 was used for statistical analysis. The data were subjected to Kolmogorov-Smirnov normality test. The continuous data such as age, duration of illness, anthropometric parameters (Ht, Wt, WC, HC, WHR, WhtR), heart and blood pressure were expressed as mean with standard deviation and the intergroup differences in mean between mild, moderate, severe and very severe COPD groups were compared using One-way ANOVA test, for normally distributed data. The difference was considered statistically significant if probability of chance was less than 0.05

**Results**

After obtaining approval from the JIPMER Scientific Advisory Committee (JSAC) and the institutional Ethics Committee for human studies, the study was conducted on 130 male COPD patients based on inclusion and exclusion criteria. Further, they were subgrouped into mild, moderate, severe and very severe COPD groups based on Gold stage criteria.
All the anthropometric, PFT, AFT, BRS, and biochemical parameters were assessed in 130 COPD patients after obtaining informed consent from them, and the data were analysed.

**Comparison of parameter among different stages of COPD:**

**Biochemical parameters:**

Comparison of PARC/CCL18 levels among patients

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Total (n=130)</th>
<th>Mild COPD (n=18)</th>
<th>Moderate COPD (n= 41)</th>
<th>Severe COPD (n= 44)</th>
<th>Very severe COPD (n= 27)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARC/CCL 18</td>
<td>50.50(22)</td>
<td>43.66 (12)</td>
<td>46.21 (19.23)</td>
<td>54.62 (24.34)</td>
<td>61.98 (30.77)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are expressed as Median ( Interquartile range); Comparison of variables between groups done using Kruskal Wallis Test

*p<0.05 is statistically significant among the four groups of COPD

PARC/CCL-18: Pulmonary and activation regulated chemokine ligand-18 (ng/ml)

Serum PARC/CCL18 levels were significantly high (Table 1)(Figure 1) in very severe, severe and moderate COPD patients when compared to mild COPD patients.

**Discussion**

This study was conducted in pulmonary function testing laboratory and autonomic function testing laboratory in Department of Physiology in collaboration with department of pulmonary medicine from January 2016 to July 2017. 130 male stable COPD patients without any major systemic illness were recruited for the study. Biochemical parameters such as PARC/CCL18 were studied in them. Later they were classified into four subgroups based on GOLD stage criteria into mild, moderate, severe and very severe COPD.

In our study, Serum PARC/CCL18 a COPD specific inflammatory biomarker was used to assess cardiovascular risk in COPD patients. We had assessed the levels of PARC/CCL18 in COPD patients and got the mean PARC/CCL18 concentration as 50.50 ng/ml.

We found that the levels of PARC/CCL18 significantly increased (p<0.05) in very severe, severe and moderate COPD patients when compared to mild COPD patients. These results were in accordance with Lung health study (LHS) and ECLIPSE study. We observed the levels of PARC/CCL18 were high in COPD patients and also associated the levels of PARC/CCL18 levels with total mortality caused by COPD. A study done by Asli Gorek Dilektasli et al. found increased levels of PARC/CCL18 in COPD patients and associated the levels of PARC/CCL18 with exacerbation of COPD. They found that patients with PARC/CCL18 more than 181.71ng/ml could differentiate COPD patients with hospitalised exacerbations from those who were not hospitalised and concluded that PARC/CCL18 is a promising biomarker for COPD.

Increased levels of PARC/CCL18 in COPD patients suggested that there is persistent inflammation exists in patients with COPD. These findings support that there is a link between increased sympathetic activity and
inflammation caused by COPD.

Conclusion
From the present study, we conclude that in COPD patients, as the disease severity increases, the levels of PARC/CCL18 were also increased. Inflammatory biomarker of serum PARC/CCL18 associated with COPD disease severity.

Conflict of Interest – No
Source of Funding - Self source
Ethical Clearance – Yes

Reference
17. Don D. Sin, Bruce E. Miller, Anneliese Duvoix, S. F. Paul Man, Xuekui Zhang, et.al. Serum PARC/CCL-18 Concentrations and Health Outcomes in Chronic Obstructive Pulmonary Disease, Am J Respir Crit Care Med. 2011 May 1; 183(9): 1187–92.