Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2016; 4(7E):2649-2652 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2016.v04i07.073

Original Research Article

Role of Plasma Fibrinogen as a Biomarker in Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a multicomponent condition characterised by airflow obstruction that is not fully reversible. It is a major global cause of morbidity and mortality. The most widely used marker of disease severity and progression is FEV1. However, FEV1 correlates poorly with both symptoms and other measures of disease progression and thus there is a need for other biological markers to better characterize individuals with COPD. Fibrinogen is an acute phase plasma protein that has emerged as a promising biomarker in COPD. Hence the current study linking fibrinogen with COPD has been carried out to establish its potential utility as a biomarker. 55 stable COPD patients in the age group 35-70 years were recruited in this study based on spirometry and 37 age and sex matched subjects were included as controls. Apart from the baseline biochemical analysis, plasma fibrinogen estimation was done in the study population. Results were analysed using SPSS software. Clinical characteristics like age, gender, smoking, biomass exposure, FEV1 % predicted and FEV1/FVC ratio were compared between controls and patients with COPD. Student's unpaired t test was used to compare fibrinogen levels in cases and controls. ANOVA was used to compare the fibrinogen values in various stages of COPD subjects. The plasma fibrinogen levels in patients with COPD were significantly higher than in controls.
Keywords: COPD, fibrinogen, biomarker, FEV1% predicted, FEV1/FVC ratio

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major worldwide health problem with increasing prevalence and incidence. Although cigarette smoking is the most commonly encountered risk factor for COPD worldwide, some genetic and environmental risk factors are also well-identified in the disease pathogenesis. The indoor air pollution resulting from biomass cooking or heating is an important risk factor for COPD among nonsmokers especially in developing countries [1]. The airflow obstruction can result from either airway disease or alveolar destruction (emphysema) and is associated with mucus hyper-secretion, loss of lean body mass and an increased risk of comorbidities such as cardiovascular disease and osteoporosis [2]. COPD is no longer considered a disease only of the lung .It is associated with systemic inflammation caused by circulating cytokines released due to inflammation of the lungs [3]. Oxidative stress, protease- antiprotease imbalance, inflammatory cells like CD8 neutrophils and macrophages leads to decreased forced expiratory volume in 1 s(FEV1) and decreased FEV1/(Forced Vital Capacity)FVC ratio. The natural course of COPD is characterised by the progressive decline in pulmonary function and exacerbations requiring hospitalisation. It represents a major burden for patients and healthcare systems.

The most widely used marker of disease severity and progression is the FEV_1. However FEV_1 correlates poorly with both symptoms and other measures of disease progression and may therefore not be a good surrogate marker of disease activity [4]. Hence there is a need for biomarkers for the early detection of disease, stratification of subjects and designing new therapeutic targets for the disease. Fibrinogen is an essential protein in the clotting cascade [5], and the plasma level of fibrinogen can be altered by various diseases. Furthermore, evidence suggesting that fibrinogen is a regulator of inflammation in diseases is increasing [6] and circulating fibrinogen has, in recent studies, been identified as a potential biomarker for COPD. Plasma fibrinogen levels are gaining recognition as a biomarker for COPD [7]. It is currently being considered for qualification as a drug development tool by the US Food and Drug

Administration and the European Medicines Agency [8].

MATERIALS AND METHODS

Study population

The study was conducted after having obtained permission from the Institutional Ethics committee, Madras Medical College, Chennai, India. 55 stable COPD patients in the age group 35-70years (mean age 51.5 yrs) who attended the Thoracic Medicine OPD, Rajiv Gandhi Government General Hospital were recruited in this study. Spirometric parameters like FVC and FEV_1 were measured using standard techniques with Spirometer Easy– one ^{TM} model 2001 SN 104921/2011. Bronchodilator was not administered prior to spirometry. The highest value from at least three FVC maneuvers by each subject was used in the analysis. Percent predicted values for spirometric parameters are presented as FEV_1 %predicted and FVC %predicted. Subjects with FEV1/FVC <70% were identified as having airflow limitation (COPD). According to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria, subjects with airflow limitation and FEV1 %predicted ≥80 were identified as having mild air flow limitation, those with FEV1 %predicted between 50 and <80 were defined as having moderate air flow limitation, and those with FEV1 %predicted <50 were defined as having severe airflow limitation[1]. 37 age and sex matched subjects were included as controls (mean age 48.7yrs). Clinical assessment included detailed physical examination, information regarding smoking history, biomass exposure and accompanying diseases were elicited from both cases and control groups.

Patients with history of pulmonary tuberculosis, asthma, angina, myocardial infarction, renal disease, liver disease, diabetes, cancer and patients on chemotherapy and radiotherapy were excluded from the study. Venous blood samples were drawn from controls and COPD patients. Renal function tests, liver function tests and electrolytes were measured using Cobas c501 fully automated clinical chemistry analyser and plasma fibrinogen was estimated with Sysmex-50 coagulation analyser using Dade fibrinogen determination reagents.

Statistical Analysis

Statistical analysis was performed for the present study using the "statistical package for social sciences (SPSS) software". Student's t-test was performed for comparison between groups. p-value of < 0.05 were considered statistically significant. Comparison of plasma fibrinogen levels between various stages of patients with COPD was performed using ANOVA.

RESULTS

Clinical characteristics of COPD patients and controls are summarized in Table no:1. FEV1% predicted was found to be highly significant among cases and controls. Smoking history, biomass exposure and FEV1/FVC ratio are found to be statistically significant.

Plasma Fibrinogen levels in controls and COPD patients shown in Table no:3 was found to be statistically highly significant.

Plasma Fibrinogen levels in various stages of patients with COPD shown in Table no:4 was found to be statistically highly significant (p-value- <0.001)

Table 1: Clinical characteristics of the study population

	Controls (n=37)	COPD patients (n = 55)	p-value
Age(years)	50.0+/- 8.7	51.9+/- 10.3	0.36
Males (n%)	24(64.9%)	37(67.3%)	0.91
Smoking history	11(29.7%)	37(67.3%)	0.04*
Biomass exposure	17(45.9%)	38(69.1%)	0.03*
FEV1% predicted	87.6±4.8	71± 15.7	0.002**
FEV1/FVC	80.7± 2.0	63.8± 4.2	0.01*

** Highly significant*Significant

Table 2: Clinical staging of COPD patients according to GOLD criteria

Stages	Number of cases
I Mild	26
II Moderate	21
III Severe	8
Total	55

Table 3: Plasma Fibrinogen levels in controls and COPD patients

	Group	N	Mean (mg/dL)	Std. Deviation	SEM	p- value
Pl.Fibrinogen	COPD	55	315.37	80.03	10.8	0.001**
	Control	37	205.95	26.81	4.41	

Table 4: Plasma Fibrinogen levels in various stages of COPD

COPD group		N	Mean (mg/dL)	Std. Deviation	p -value
Pl.Fibrinogen	mild	26	246.6	24.81	<0.001**
	moderate	21	345.33	27.73	
	severe	8	460.25	27.60	
	Total	55	315.37	80.03	

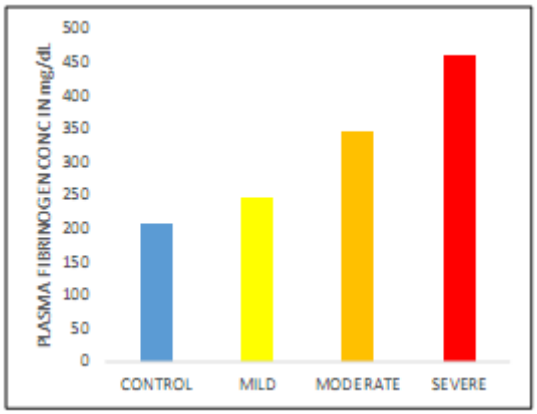

Fig-1: Comparison of plasma Fibrinogen values among controls and patients in various stages of COPD

DISCUSSION

Chronic obstructive pulmonary disease is a progressive lung disease that is not fully reversible, significantly impacting healthcare resources [9]. Airway inflammation, increased airway resistance, parenchymal destruction, decrease of elastic recoil and loss of alveolar attachments causes airflow limitations leading to COPD. It results from an aberrant inflammatory reaction to cigarette smoke, aero toxins and indoor air pollution [2]. Burning wood, animal dung, crop residues and coal in open fires or improper stoves may lead to serious indoor air pollution [1]. Subjects with airflow limitations are prone to chronic, low-grade systemic inflammation as a result of the same inflammatory pathways that are activated in COPD or due to the direct toxic effect of cigarette smoking.

Biomarkers are required in COPD to aid diagnosis, define clinical phenotypes and monitor response to existing and new therapeutic strategies, particularly in the clinical trial setting. An individual or composite biomarker must therefore be useful. Furthermore, blood biomarkers can be readily measured in patients without the need for invasive procedures [10].

Profiling of blood biomarkers has helped in distinguishing individuals with COPD from control subjects, including lung-derived Clara cell protein-16 (CC-16), surfactant protein-D (SP-D) and CCL-18, markers of extracellular matrix breakdown including matrix metalloproteinases (MMPs) 8 and 9, and systemic inflammatory biomarkers like C-reactive protein (CRP), interleukin (IL)-6 and IL-8 [11, 12].

Plasma fibrinogen may be an ideal biomarker for the existence of systemic inflammation. The levels are easily measured and are already integrated into clinical diagnostic practice. These practical reasons have made it a candidate biomarker in a number of diseases including COPD[10].Fibrinogen is an acute phase soluble plasma glycoprotein, synthesized primarily in the liver and converted by thrombin into fibrin during blood coagulation. Normal fibrinogen levels in blood are between 1.5 and 3.5 g/L but can increase threefold during acute phase stimulation in response to increased IL-6 production [13-15].

Plasma Fibrinogen level is raised in individuals with COPD and in cardiovascular disease[16]. Circulating fibrinogen is an independent risk factor for the development of heart disease in a healthy cohort [17]. Studies also show a high prevalence of cardiovascular disease in patients with COPD [18]. p38 Mitogen- Activated Protein Kinase(MAPK) inhibitors affect fibrinogen, hence using fibrinogen as a biomarker will aid in phenotyping individuals with COPD for enrolment in future trials of p38 MAPK inhibitors and tailor treatments accordingly [7].

Studies showed that higher fibrinogen levels could be associated with a faster decline in lung function [19]. In the Third National Health and Nutrition Examination, plasma levels of fibrinogen were higher in COPD patients, and these levels were associated with a degree of airflow limitation, which is one of the parameters used to assess the severity of COPD [20].

In addition, elevated levels of plasma fibrinogen, were associated with a risk of major comorbidities in COPD, including cardiovascular diseases, type II diabetes, lung cancer, and pneumonia

[21]. Therefore, it is thought that measuring plasma fibrinogen levels in patients with COPD is important, because it could indicate disease severity and comorbidities and assist in predicting the disease prognosis.

CONCLUSION

We found that the plasma fibrinogen level correlated with the pulmonary functions like FEV1 % predicted and FEV1/FVC ratio. The plasma fibrinogen level in patients with stable COPD were significantly higher when compared to that of controls. Plasma fibrinogen level could thus serve as a useful biomarker for the evaluation of severity of COPD and may help in assessing cardiovascular risk at an earlier stage.

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