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IMPORTANCE OF CRP AND FIBRINOGEN IN COPD PATIENTS – AN OBSERVATION STUDY

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Abstract:

Aim: Association of systemic inflammatory biomarkers with COPD has been studied by various authors. Present study aims to establish a relation between routinely used and cost effective markers and COPD. **Material and Methods** A total of 100 patients were enrolled only 50 patients were fitting the criteria. Diagnosis of COPD (chronic obstructive pulmonary disease) patients was based on spirometry and post bronchodilator FEV1/FVC <0.7 were selected as cases for the study and equal no of controls were selected with no history of SOB, use of bronchodilators and spirometry with post bronchodilator FEV1/FVC > 0.7. **Results:** Total of 100 patients were screened. Only 50 patients were selected based on the criteria, 25 were case group and 25 are control group. The data obtained was analyzed using SPSS v 17. Mean BMI in cases was 21.36 ± 1.92 which was significantly lower than controls 22.5 ± 2.29, Mean CRP in cases was 4.64 ± 3.6 which was significantly higher than controls 0.45 ± .28 ($p < 0.05$). Mean Fibrinogen in cases was 485.3 ± 187.9 which was significantly higher than controls 292.20 ± 73.9 ($p < 0.05$). There was a significant and negative correlation observed between BMI and severity of COPD ($r = -0.654$, $p < 0.05$) where as significant and positive correlation was observed between severity of COPD and Fibrinogen ($r = 0.685$, $p < 0.05$) and between severity of COPD and CRP ($r = 0.353$, $p < 0.05$). **Conclusion:** Plasma levels of fibrinogen and serum CRP levels are reliable inflammatory markers with a strong positive correlation to severity of COPD. Ease of availability of both these cost effective markers in COPD helps in early intensification of therapy. It is concluded that use of biomarkers to establish systemic inflammation in COPD helps in both reflecting disease severity and assessing prognosis in patients. These observations from our study provide the significance of high sensitivity CRP and Fibrinogen assays in patients with COPD.

Introduction: Chronic obstructive pulmonary disease (COPD) is a growing healthcare burden and it is expected to get worsen as population ages due to wide usage of tobacco products is increased over a period of time. It is progressive in nature and life threatening lung disease. By the year passing after 2020, it is estimated that COPD would be the most common cause of death. It is one of major cause of worldwide mortality and morbidity.[1-2]

Chronic obstructive pulmonary disease (COPD) is a multifactorial disease and it is characterized by airflow obstruction which is not reversible completely due to aero toxin causing inflammatory reaction, cigarette smoke, cigar smoke, and biomass. The obstruction of airflow results in either airway disease or alveolar destruction (emphysema). It is associated with loss of lean body mass, mucus hypersecretion, and an increased risk of comorbidities. The severity and progression of disease is assessed by ratio of FEV1 (forced expiratory volume)/ FVC. Majority of times the emphasis is laid on Biomarkers which can be helpful in early detection of disease, subjects risk stratification and endpoints of clinical trials.[3-6]

Various studies and evidence are there in regards to COPD and its association with systemic oxidative stress, circulating inflammatory cells activation and proinflammatory cytokines levels increased such as C-reactive protein (CRP), IL-6, fibrinogen and TNF.

There are some studies which have shown correlation of fibrinogen levels variation in COPD patients. Basically fibrinogen is a glycoprotein which is synthesized in the hepatocytes and released into circulation. It plays a critical role in coagulation, and it also plays a pivotal role as an acute-phase reactant. Elevated fibrinogen levels in plasma have been reported to be associated with COPD risk and other inflammatory diseases. There are multiple studies showing Fibrinogen level might correlate with severity of disease and exacerbation risk of COPD.[4-6]

Material and Methods

A total of 100 patients were enrolled only 50 patients were fitting the criteria. Diagnosis of COPD (chronic obstructive pulmonary disease) patients was based on spirometry and post bronchodilator FEV1/FVC <0.7 were selected as cases for the study and equal no of controls were selected with no history of SOB, use of bronchodilators and spirometry with post bronchodilator FEV1/FVC > 0.7. Patients with COPD were further classified based on severity based on GOLD guidelines as mild, moderate and severe obstruction. Both males and female between age group 30 – 70 yrs were enrolled for the study and Patients with airway disease other than COPD were excluded.

Inclusion Criteria

1. males and female between age group 30 – 70 yrs
2. Copd patients diagnosed based on spirometry and post bronchodilator FEV1/FVC <0.7 were selected as cases for the study.
3. Patients were clinically stable (no exacerbation for 2 months) at the time of evaluation.

Exclusion criteria:

1. Age less than 29years and more than 71years
2. Patients with airway disease other than COPD
3. History of asthma, malignancy, autoimmune disorders
4. History of renal insufficiency,
5. History of cirrhosis and other serious liver diseases

The BMI was then calculated by dividing the weight in kilograms by height in meter square. Serum CRP and plasma Fibrinogen was estimated in both groups.

Results:

Total of 100 patients were screened. Only 50 patients were selected based on the criteria, 25 were case group and 25 are control group. The data obtained was analyzed using SPSS v 17. The mean age of study population was 51.64 ± 12.19 in case group and 51.59 ± 12.02

in controls p (>0.05). Case group comprised of 88% males and 12% females compared to 84% males and 16% females in controls (p>0.05). In patients with COPD 44% (n=11) had history of Hypertension and 32% (n=8) had history of diabetes compared to 32% Hypertension patients and 44% diabetic patients in control group p (>0.05).

Mean BMI in cases was 21.36 ± 1.92 which was significantly lower than controls 22.5 ± 2.29, Mean CRP in cases was 4.64 ± 3.6 which was significantly higher than controls 0.45 ± .28 (p <0.05). Mean Fibrinogen in cases was 485.3 ± 187.9 which was significantly higher than controls 292.20 ± 73.9 (p <0.05). There was a significant and negative correlation observed between BMI and severity of COPD (r = -0.654, p <0.05) where as significant and positive correlation was observed between severity of COPD and Fibrinogen (r = 0.685, p <0.05) and between severity of COPD and CRP (r = 0.353, p <0.05).

Patients were divided into nonsmokers and Smokers; smokers were further classified as ex-smokers and current smokers. It was observed that current smokers contributed 56% of COPD cases compared to 40% on non-Controls there was a significant and positive correlation observed between smoking and fibrinogen (r = 0.42, p <0.05). There was a significant and positive correlation between smoking and severity of COPD (r = 0.473, p <0.05).

Table 1:

	COPD	Controls	
	Mean ±SD	Mean ± SD	p value
Age	51.64 ± 12.19	51.59 ± 12.02	0.98
BMI	21.36 ± 1.92	22.50 ± 2.29	0.026
CRP	4.64 ± 3.6	0.45 ± .28	<0.001
Fibrinogen	485.30 ± 187.90	292.20 ± 73.90	<0.001

Table 2 :

	COPD	Controls	
	Mean ±SD	Mean ± SD	p value
Gender			
Males	22 (88%)	21 (84%)	0.538
Females	3 (12%)	4 (16 %)	
DM	8 (32 %)	11 (44%)	0.151
HTN	11 (44 %)	8 (32%)	0.410
Non-Smoker	4 (16 %)	9 (36%)	
Ex-smoker	11 (44 %)	5 (20 %)	
Current smoker	14 (56 %)	10(40%)	

Discussion:

COPD is diagnosed based on Pulmonary Function test (PFT), Signs and Symptoms apart from past History of exacerbation episodes. Guidelines of GOLD (Global Initiative for Chronic Obstructive Lung Disease) have been formulated based on the criteria above[7]

Based on limitation of airflow GOLD classification is as follows, In patients with FEV1/FVC <0.70:

- GOLD 1 – if FEV1 ≥ 80% predicted, it is suggested as Mild
- GOLD 2 – if 50% ≤ FEV1 < 80% predicted, it is suggested as Moderate
- GOLD 3 – if 30% ≤ FEV1 < 50% predicted it is suggested as Severe
- GOLD 4 – if FEV1 <30% predicted. it is suggested as Very Severe.

Apart from limitation of airflow, Gold Guidelines have considered various other parameters in the assessment of COPD such as active symptoms (using MRC and CAT scale) previous history of exacerbations.

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- Group A: none or atleast one episode of exacerbation per year or not hospitalisation and mMRC symptoms scoring 0-1 or CAT scoring lesser than 10 – considered as Low Risk.
- Group B: none or exacerbation episode atleast once a per year or not hospitalisation and mMRC symptoms scoring greater than 2 or CAT scoring greater than 10 - considered as Low Risk.
- Group C: More than two and above episodes of exacerbation per year or once or many times requiring hospitalisation and mMRC symptoms scoring 0-1 or CAT scoring lesser than 10 - considered as High risk.
- Group D: More than two episodes of exacerbation per year or requiring hospitalisation one or more times and mMRC symptoms scoring greater than 2 or CAT scoring also more than 10 - considered as High risk.

In COPD cases, there have been various biomarkers centered around proteins and on other molecules, such as in BAL, sputum, blood, urine. Identification of various blood biomarkers may help in people suffering from COPD or other ailments, such as SP-D (surfactant protein-D), CC-16(lung-derived Clara cell protein-16), and CCL-18, extracellular matrix. However the above availability of markers for routine diagnostics is very difficult.

Fibrinogen is principal acute-phase reactant which is well known now, and CRP is the biomarker which is commonly used for systemic inflammation. Estimation of three inflammatory markers, such as leukocyte count, CRP level and fibrinogen level has shown its positive correlation in patients with COPD. Especially, the CRP level significantly correlated with fibrinogen, and was elevated in the high-level group. Previous studies have shown that these three markers could enhance the predictability of all-cause mortality in patients with obstructive lung functions or exacerbations in individuals with COPD.

In the Present study, it was noted that the serum fibrinogen was increased in patients with COPD and there was a clear positive correlation observed between fibrinogen and COPD. Fibrinogen is an acute phase soluble plasma glycoprotein. Fibrinogen is synthesized in the liver and it is converted into fibrin during coagulation cascade in presence of thrombin. During acute phase stimulation in response to increased production of IL-6 there is increased production of fibrinogen levels that can increase upto threefold.[6-8]

It has also shown by various studies that increasing levels of serum CRP levels is associated with inflammation in atherosclerosis and also increasing the risk of Myocardial infarction and CHD (coronary heart disease). Large evidence suggests that even in stable COPD if there is an increased level of serum CRP levels it is associated with inflammation in lung. Hence serum CRP can be used as a marker in COPD patients with ongoing lung inflammation.

Dahl et. al. (2011), Fisun et.al.(2008) have also shown that elevated levels of CRP plays an important role in relation to outcome of patients in COPD and further subsequent hospital admission.[9-10] Tae Hoon Kim et.al (2018) study has shown that High level of fibrinogen seems to have a reflection on the frequent exacerbation and severe symptomatic phenotypes in Korean patients with COPD. [11]

Conclusion: Plasma levels of fibrinogen and serum CRP levels are reliable inflammatory markers with a strong positive correlation to severity of COPD. Ease of availability of both these cost effective markers in COPD helps in early intensification of therapy. It is concluded that use of biomarkers to establish systemic inflammation in COPD helps in both reflecting disease severity and assessing prognosis in patients. These observations from our study provide the significance of high sensitivity CRP and Fibrinogen assays in patients with COPD.

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