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Clinical evaluation of level of C-reactive protein in stable chronic obstructive pulmonary disease (COPD) patients from Bihar region

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Abstract
Chronic Obstructive Pulmonary Disease (COPD) being a multisystem disorder is frequently associated with significant extra-pulmonary manifestations. The mechanisms underlying the systemic manifestations of COPD should attract great interest, because these account for a large part of morbidity and its assessment and management is critically important for the improvement in future treatment and outcome of COPD patients. These systemic manifestations have been associated with systemic changes including evidence of increased oxidative stress, activation of circulating inflammatory cells and increased levels of pro-inflammatory cytokines. Hence based on the above findings the present study was planned for clinical evaluation of Level of C - Reactive protein in Stable COPD Patients from Bihar Region.
The present study was planned in Department of General Medicine, Patna Medical College and Hospital, Patna, Bihar. The study was done from Nov 2015 to Dec 2016. Total 50 patients were included in the present study. Out of that 25 cases of COPD were enrolled in study group and 25 cases of the normal patients were enrolled as control cases. The diagnosis of COPD was based on pulmonary function tests which were performed according to American Thoracic Society guidelines and COPD was defined on the basis of post bronchodilator FEV1/FVC ratio of less than 0.70 and FEV1< 80%. Patients were staged based on FEV1/FVC ratio according to GOLD stage I-IV.
Our study confirms that C-reactive protein levels are higher in COPD patients. So C-reactive protein levels indirectly reflect exercise capacity of stable COPD patients. Thus we conclude that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients.

Keywords: C-reactive protein, CRP, stable chronic obstructive pulmonary disease, COPD

Introduction
Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterized by long-term breathing problems and poor airflow. The main symptoms include shortness of breath and cough with sputum production. COPD is a progressive disease, meaning it typically worsens over time. Eventually, everyday activities such as walking or getting dressed become difficult. Chronic bronchitis and emphysema are older terms used for different types of COPD. The term "chronic bronchitis" is still used to define a productive cough that is present for at least three months each year for two years. Those with such a cough are at a greater risk of developing COPD. The term "emphysema" is also used for the abnormal presence of air or other gas within tissues [1].
Tobacco smoking is the most common cause of COPD, with factors such as air pollution and genetics playing a smaller role. In the developing world, one of the common sources of air pollution is poorly vented heating and cooking fires. Long-term exposure to these irritants cause an inflammatory response in the lungs, resulting in narrowing of the small airways and breakdown of lung tissues. The diagnosis is based on poor airflow as measured by lung function tests. In contrast to asthma, the airflow reduction does not improve much with the use of a bronchodilator [2].
Most cases of COPD can be prevented by reducing exposure to risk factors. This includes decreasing rates of smoking and improving indoor and outdoor air quality. While treatment can slow worsening, no cure is known. COPD treatment include smoking cessation, vaccinations, respiratory rehabilitation, and often inhaled bronchodilators and steroids. Some people may benefit from long-term oxygen therapy or lung transplantation. In those who have periods of acute worsening, increased use of medications and hospitalization may be needed [3].
A chronic cough is often the first symptom to develop. Early on it may just occur occasionally or may not result in sputum. When a cough persists for more than three months, each year for at least two years, in combination with sputum production and without another explanation, it is by definition chronic bronchitis. Chronic bronchitis can occur before the restricted airflow and thus COPD fully develops. The amount of sputum produced can change over hours to days. In some cases, the cough may not be present or may only occur occasionally and may not be productive. Some people with COPD attribute the symptoms to a "smoker's cough". Sputum may be swallowed or spit out, depending often on social and cultural factors. In severe COPD, vigorous coughing may lead to rib fractures or to a brief loss of consciousness. Those with COPD often have a history of "common colds" that lasts a long time [4].
Shortness of breath is often the symptom that most bothers people. It is commonly described as: "my breathing requires effort," "I feel out of breath," or "I can't get enough air in". Different terms, however, may be used in different cultures. Typically, the shortness of breath is worse on exertion of a prolonged duration and worsens over time. In the advanced stages, or end stage pulmonary disease, it occurs during rest and may be always present. It is a source of both anxiety and a poor quality of life in those with COPD. Many people

with more advanced COPD breathe through pursed lips and this action can improve shortness of breath in some [5].

COPD can result in a decrease in physical inactivity. Low levels of physical activity are also associated with worse outcomes in COPD. In COPD, breathing out may take longer than breathing in. Chest tightness may occur, but is not common and may be caused by another problem. Those with obstructed airflow may have wheezing or decreased sounds with air entry on examination of the chest with a stethoscope. A barrel chest is a characteristic sign of COPD, but is relatively uncommon. Tripod positioning may occur as the disease worsens. Advanced COPD leads to high pressure on the lung arteries, which strains the right ventricle of the heart. This situation is referred to as cor pulmonale, and leads to symptoms of leg swelling and bulging neck veins. COPD is more common than any other lung disease as a cause of cor pulmonale. Cor pulmonale has become less common since the use of supplemental oxygen [6].

COPD often occurs along with a number of other conditions, due in part to shared risk factors. These conditions include ischemic heart disease, high blood pressure, diabetes mellitus, muscle wasting, osteoporosis, lung cancer, anxiety disorder, sexual dysfunction, and depression. In those with severe disease, a feeling of always being tired is common. Fingernail clubbing is not specific to COPD and should prompt investigations for an underlying lung cancer [7].

An acute exacerbation of COPD is defined as increased shortness of breath, increased sputum production, a change in the color of the sputum from clear to green or yellow, or an increase in cough in someone with COPD. They may present with signs of increased work of breathing such as fast breathing, a fast heart rate, sweating, active use of muscles in the neck, a bluish tinge to the skin, and confusion or combative behaviour in very severe exacerbations. Crackles may also be heard over the lungs on examination with a stethoscope [8].

COPD is a type of obstructive lung disease in which chronic, incompletely reversible poor airflow (airflow limitation) and inability to breathe out fully (air trapping) exist. The poor airflow is the result of breakdown of lung tissue (known as emphysema), and small airways disease known as obstructive bronchiolitis. The relative contributions of these two factors vary between people. Severe destruction of small airways can lead to the formation of large focal lung pneumatoses, known as bullae, that replace lung tissue. This form of disease is called bullous emphysema [9].

COPD develops as a significant and chronic inflammatory response to inhaled irritants. Chronic bacterial infections may also add to this inflammatory state. The inflammatory cells involved include neutrophil granulocytes and macrophages, two types of white blood cells. Those who smoke additionally have Tc1 lymphocyte involvement and some people with COPD have eosinophil involvement similar to that in asthma. Part of this cell response is brought on by inflammatory mediators such as chemotactic factors. Other processes involved with lung damage include oxidative stress produced by high concentrations of free radicals in tobacco smoke and released by inflammatory cells, and breakdown of the connective tissue of the lungs by proteases that are insufficiently inhibited by protease inhibitors. The destruction of the connective tissue of the lungs leads to emphysema, which then contributes to the poor airflow, and finally, poor absorption and release of respiratory gases. General muscle wasting that often occurs in COPD may be partly due to inflammatory mediators released by the lungs into the blood [10].

Narrowing of the airways occurs due to inflammation and scarring within them. This contributes to the inability to breathe out fully. The greatest reduction in air flow occurs when breathing out, as the pressure in the chest is compressing the airways at this time. This can result in more air from the previous breath remaining within the lungs when the next breath is started, resulting in an increase in the total volume of air in the lungs at any given time, a process called hyperinflation or air trapping. Hyperinflation from exercise is linked to shortness of breath in COPD, as breathing in is less comfortable when the lungs are already partly filled. Hyperinflation may also worsen during an exacerbation.

Some also have a degree of airway hyperresponsiveness to irritants similar to those found in asthma. Low oxygen levels, and eventually, high carbon dioxide levels in the blood, can occur from poor gas exchange due to decreased ventilation from airway obstruction, hyperinflation, and a reduced desire to breathe [9]. During exacerbations, airway inflammation is also increased, resulting in increased hyperinflation, reduced expiratory airflow, and worsening of gas transfer. This can also lead to insufficient ventilation, and eventually low blood oxygen levels. Low oxygen levels, if present for a prolonged period, can result in narrowing of the arteries in the lungs, while emphysema leads to breakdown of capillaries in the lungs. Both of these changes result in increased blood pressure in the pulmonary arteries, which may cause cor pulmonale [11].

COPD usually gets gradually worse over time and can ultimately result in death. It is estimated that 3% of all disability is related to COPD. The proportion of disability from COPD globally has decreased from 1990 to 2010 due to improved indoor air quality primarily in Asia. The overall number of years lived with disability from COPD, however, has increased [12].

The rate at which COPD worsens varies with the presence of factors that predict a poor outcome, including severe airflow obstruction, little ability to exercise, shortness of breath, significant underweight or overweight, congestive heart failure, continued smoking, and frequent exacerbations. Long-term outcomes in COPD can be estimated using the BODE index which gives a score of zero to ten depending on FEV1, body-mass index, the distance walked in six minutes, and the modified MRC dyspnea scale. Significant weight loss is a bad sign. Results of spirometry are also a good predictor of the future progress of the disease but are not as good as the BODE index [13].

COPD being a multisystem disorder, is frequently associated with significant extra-pulmonary manifestations. The mechanisms underlying the systemic manifestations of COPD should attract great interest, because these account for a large part of morbidity. Its assessment and management is critically important for the improvement in future treatment and outcome of COPD patients. These systemic manifestations have been associated with systemic changes including evidence of increased oxidative stress, activation of circulating inflammatory cells and increased levels of pro-inflammatory cytokines. Various stages of

disease in lung and systemic tissues of COPD patients, could also be associated with raised circulating biomarker levels. C-reactive protein is an excellent and stable biomarker for low grade systemic inflammation. It is also useful as an indirect biomarker of COPD severity, systemic inflammatory response associated with COPD and downstream respiratory and systemic complications. Hence based on the above findings the present study was planned for Clinical Evaluation of Level of C - Reactive protein in Stable COPD patients from Bihar Region.

Methodology

The present study was done in Department of General Medicine, Patna Medical College and Hospital, Patna, Bihar. . The study was done from Nov 2015 to Dec 2016. Total 50 patients were included in the present study. Out of that 25 cases of Chronic Obstructive Pulmonary Disease were enrolled in study group and 25 cases of the normal patients were enrolled as control cases. The diagnosis of COPD was based on pulmonary function tests which were performed according to American Thoracic Society guidelines [14] and COPD was defined on the basis of post bronchodilator FEV1/FVC ratio of less than 0.70 and FEV1< 80%. Patients were staged based on FEV1/FVC ratio according to GOLD stage I-IV [15].

After selection of patients, detailed history was taken to obtain information regarding age, education, occupation, socioeconomic status, personal habits, smoking, diabetes mellitus, hypertension etc. A thorough clinical examination was done. Routine investigations including complete blood count, erythrocyte sedimentation rate to exclude any infection, sputum for acid fast bacilli to rule out pulmonary Koch's, serum bilirubin and SGPT to exclude liver pathology (as CRP is mostly produced by liver) was done. Patients were then subjected to 6 minute walk test and spirometry.

Blood samples for inflammatory markers i.e. hs-CRP and TNF-α were taken from the eligible participants and centrifuged to obtain the sera and then stored and processed as per manufacturer's instructions provided with each of the ELISA kits of hs-CRP and TNF-α. Commercially available hs-CRP ELISA kits (The EiAsyTM Way; Diagnostic Biochem Canada Inc.) and Human TNF-α ELISA Kits (Gen Probe Diaclone SAS, France) was used to estimate the serum levels of hs-CRP and TNF-α.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Inclusion Criteria

Included patients were free from any disease exacerbation for the preceding 2-months and their lack of systemic steroid intake in previous 3 months.

Exclusion Criteria

Patients with any other systemic disease other than COPD were also excluded from the study.

Patients suffering from Alcoholic, Autoimmune, Liver, Kidney, Malignant disorders, Bronchial asthma, Bronchiectasis, Cardiovascular Diseases, Diabetes Mellitus, Pleural effusion, Pulmonary Tuberculosis, Osteoarthritis.

Patients on medications like steroids and antioxidants.

Results & Discussion

Chronic obstructive pulmonary disease (COPD) is a complex disease characterized by air flow obstruction due to chronic bronchitis and emphysema. COPD is associated with systemic inflammation, recognized as a risk factor for its systemic complications such as coronary artery disease, stroke and skeletal muscle dysfunction.

C-Reactive protein (CRP) is an acute phase reactant, synthesized predominantly by the hepatocyte in response to tissue damage or inflammation, may serve as a surrogate marker of systemic inflammation that predicts incident myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death among healthy individuals with no history of cardiovascular disease. There are limited studies that evaluate the relationship between C-reactive protein and COPD.

COPD is a major and increasing global health problem. The diagnosis of COPD largely relies on a history of exposure to noxious stimuli (mainly tobacco smoke) and abnormal lung function tests. Persistent reduction in FEV1 (forced expiratory volume in first second) is the most typical finding in COPD. Another is airflow obstruction, which is typically determined by spirometry. Key phenotypes obtained are FEV1 and FVC (forced vital capacity). Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV1/FVC. A classification of disease severity into four stages has been proposed by GOLD guidelines based primarily on FEV1.

Table 1

Stage I	Mild COPD	FEV1/FVC<0.70	FEV_1≥ 80% normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV_1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV_1 30-49% normal
Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV_1 <30% normal, or <50% normal with chronic respiratory failure

Table 2: Comparison of Different Parameters in both study groups

Group	**Group I**	**Group II**
Group of	**COPD Cases**	**Normal Control Patient**
No. of Cases	25	25
Age in years	52 - 65	53 - 64
Males	17	13
Females	8	12
BMI Kg/m2	21.4 – 26.7	20.6 – 25.4
hs-CRP levels ng/ml	3352 - 7892	389 - 1482
TNF – α levels pg/ml	224- 53 9	58 - 261

Table 3: GOLD stage and No. of Cases

GOLD Stage	Stage-I		Stage-II		Stage-III		Stage-IV	
No. of Cases	1		10		11		3	
Metabolic syndrome	Yes	No	Yes	No	Yes(9)	No(13)	Yes	No
No. of Cases	-	1	3	7	4	7	-	3

Although pulmonary function test is the mainstay for diagnosis of COPD, the staging on the basis of FEV1 alone as an index of severity for COPD has been debated. This includes only functional respiratory impairment. Moreover, GOLD has defined COPD as "a disease state characterized by airflow limitation that is not fully reversible", and airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases [16].

Patients with COPD experience a systemic inflammation which can be assessed by measuring inflammatory mediators like C-reactive protein (CRP) [17], LDH-3 isoenzyme, TNF-□ and IL-6. Systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute-phase proteins [18-23]. C-reactive protein (CRP), an acute-phase protein synthesized predominantly by hepatocytes in response to tissue damage or inflammation, has attracted much attention recently. It reflects the total systemic burden of inflammation in several disorders including cardiovascular diseases, COPD, osteoporosis, and even depression [18, 21-23]. The main clinical value of CRP is its ability to reveal early inflammation when other clinical parameters are equivocal. [24] Recently, High-Sensitivity C-reactive Protein (HSCRP) measuring methods have made it possible to assess this protein in lower levels of inflammation.

Gan and co-workers [25] showed that C-reactive protein is elevated in patients who actively smoked, had reduced lung function or even stable COPD. Study by Sin DD et al [26], demonstrated that in COPD patients- C-reactive protein levels predicted cardiovascular mortality. Lacy P et al [27] 2004, demonstrated that cardiovascular mortality and inflammation decreased with treatment with inhaled fluticasone. Pinto Plata et al [28], have shown that patients with COPD have higher levels of C-reactive protein independent of cardiovascular risk factors.

Now there is a large body of research focusing on cellular and biochemical mechanisms of COPD. Moreover, GOLD has defined the COPD as "a disease state characterized by airflow limitation that is not fully reversible", and the airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases [29].

However, presently there are no inflammatory markers to be included in the diagnosis of COPD. There are a few suggestions given by GOLD regarding inflammatory response to smoking and cellular and molecular mechanisms in stable COPD that are responsible for the persistence of the inflammatory response in COPD [30]. Components of inflammatory cascade such as inflammatory cells, cytokines, oxidative stress biomarkers, and inflammatory indicators like C-reactive protein (CRP) are the potential biomarkers that can be used in the diagnosis and prognosis of COPD.

Furthermore, chronic inflammation in the pulmonary tissue is also associated with systemic effects. A clear communication is present between the disease mechanisms in the pulmonary compartment and peripheral tissues leading to concept of COPD as a systemic inflammatory disease [30-31]. In addition to pulmonary alterations, other organ systems may be affected in COPD. Systemic effects of COPD include weight loss, nutritional abnormalities, and musculoskeletal dysfunction. CRP in the serum was proposed to measure as a marker of systemic inflammation. CRP is often used as a clinical marker of acute systemic inflammation. Since low-grade inflammation is evident in COPD, we studied high sensitive CRP (hs-CRP) levels in these patients.

Chronic obstructive pulmonary disease (COPD) affects over 5% of adult population worldwide. By 2020, the World Health Organization predicts that COPD will become the leading cause of death and the fifth leading cause of disability word wide. COPD is considered as a multi-component disease associated with chronic low grade systemic inflammatory response [32]. C-reactive protein evaluated in chronic obstructive airway disease patients, in order to establish a possible association with basal systemic inflammation in stable period, cardiovascular risk events, disease prognosis and identification of infectious exacerbations. When considering the stable state, CRP levels tend to be independent of smoking, lung function, strongly associated with arterial oxygen tension and 6-minute walk distance [33].

Conclusion

Our study confirms that C-reactive protein levels are higher in COPD patients. So C-reactive protein levels indirectly reflect exercise capacity of stable COPD patients. Thus we conclude that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients.

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