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Plasma Fibrinogen in Chronic Obstructive Pulmonary Disease – A Cross Sectional Study Conducted in a Tertiary Care Hospital in Puducherry, India

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Authors' contributions

This work was carried out by both the authors. The second author suggested the idea and streamlined the process of undertaking this research stud. The first author designed the study, wrote the protocol and wrote the first draft of the manuscript. The second author helped with literature searches, analyses of the study performed, spirometric and bioassay analysis. Both the authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a systemic disorder rather than a respiratory disease. A significant complication that COPD can lead to a hypercoagulable state, which can lead to life-threatening diseases like Ischemic heart disease, deep vein thrombosis and Pulmonary embolism. Therefore, Fibrinogen is a useful biomarker to predict the risk of such hyper-coagulable state in COPD patients.
Objectives: The study was aimed to measure the fibrinogen levels in COPD patients, to correlate the fibrinogen levels with severity of airway obstruction based on spirometry and also to compare

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the fibrinogen levels in COPD exacerbation patients with stable COPD individuals and healthy non-smokers.
Methods: Spirometric measurement and measurement of Plasma Fibrinogen was performed on 60 patients (20 COPD patients with exacerbation; 20 stable COPD patients and 20 healthy non-smokers).
Results: Raised plasma fibrinogen levels were observed in COPD patients when compared to healthy non-smokers. There was increase in the fibrinogen levels with severity of air obstruction. Among the COPD patients, raised fibrinogen levels were observed in exacerbation individuals when compared to stable COPD individuals.
Conclusion: Plasma fibrinogen is a useful biomarker to monitor the disease severity in addition to the spirometric parameters in COPD patients. It gives a clue to the possibility of developing systemic complication of a hypercoagulable in COPD patients.

Keywords: COPD; plasma fibrinogen; exacerbation; hypercoagulation; biomarker.

1. INRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease of increasing public health importance around the world. COPD is now considered to be a systemic disease rather than a respiratory disease. COPD is the fourth leading cause of death worldwide [1], according to the 2013 report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and will become the third leading cause of worldwide death by the year 2020 [2].

In India, half a million people die every year due to COPD [3]. The report published by the Maharashtra State Health Resource Centre indicates that COPD is the leading cause of death in Maharashtra, more than Ischaemic Heart Disease, Stroke, Diabetes Mellitus all taken together [3,4].

The definition for COPD that GOLD lays down in its 2013 report is that, “COPD is defined as a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients” [5].

A significant complication in COPD patients is the development of a hyper-coagulable state, which can lead to life - threatening complications such as ischaemic heart disease, deep vein thrombosis and pulmonary embolism. A valuable tool to check the hyper-coagulable state in such individuals is the measurement of plasma fibrinogen levels.

Fibrinogen, which is an acute phase plasma protein is formed primarily in the liver [6]. This is later converted into fibrin by thrombin during blood coagulation. A three times increase in fibrinogen levels occurs during acute phase stimulation in response to IL – 6 production [7]. In COPD there is pulmonary inflammation which is associated with increased levels of acute phase reactants, and these reactants can be very useful to predict risk of future of COPD patients [6].

2. METHODOLOGY

This study was carried out in the department of Pulmonary Medicine of Sri Manakula Vinayagar Medical College and Hospital from September 2012 to December 2013 on sixty subjects (based on the prevalence and study subjects from previous study, using Free Cal software) [7]. The subjects were made into three groups namely; COPD exacerbation individuals, stable COPD and normal healthy non-smokers.

Patients who are having typical symptoms of chronic cough with or without expectoration and/or shortness of breath on exertion were included in the study after confirming the diagnosis by FEV_1 / FVC < 70% and post bronchodilator FEV_1< 70% on spirometry as per the GOLD guidelines.

The exclusion criteria included ,those who were having fever more than 38 degree centigrade by oral measurement; underlying diseases like any infections, cancers, Rheumatic diseases, acute and chronic liver disease, acute and chronic kidney disease, congestive heart failure, acute myocardial infarction; those who were on oral steroids; those who were sputum positive pulmonary tuberculosis; those who were

diagnosed having asthma and those who were diagnosed having bronchiectasis.

COPD patients were labeled having exacerbations who had worsening of their respiratory symptoms that is beyond normal day to day variations and lead to a change in medication. This is the standard criteria for exacerbation based on the GOLD guidelines.

The study was carried out after approval from the institutional ethical committee and with fully informed written consent from the subjects.

After performing and diagnosing to have COPD with the aid of pneumotach spirometry, 2 ml of venous blood sample was drawn out and fibrinogen was assessed by turbidimetric immunoassay using **Quantia-FIBRINOGEN**®.

Quantia-FIBRINOGEN® is a turbidimetric immunoassay for the determination of fibrinogen and is based on the principle of agglutination reaction. The test specimen (blood sample) is mixed with **Quantia-FIBRINOGEN**® antibody reagent (R2) and activation buffer (R1) and was allowed to react. Presence of fibrinogen in the test specimen resulted in formation of an insoluble complex resulting in an increase in turbidity, which was measured at wavelength 340 nm. The increase in turbidity corresponded to the concentration of fibrinogen in the test specimen [8].

2.1 Statistical Analysis

The data was analysed using **epi info** software version 3.4.3. ANOVO was "performed to compare the distribution of Plasma Fibrinogen level (PFL) based on severity of obstruction and to compare the PFL among stable COPD, COPD exacerbation and normal subjects. $p < 0.001$ was considered as statistically significant.

3. RESULTS

Based upon GOLD guidelines, severity of airway obstruction can be classified as follows:

$FEV_1/FVC < 0.7$ and $FEV_1 >/= 80\%$: MILD

$FEV_1/FVC < 0.7$ and $50\% </= FEV_1 < 80\%$: MODERATE

$FEV_1/FVC < 0.7$ and $30\% </= FEV_1 < 50\%$: SEVERE

$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$: VERY SEVERE

Table 1. Comparison of spirometric parameters between COPD cases and healthy non-smokers

	COPD cases	Healthy non-smokers
FVC % pred	56.72	92.7
FEV_1 % pred	45.95	96.8
FEV_1/FVC % pred	57.17	91.7

From Table 1, it is seen that the FVC, FEV_1 and FEV_1/FVC predicted percentage is lower in COPD patients compared to healthy non-smokers.

Table 2. Distribution of plasma fibrinigen level among COPD patients with non-smoking healthy individuals

Subjects	Mean plasma fibrinogen level (mg/dl)	Significance
COPD	250.87	0.0001
Healthy non-smokers	162.7	0.0001

From Table 2, it is evident that there is increased levels of PFL in COPD individuals when compared to healthy non-smokers ($p<0.05$).

From Table 3, it is seen that there is an increase in Plasma Fibrinogen Level in COPD patients when compared to normal healthy subjects. Among the COPD patients, those having exacerbation was having higher fibrinogen levels when compared to stable COPD patients.

Table 3. Distribution of plasma fibrinogen level among COPD exacerbations individuals, stable COPD patients and non-smoking healthy controls

Subject	Percentage	Mean plasma fibrinogen levels (mg/dl)	
COPD exacerbation	33.33% (n=20)	275.55	0.0001
Stable COPD	33.33% (n=20)	226.2	
Controls	33.33% (n=20)	162.7	

Table 4. Distribution of plasma fibrinogen level based on severity of obstruction

Severity of airway obstruction	Percentage of individuals	Plasma fibrinogen level (mean) (mg/dl)	Test of significance
Mild	10% (n=4)	211	
Moderate	37.5% (n=15)	228.8	
Severe	47.5% (n=19)	275.21	p=0.001
Very severe	5% (n=2)	315	

From Table 4, the Plasma Fibrinogen Level shows a steady increase with increasing severity of airway obstruction.

4. DISCUSSION

According to WHO estimates, 65 million people have moderate to severe COPD. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. Most of the information available on COPD prevalence, morbidity and mortality comes from high-income countries. Even in those countries, accurate epidemiological data on COPD are difficult and expensive to collect. It is known that almost 90% of COPD deaths occur in low and middle income countries.

At one time, COPD was more common in men, but because of increased tobacco use among women in high-income countries and the higher risk of exposure to indoor air pollution (such as biomass fuel used for cooking and heating) in low-income countries, the disease now affects men and women almost equally. In 2002, COPD was the fifth leading cause of death. Total deaths due to COPD are estimated to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. Estimates show that in 2020, COPD becomes the third leading cause of death worldwide.

The most evolved and promising blood biomarker in COPD is fibrinogen, which is currently being evaluated by the US Food and Drug Administration (FDA) for qualification [35]. Plasma fibrinogen has been variably associated with the risk of COPD, disease progression, and mortality (both total and disease specific), independent of other well-established risk factors, such as age, cigarette smoking, and lung function [9]. The relationship of mortality is particularly to be noted and strong in COPD specifically as well as general population cohorts.

Plasma fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. Various epidemiological studies suggest that elevated PFL are associated with an increased risk of cardiovascular disorders, including ischaemic heart disease (IHD), stroke and thromboembolism [10,11]. This increase in PFL may promote a pro-thrombotic or hyper-coagulable state, and may in part explain the risk of stroke and thrombo-embolism in conditions such as atrial fibrillation (AF).

Fibrinogen is a soluble glycoprotein found in the plasma, with a molecular weight of 340 kDa [12]. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver [13]. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. However, at the 'usual' plasma levels of 1.5 to 4.5 g/l, its concentration far exceeds the minimum concentration of 0.5–1 g/l necessary for haemostasis.

Fibrinogen plays a vital role in a number of physio-pathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, haemorrheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation besides a prominent acute-phase reactant. It augments the de-granulation of platelets in response to adenosine diphosphate (ADP), when taken up by the α-granules.

Epidemiological studies indicate that there is strong and unequivocal evidence on plasma fibrinogen levels that are independently related to the presence of, and the subsequent development of, vascular disease.

Table 5. Comparison of present study with previous studies- PFL in COPD patients and normal individuals

Author (year)	Number of subjects	Inference
Alessandri (1994) [14]	37 cases with COPD and 30 controls.	Fibrinogen higher in patients with COPD (p=0.0005) independent of smoking status
Eickhoff (2008) [15]	60 individuals with stable COPD, 20 healthy smokers, 20 healthy non-smokers	Higher fibrinogen in individuals with COPD compared with non-smoking controls
Mannino (2003) [16]	15 697 individuals from NHANES III study	Fibrinogen higher in patients with COPD.
Gan (2004) [17]	Meta-analysis comprising four studies and >9000 individuals.	Fibrinogen higher in patients with COPD; standardised mean difference 0.37 g/ litre between patients with COPD and controls
Garcia-Rio (2010) [18]	324 individuals with COPD and 110 controls from EPI-SCAN cohort	Fibrinogen associated with diagnosis of COPD in crude data
Samareh (2010) [19]	31 COPD patients, 29 controls.	No significant difference between COPD cases (3.81 +/- 0.93 mg/dl) and controls (3.72 +/- 0.9 mg/dl) (p=0.82)
Present study	**40 COPD patients, 20 healthy controls**	**Fibrinogen level significant rise in COPD patients when compared to controls (p<0.05)**

Table 6. Comparison of present study with previous studies –level of plasma fibrinogen in COPD exacerbation with stable COPD and healthy non-smokers

Author (year)	Number of subjects	Inference
Polalti (2008) [20]	33 individuals with stable COPD, 26 individuals with acute exacerbations, 16 controls	Fibrinogen level higher in COPD than controls and significantly higher during an exacerbation of COPD than in stable disease
Saldias (2011) [21]	85 individual with mild to moderate exacerbation of COPD	Fibrinogen level are higher during exacerbations and return to baseline after 30 days
Koutsokera (2009) [22]	30 individuals with an acute exacerbation of COPD	Fibrinogen level return to baseline 40 days after exacerbation
Valipour (2008) [23]	30 individuals with stable COPD, 30 individuals with acute exacerbations, 30 controls	No difference in fibrinogen between stable COPD and exacerbation.
Present study	**20 COPD exacerbation patients, 20 stable COPD patients, 20 healthy non-smokers**	**Increase in the mean PFL in COPD exacerbation when compared to stable COPD & healthy non-smokers (p<0.05)**

Table 7. Comparison of present study with previous studies –PFL with severity of air way obstruction

Author (year)	Number of subjects	Inference
Donaldson (2005) [24]	148 individuals with COPD	Fibrinogen increased over time. Higher baseline level associated with faster decline in FEV1
Higashimoto (2009) [25]	73 individuals with COPD	Trend towards faster decline in lung function in those with higher levels of fibrinogen (p=0.054)
Vestbo (2011) [26]	1793 individuals with COPD	Fibrinogen associated with FEV1 at baseline but no association seen with annual decline in FEV1
Eickhoff (2008) [15]	60 individuals with stable COPD, 20 healthy smokers, 20 healthy non-smokers	No association with disease severity
Mannino (2003) [16]	15 697 individuals from NHANES III study	Association with disease severity in moderate and severe disease
Present study	**40 subjects with COPD, 20 healthy controls**	**Increase in mean PFL with increasing levels of airway obstruction. (p<0.05)**

PFL can be altered by various infections. A marked increase in PFL has been reported in patients suffering from viral pathogens [27]. Reduced level of physical activity has been reported in COPD individuals with elevated PFL [28]. PFL has been found to decline by steroids during exacerbation and it may be useful to study responses to different treatments [29]. Further, it has also been has been emerging as a drug development tool [29]. In Japanese men, PFL has been found to be positively correlated with pulmonary dysfunction but not in women. Relationship between PFL and pulmonary function in Western populations has been established but it has not been evaluated in an Asian population [30]. The above findings indicate that PFL could be considered as a biomarker for diagnosing and treating the complications due to COPD and also for enriching clinical trials among COPD populations.

5. CONCLUSION

Present study showed that PFL were elevated in COPD cases when compared to normal healthy non-smokers. There is increased PFL during exacerbations when compared to stable COPD cases. There is also elevation of PFL as the severity of airway obstruction increases. Thus plasma fibrinogen is a useful marker to monitor the disease severity in addition to spirometric parameters like FVC, FEV_1 and FEV_1/FVC. Therefore, it is concluded that PFL is helpful to assess the risk of systemic complications due to COPD. But there can be other systemic illness like myocardial infarction and liver diseases that can elevate fibrinogen levels. However, further investigations with respect to age, sex, ethnic groups, genetic factors, patient characterization etc. are required to assess and confirm the validity of PFL as a biomarker in COPD.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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