Introduction

COPD is a preventable and treatable disease state characterized by airflow limitation which is progressive, not fully reversible, associated with airway inflammation, hyper responsiveness and systemic manifestations including skeletal muscle dysfunction, cachexia, cardiovascular and osteo - skeletal alteration. The airflow obstruction is generally due to chronic bronchitis or emphysema **(ATS 2007).**

CRP is a member of an ancient family of molecules called pentraxins. It was discovered in human in 1930 as serum component that binds the C- polysaccharide of streptococcus pneumonae and composed of five identical subunits which are linked non covalently to form a disk like pentagonal ring **(Carlson et al., 2005).**

CRP is also a member of a diverse class of defense molecules called acute phase proteins. The levels of acute phase proteins rise rapidly during infection and after injury. Inflammatory mediators especially IL- 6 & IL- 1β triggers its production in the liver. Non hepatic production has been demonstrated by monocytes and lymphocytes **(Broekhuizen et al., 2005).**

Although COPD primarily involves the lung, the chronic inflammatory process causes systemic manifestations. One of the inflammatory markers which are increasingly evaluated in COPD patients is CRP **(Yende et al., 2006).**

This factor is increased in patients with chronic obstructive pulmonary disease (COPD). It is used as a predictive factor for extra-

pulmonary complications determining the prognosis of the disease **(Halvani et al., 2007).**

It can also predict the incidence of ischemic heart disease complicating COPD patients **(Ridker, 2003).**

It has not yet been defined whether this increase is due to the disease itself or is accompanied by ischemic heart diseases and cigarette smoking **(Halvani et al., 2007).**

Aim of the work

The aim of this work was to study the usefulness of serum CRP as a systemic inflammatory marker for COPD patients and to evaluate ischemic heart diseases (IHD) and smoking as potential causes of raised CRP levels in COPD.

Chronic obstructive pulmonary disease

Definitions:

The guidelines published by the **American Thoracic Society (1995)** defined COPD as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; and may be partially reversible.

The British Thoracic Society (1997) defined COPD as a slowly progressive disorder characterized by airways obstruction (reduced FEV1 and FEV1/FVC ratio), which did not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator or other therapy.

The Global Initiative for Chronic Obstructive Lung Disease **(GOLD, 2003)** stated that it is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

(GOLD, 2009) stated that Chronic Obstructive Pulmonary Disease **(COPD)** is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Chronic bronchitis is defined as the presence of chronic productive cough on most days for 3 months, in each of two consecutive years, in a

patient in whom other causes of chronic cough have been excluded **(Jud, 1998).**

Emphysema is defined as abnormal, permanent enlargement of the airspaces, distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis **(Snider et al., 1985).**

Extra pulmonary effects of COPD include, weight loss, nutritional abnormalities, skeletal muscle dysfunction, risk for myocardial infarction, angina, osteoporosis, bone fractures, depression and sleep disorders **(Van Weel and Schellevis, 2006).**

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates change in regular medication **(Rodriguez-Roisin, 2000**).

Aetiology:

Risk factors for COPD (Gold 2009):

- Genes.
- Inhalation exposure:
  - Tobacco smoking.
  - Occupational dusts.
  - Indoor air pollution.
  - Outdoor air pollution.
- Oxidative stress.
- Gender.
- Respiratory infection.
- Socioeconomic status.
- Nutrition.
- Comorbidities.

- Previous tuberculosis.
- Lung growth and development.

Genes

COPD is a polygenic disease and a classic example of gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin (**Stoller and Aboussouan, 2005)**, a major circulating inhibitor of serine proteases. Although alpha-1 antitrypsin deficiency is relevant to only a small part of the world's population, it illustrates the interaction between genes and environmental exposures leading to COPD. A significant familial risk of airflow obstruction has been observed in smoking siblings of patients with severe COPD **(Maccloskey et al., 2001)** suggesting that genetic factors could influence this susceptibility. Through genetic linkage analysis, several regions of the genome have been identified that likely contain COPD susceptibility genes, including chromosome 2q **(Silverman et al., 2002)**. Genetic association studies have implicated a variety of genes in COPD pathogenesis, including transforming growth factor beta 1 (TGF-β1**) (Wu et al., 2004)** microsomal epoxide hydrolase 1 (mEPHX1**) (Smith and Harrison, 1997)** and tumor necrosis factor alpha (TNF-α) **(Huang et al.,1997)**. However, the results of these genetic association studies have been largely inconsistent, and functional genetic variants influencing the development of COPD (other than alpha-1 antitrypsin deficiency) have not been definitively identified **(Silverman et al., 2002)**.

Inhalational Exposures

Because individuals may be exposed to a variety of different types of inhaled particles over their lifetime, it is helpful to think in terms of the total burden of inhaled particles. Of the many inhalational exposures that

may be encountered over a lifetime, only tobacco smoke**(Burrows et al., 1977)** and occupational dusts and chemicals (vapors, irritants, and fumes) **(Matheson et al., 2005)** are known to cause COPD on their own. Tobacco smoke and occupational exposures also appear to act additively to increase the risk of developing COPD. However this may reflect an inadequate data base from populations who are exposed to other risk factors, such as heavy exposures to indoor air pollution from poorly vented biomass cooking and heating **(GOLD 2009).**

A) Tobacco Smoke:

Cigarette smoking is by far the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than nonsmokers. Pipe and cigar smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers **(Anthonisen et al., 2002)**.

The risk for COPD in smokers is dose-related **(Burrows et al., 1977)**. Age at starting to smoke, total pack/years smoked, and current smoking are also risk factors for COPD **(Jindal et al., 2006)**, Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms (**The Health Consequences of Involuntary Exposure to Tobacco Smoke., 2006)** and COPD **(Eisner et al., 2005)** by increasing the lungs total burden of inhaled particles and gases **(Dayal et al., 1994)**.

B) Occupational Dusts and Chemicals:

Occupational exposures to organic and inorganic dusts and chemical agents and fumes are an underappreciated risk factor for COPD **(Hnizdo et al., 2004)**.

C) Indoor air pollution:

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (especially among women in developing countries) continues to grow (**Sezer et al., 2006)**.

Indoor air pollution is estimated to kill two million women and children each year **(Smith, 1999)**.

D) Outdoor air pollution:

The role of outdoor air pollution in causing COPD is unclear; it has also been difficult to assess the effects of single pollutants in long-term exposure to atmospheric pollution. However, air pollution from fossil fuel combustion, primarily from motor vehicle emissions in cities, is associated with decrements of respiratory function **(Abbey et al., 1998).**

Lung Growth and Development

Lung growth is related to processes occurring during gestation, birth, and exposures during childhood **(Stein et al., 1997)**. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD **(Tager et al., 1988).**

There is positive association between birth weight and FEV1 in adulthood **(Lawlor et al. 2005)**.

Oxidative Stress

Oxidative stress not only produces direct injurious effects in the lungs but also activates molecular mechanisms that initiate lung inflammation. Thus, an imbalance between oxidants and antioxidants is considered to play a role in the pathogenesis of COPD **(MacNee, 2005).**

Gender

Studies from developed countries **(National Heart, Lung, and Blood Institute, 2004)** showed that the prevalence of the disease is now almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men **(Anthonisen et al., 1994).**

Infections

Infections (viral and bacterial) may contribute to the pathogenesis and progression of COPD **(Retamales et al., 2001)**, and the bacterial colonization associated with airway inflammation **(Sethi et al., 2006)**, HIV infection has been shown to accelerate the onset of smoking-related emphysema **(Diaz et al., 2000)**

Nutrition

Malnutrition and weight loss can reduce respiratory muscle strength and endurance, apparently by reducing both respiratory muscle mass and the strength of the remaining muscle fibers **(Wilson et al., 1989)**. Lung CT scans of women chronically malnourished because of anorexia nervosa showed emphysema-like changes **(Coxson et al., 2004).**

Socioeconomic status:

COPD may be inversely related to socioeconomic status **(Prescott et al., 1999).**

It may reflect exposures to air pollutants, crowding or poor nutrition **(US Centers for Disease Control and Prevention, 1995).**

Comorbidities:

Asthma may be a risk factor for the development of COPD, although the evidence is not conclusive. A longitudinal study of people with

asthma found that around 20% of subjects developed functional signs of COPD; irreversible airflow limitation **(Vonk et al., 2003).**

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

PATHOLOGY

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair that contribute to airway obstruction **(Hogg and Timens, 2009).**

Proximal airways (trachea, bronchi > 2 mm internal diameter)

Bronchial glands hypertrophy and goblet cell metaplasia occurs. This results in excessive mucous production or chronic bronchitis **(Reid, 1960).**

Airway wall changes include squamous metaplasia of the airway epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue **(Saetta et al., 2001).**

Different inflammatory cells predominate in different compartments of the central airways. In the airways wall these are lymphocytes, predominantly of the CD8+ type, but as the disease progresses neutrophils also become prominent **(O′Shaughnessy et al., 1997).** In the airspaces, in addition to lymphocytes, neutrophils and macrophages can also be identified **(Pesci et al., 1998).**

Peripheral airways (bronchioles < 2mm)

Bronchiolitis is present in the peripheral airways at an early stage of the disease **(Niewoehner et al., 1974)**.

There is pathological extension of goblet cells and squamous metaplasia in the peripheral airways **(Cosio et al., 1978).**

The inflammatory cells in the airway wall and airspaces are similar to those in the larger airways **(Saetta et al,. 1998)**.

As the disease progresses, there is fibrosis and increased deposition of collagen and scar tissue formation in the airway walls, that narrows the lumen and produces fixed airways obstruction **(Rennard, 1999).**

Increased inflammatory response and exudate correlated with disease severity **(Hogg et al., 2004).**

Lung parenchyma (respiratory bronchioles and alveoli)

The most common type of parenchymal destruction in COPD patients is the centrilobular form of emphysema. As a result of emphysema there is a significant loss of alveolar attachments, which contributes to peripheral airway collapse **(Lamb et al., 1993).**

There are two major types of emphysema, according to the distribution within the acinus: 1) centrilobular (which involves dilatation and destruction of the respiratory bronchioles); and 2) panlobular emphysema (which involves destruction of the whole of the acinus). The former is the most common type of emphysema in COPD and is more prominent in the upper zones, while the latter predominates in patients with α1-antitrypsin deficiency and is more prominent in the lower zones. In the early stages of the disease, these are microscopic lesions. During the course of the disease, they may progress to macroscopic lesions or bullae (defined as an emphysematous space >1 cm in diameter). The inflammatory cell profile in the alveolar walls and the airspaces is similar to that described in the airways and persists throughout the course of the disease **(Finkelstein et al., 1995).**

One of the perplexing features of COPD is that smoldering inflammation and slow progressive destruction of the lung parenchyma often continue for decades after cessation of smoking **(Stewart and Voekel, 2008).**

Pulmonary vasculature

Pulmonary vascular changes begin early during the course of the disease **(Peinado et al., 1999).** Initially, these changes are characterised by thickening of the vessel wall and endothelial dysfunction **(Wright et al., 1983)**. These are followed by increased vascular smooth muscle and infiltration of the vessel wall by inflammatory cells, including macrophages and CD8+ T lymphocytes (**Peinado et al., 1999**).

In advanced stages of the disease, there is collagen deposition and emphysematous destruction of the capillary bed. Eventually, these structural changes lead to pulmonary hypertension and right ventricular dysfunction (cor pulmonale) **(Wright et al., 2005)**.

PATHOGENESIS

Inflammation is present in the lungs, particularly the small airways, of all people who smoke. This normal protective response to the inhaled toxins is amplified in COPD, leading to tissue destruction, impairment of the defense mechanisms that limit such destruction, and disruption of the repair mechanisms. In general, the inflammatory and structural changes in the airways increase with disease severity and persist even after smoking cessation. Besides inflammation, two other processes are involved in the pathogenesis of COPD; an imbalance between proteases and antiproteases and an imbalance between oxidants and antioxidants (oxidative stress) in the lungs **(MacNee, 2007).**

(A)Inflammation:

COPD is characterized by the presence of a chronic low grade systemic inflammatory response which is not significantly related to indices of lung function. Furthermore during acute exacerbation of COPD increased levels of acute phase proteins (C-reactive protein and lipopolysaccharide binding protein) are found **(Dentener et al., 2001).**

1-Inflammatory Cells

COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes **(Barnes et al., 2003)**. These cells release inflammatory mediators and interact with structural cells in the airways and lung parenchyma.

a) Neutrophils: Increased in sputum of normal smokers. Further increased in COPD and related to disease severity. Few neutrophils are seen in tissue. They may be important in mucus hypersecretion and through release of proteases **(Stockley, 2002).**

b) Macrophages: Greatly increased in number are seen in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid. It produces increased inflammatory mediators and proteases in COPD patients in response to cigarette smoke and may show defective phagocytosis **(Barnes, 2004 A).**

c) T lymphocytes: Both CD4+ and CD8+ cells are increased in the airway wall and lung parenchyma, with increased CD8+:CD4+ ratio. Increased CD8+ T cells (Tc1) and Th1 cells which secrete interferon-γ and express the chemokine receptor CXCR3. CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction **(Liu et al., 1999).**

d) B lymphocytes: Increased in peripheral airways and within lymphoid follicles, possibly as a response to chronic colonization and infection of the airways **(Hogg et al., 2004).**

e) Eosinophils: Increased eosinophil proteins in sputum and increased eosinophils in airway wall during exacerbations **(GOLD 2009)**.

f) Epithelial cells: May be activated by cigarette smoke to produce inflammatory mediators, including eicosanoids, cytokines, and adhesion molecules **(Mills et al., 1999).**

2-Inflammatory Mediators

The wide variety of inflammatory mediators that have been shown to be increased in COPD patients attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors) **(Barnes, 2004 B)**.

Many inflammatory mediators are increased in COPD, including:

●Leukotriene B4, a neutrophils and T cell chemoattractant which is produced by macrophages, neutrophils, and epithelial cells **(Hill et al., 1999)**.

● Chemotactic factors such as the CXC chemokines interleukin 8 and growth related oncogene α, which are produced by macrophages and epithelial cells. These attract cells from the circulation and amplify pro-inflammatory responses **(Yamamoto et al., 1997).**

● Pro-inflammatory cytokines such as tumour necrosis factor α and interleukins 1β and 6 **(Mueller et al., 1996).**

● Growth factors such as transforming growth factor β, which may cause fibrosis in the airways either directly or through release of another cytokine, connective tissue growth factor) **(Gold 2009)**.

(B)Oxidative stresses:

Oxidative stress may be an important amplifying mechanism in COPD **(Rahman, 2005)**. Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of .COPD patients. Oxidants are generated by cigarette smoke and other inhaled particulates, and released from activated inflammatory cells such as macrophages and neutrophils **(MacNee et al., 2001).**

Oxidative stress has several adverse consequences in the lungs, including activation of inflammatory genes, inactivation of antiproteases,

stimulation of mucus secretion, and stimulation of increased plasma exudation. Many of these adverse effects are mediated by peroxynitrite, which is formed via an interaction between superoxide anions and nitric oxide. In turn, the nitric oxide is generated by inducible nitric oxide synthase, which is expressed in the peripheral airways and lung parenchyma of COPD patients. Oxidative stress may also account for a reduction in histone deacetylase activity in lung tissue from COPD patients, which may lead to enhanced expression of inflammatory genes and also a reduction in the anti-inflammatory action of glucocorticosteroids **(Ito et al., 2005).**

(C)Protease-Antiprotease Imbalance

There is evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other. Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is an important feature of emphysema. The major proteinases include Serine proteases, Neutrophil elastase, Cathepsin G, Proteinase 3, Cysteine proteinases, Cathepsins B, K, L, S, Matrix metalloproteinases (MMPs), MMP-8, MMP-9, and MMP-12. On the other hand, the major antiproteinases include alpha-1 antitrypsin, alpha-1 antichymotrypsin, Secretory leukoprotease inhibitor, Elafin, Cystatins, Tissue inhibitors of MMP 1-4 (TIMP1-4) **(ATS/ERS ,2004).**

PATHOPHYSIOLOGY

The previous pathogenic mechanisms result in the pathological changes found in COPD. These in turn result in physiological abnormalities: mucous hypersecretion and ciliary dysfunction, airflow

obstruction and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects **(MacNee 2007).**

1- Mucous hypersecretion and ciliary dysfunction:

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, it is due to mucous metaplasia with increased numbers of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Ciliary dysfunction is due to squamous metaplasia of epithelial cells and results in an abnormal mucociliary escalator and difficulty in expectorating. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR) **(Burgel et al., 2004).**

2-Airflow obstruction and hyperinflation or air trapping:

The main site of airflow obstruction occurs in the small conducting airways that are < 2 mm in diameter. This is because of inflammation and narrowing (airway remodeling) , inflammatory exudates in the small airways, loss of the lung elastic recoil (due to destruction of alveolar walls) and destruction of alveolar support (from alveolar attachments) **(MacNee, 2007).**

The airway obstruction progressively traps air during expiration, resulting in hyperinflation at rest and dynamic hyperinflation during exercise. Dynamic hyperinflation is closely linked to shortness of breath (dyspnea) in COPD **(O'Donnell, 2001)**.

3-Gas Exchange Abnormalities:

Gas exchange abnormalities result in hypoxemia and hypercapnia, In general, gas transfer worsens as the disease progresses. The severity of

emphysema correlates with arterial PO2 and other markers of ventilation-perfusion imbalance. Peripheral airway obstruction also results in ventilation-perfusion imbalance and combines with ventilatory muscle impaired function in severe disease to reduce ventilation, leading to carbon dioxide retention **(Rodriguez-Roisin and MacNee, 1998).**

4-Pulmonary hypertension:

Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure (cor pulmonale) **(Barbera et al., 2003).**

Diagnosis OF COPD

1-History:

The diagnosis of COPD should be considered in anyone who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease such as regular tobacco smoking **(Rabe et al., 2007).** No single symptom or sign can adequately confirm or exclude the diagnosis of COPD although COPD is uncommon under the age of 40 years **(Holleman and Simel , 1995).**

A detailed medical history of a new patient known or thought to have COPD should assess **(Currie and Legge, 2007):**

• Patient's exposure to risk factors particularly with regard to exposure to dusts, chemicals, patient's current smoking status and the number of smoking pack years.

• Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases such as tuberculosis.

• Family history of COPD.

• Pattern of symptom development (dyspnea, cough, sputum production and chest tightness).

• History of exacerbations or previous hospitalizations for respiratory disorder.

• Presence of comorbidities which may also contribute to restriction of activity.

2-Assessment of Symptoms:

Since COPD may be diagnosed at any stage, any of the symptoms described below may be present in a patient presenting for the first time.

a) Dyspnea:

The hallmark symptom of COPD, typical COPD patients describe their dyspnea as a sense of increased effort to breath, heaviness, air hunger, or gasping **(Simon et al., 1990).**

As lung function deteriorates, breathlessness becomes more intrusive, and patients may notice that they are unable to walk at the same speed as other people of the same age or carry out activities that require the use of accessory respiratory muscles (e.g., carrying grocery bags) **(Celli et al.,1986).**

b) Cough:

Chronic cough, often the first symptom of COPD to develop **(Georgopoulas et al., 1991).**

Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive **(Burrows et al., 1965).**

c) Sputum production:

COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. The presence of purulent sputum reflects an increase in inflammatory mediators **(Hill et al., 1999),** and its development may identify the onset of an exacerbation **(Stockley et al., 2000).**

d) Wheezing and chest tightness:

These are nonspecific symptoms that may be present in Stage I: Mild COPD, but are more characteristic of asthma or Stage III: Severe COPD and Stage IV: Very Severe COPD. But absence of wheezing or chest tightness does not exclude a diagnosis of COPD **(GOLD 2009).**

3-Physical Examination:

a) General:

COPD may show signs consistent with cor pulmonale (raised jugular venous pressure, loud P2 heart sounds due to pulmonary hypertension, tricuspid regurgitation, pitting peripheral oedema, and hepatomegaly). Skeletal muscle wasting and cachexia, which may be present in those with advanced disease. Finger clubbing is not found in COPD, and its presence should prompt thorough evaluation to exclude a cause such as lung cancer, bronchiectasis, or idiopathic pulmonary fibrosis **(Currie and Legge, 2007).**

b) Local:

Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred **(Kestin and Chapman, 1993).**

Inspection (GOLD 2009):

• Central cyanosis.

•Barrel-shaped chest, and protruding abdomen.

• Flattening of the hemi-diaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, and widening of the xiphisternal angle.

• Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow.

• Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying**.**

• Ankle or lower leg edema can be a sign of right heart failure**.**

Palpation and percussion.

• Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without being enlarged **(Celli and MacNee, 2004).**

Auscultation.

• Patients with COPD often have reduced breath sounds **(Badgett et al., 1993).**

• The presence of wheezing during quiet breathing is a useful pointer to airflow limitation **(ATS/ERS 2004).**

4- Investigations:

a) Measurement of Airflow Limitation (Spirometry):

The diagnosis of COPD is confirmed by spirometry. Spirometry measures the forced expiratory volume in one second (FEV1) which is the greatest volume of air that can be breathed out in the first second of a deep breath. Spirometry also measures the forced vital capacity (FVC) which is the greatest volume of air that can be breathed out in a whole deep breath. Normally at least 70% of the FVC comes out in the first second (i.e. the FEV1/FVC ratio is >70%). In COPD, this ratio is less than normal, (i.e. FEV1/FVC ratio is <70%) even after a bronchodilator medication has been given **(Rabe et al., 2007).**

Table 1: Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1 (GOLD 2009)

Stage I: Mild	FEV1/FVC < 0.70 FEV1 ≥80% predicted
Stage II: Moderate	FEV1/FVC < 0.70 50% ≤FEV1 < 80% predicted
Stage III: Severe	FEV1/FVC < 0.70 30% ≤FEV1 < 50% predicted
Stage IV: Very Severe	FEV1/FVC < 0.70 FEV1 < 30% predicted or FEV1 <50% predicted plus chronic respiratory failure

b) Reversibility testing:

Reversibility testing to oral corticosteroids or inhaled bronchodilator is not always necessary, but it should be performed if asthma is thought likely or if the response to treatment (β2 agonists or corticosteroids) is surprisingly good. However, asthma can often be distinguished from COPD by the history, examination, and baseline spirometry. More detailed lung function measurements such as lung volumes (total lung capacity and residual volume), gas transfer coefficient, and walking distance in six minutes can be done if diagnostic doubt persists or more thorough evaluation is required **(Currie and Legge, 2007).**

c) Peak expiratory flow:

Solitary peak expiratory flow readings can seriously underestimate the extent of airflow obstruction, while serial monitoring of peak expiratory flow is not generally useful in the diagnosis of COPD **(Currie and Legge, 2007).**

d) Imaging:

1-Chest X-ray:

It is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation, hyperlucency of the lungs, and rapid tapering of the vascular markings **(Pauwels et al., 2001).**

2-Computed tomography (CT):

Not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution computed tomography (HRCT) scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability **(Fishman et al., 2008).**

e) Additional Investigations:

1-Arterial blood gas measurement:

In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with FEV1 < 50% predicted or with clinical signs suggestive of respiratory failure or right heart failure **(GOLD 2009).**

Screening patients by pulse oximetry and assessing arterial blood gases in those with oxygen saturation (SaO2) < 92% is a useful way of selecting patients for arterial blood gas measurement **(Roberts et al., 1993).**

2-Alpha-1 antitrypsin deficiency screening:

In patients of Caucasian descent who develop COPD at a young age (< 45 years) or who have a strong family history of the disease. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency **(Gold 2009).**

3-Hematocrit*:*

Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers **(Calverly et al., 1982)**, and can be identified by hematocrit > 55% **(Siafakas et al., 1995).**

A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment **(Chambellan et al., 2005).**

4- Electrocardiography (ECG):

Electrocardiography may show typical changes of chronic right sided heart strain. However, echocardiography is more sensitive in detecting tricuspid valve incompetence, as well as right atrial and ventricular hypertrophy, It is also useful in determining whether left ventricular dysfunction is present **(Currie and Legge, 2007).**

Differential Diagnosis

Table 2: differential diagnosis of COPD (GOLD 2009)

Diagnosis	Suggestive Features
COPD	Onset in mid-life. Symptoms slowly progressive. Long history of tobacco smoking. Dyspnea during exercise. Largely irreversible airflow limitation.
Asthma	Onset early in life (often childhood). Symptoms vary from day to day. Symptoms at night/early morning. Allergy, rhinitis, and/or eczema also present. Family history of atopy. Largely reversible airflow limitation.
Congestive Heart Failure	Fine basilar crackles on auscultation. Chest X-ray shows dilated heart, pulmonary edema. Pulmonary function tests indicate volume restriction, not airflow limitation.
Bronchiectasis	Large volumes of purulent sputum, clubbing. Commonly associated with bacterial infection. Coarse crackles on auscultation. Chest X-ray/CT shows bronchial dilatation, bronchial wall thickening.
Tuberculosis	Onset all ages Chest X-ray shows lung infiltrate. Microbiological confirmation. High local prevalence of tuberculosis.
Obliterative Bronchiolitis	Onset in younger age, nonsmokers. May have history of rheumatoid arthritis or fume exposure. CT on expiration shows hypodense areas.
Diffuse Panbronchiolitis	Most patients are male and nonsmokers. Almost all have chronic sinusitis. Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation.

Systemic features of COPD

It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases **(Agusti et al., 2003)** .Cachexia is commonly seen in patients with severe COPD. There may be loss of skeletal muscle mass and weakness as a result of increased apoptosis and/or muscle disuse. Patients with COPD also have increased likeliness of having osteoporosis, depression and chronic anemia **(Similowski 2006)**.

Increased concentrations of inflammatory mediators, including TNF-α, IL-6, and oxygen-derived free radicals, may mediate some of these systemic effects. There is an increase in the risk of cardiovascular diseases, which is correlated with an increase in C-reactive protein (CRP) **(Gan et al., 2004).**

The systemic effects of COPD include:

1-Bones:

The incidence of osteoporosis and osteopenia was higher the more the severity of COPD **(EL-Khattib et al., 2006).**

There are several proposed mechanisms:

A) Smoking:

Smoking has been recognized as a contributing factor to bone loss **(Jensen1986)**, smoking also is considered as a risk factor for osteoporosis in men and women **(Slemenda et al., 1992).**

b) Systemic and inhaled corticosteroids:

Despite beneficial effects on lung function and well being of the patient, its use was associated with side effects, one of which is osteoporosis**(Gross, 2001).**

c) Reduced skeletal muscle mass:

Skeletal muscle dysfunction in COPD is due to reduced mobility due to shortness of breath and steroid myopathy became more obvious in patients with severe disease **(Ionescu and schoon, 2003).**

d) Body mass index and changes in body composition:

Weight loss and a low BMI are predictors of mortality in patients with COPD **(Wouters et al., 2002).**

Loss of bone mineral density (BMD) may also occur with lumbar spine fractures reported in nearly 20% of male patients. A key feature of the patients was the stronger association of both lung disease and the link between fat free mass (FFM) and loss at the hip compared with the lumbar spine **(Bolton et al., 2004).**

e) The role of chronic systemic inflammation:

Increased levels of systemic inflammatory markers (TNF-α, IL-6 and CRP) have been reported in COPD, mainly in patients who lose weight and in those with low skeletal muscle mass **(Eid et al., 2001).**

2-Endocrinal system:

a) Testosterone:

Anabolic hormone levels are low in COPD; it is attributed to chronic hypoxia, disease severity, smoking, corticosteroids and chronic inflammation **(Kamishke et al., 1998).**

Low testosterone level can predict low bone density and low muscle strength **(Creutzberg and Casaburi, 2003).**

b) Leptin:

Serum Leptin, a hormone that can promote atherothrombosis is raised in COPD with impaired lung function **(Calikoglu et al., 2004).**

c) Thyroid hormone:

The severity of airway obstruction in COPD is associated with impairment of thyroid gland function. There is an apparent clinical

resemblance between hyperthyroid state and advanced COPD. Early detection of thyroid disturbances may therefore be clinically important in COPD (**Uzun et al., 2007).**

3-Cardiovascular Effects:

Cardiovascular disease is a major cause of mortality and morbidity in patients with COPD. Although there are common causal factors including smoking and sedentarism, the increase in cardiovascular disease is independent of these known risk factors **(Mannino et al., 2008).**

Several studies have shown that COPD patients have increased arterial stiffness, which may explain the epidemiological link between reduced FEV1 (forced expiratory volume in 1 second) and cardiovascular mortality (**Sabit et al., 2007).**

Recent study was not able to demonstrate any defect in endothelial function in COPD patients with arterial stiffness, suggesting that it may be due to an abnormality in the arterial wall **(Maclay et al., 2009)**.

Systemic inflammation may predispose to atherosclerotic plaques, which may account for the high prevalence of myocardial infarction in patients with COPD **(Barnes, 2010).**

4-COPD and Metabolic Diseases

There is an increased risk of diabetes in COPD patients. Systemic inflammation, and particularly the proinflammatory cytokines TNF-α and IL-6, may induce insulin resistance **(Mannino et al., 2008).**

Metabolic syndrome, characterised by central obesity, diabetes, hypertension, and hyperlipidaemia, is also known to occur with COPD. In a recent study of COPD patients, metabolic syndrome was found in almost half of the patients irrespective of disease stage and was associated with increased markers of systemic inflammation, including IL-6, CRP, and fibrinogen **(Watz et al., 2009).**

Cachexia and weight loss has also been associated with COPD, particularly in severe disease and may be related to increased concentrations of certain cytokines, such as TNF-α. There is selective loss of skeletal muscle, measured as fat-free mass, and this is associated with a selective loss of type IIA fibers **(Barnes, 2010).**

5-COPD and lung cancer:

Patients with COPD are 3 to 4 times more likely to develop lung cancer than are smokers with normal lung function. Lung cancer is found in 40%–70% of patients with COPD, particularly in severe disease, and is a common cause of death in COPD patients **(Young et al., 2009).**

The most likely explanation for the increased risk of lung cancer in COPD is the presence of chronic inflammation, with increased production of growth factors and angiogenic factors. Stopping smoking in COPD patients reduces but does not eliminate the risk of lung cancer, probably because inflammation persists even after smoking cessation **(Anthonisen et al., 2005).**

6-Others:

Anxiety, depression and Cognitive dysfunction are increasingly recognized in patients with COPD, especially in severe disease, and this may have an important impact on self management and adherence to therapy **(Hung et al., 2009)**.

Polycythaemia is the major haematological complication predisposing to vascular events. Hypoxia, hypercapnia and Polycythaemia together or alone lead to impaired neuropsychiatric performance **(Agusti, 2005).**

Treatment of COPD

1-Risk factor reduction

a)Smoking cessation:

Smoking cessation is one of the most important factors in slowing down the progression of COPD. Once COPD has been diagnosed, stopping smoking slows down the rate of progression of the disease. Even at a late stage of the disease it can significantly reduce the rate of deterioration in lung function and delay the onset of disability and death **(Anthonisen et al., 2005).**

Some smokers can achieve long-term smoking cessation through "willpower" alone. However many smokers need further support to quit. The chance of successfully stopping smoking can be greatly improved through social support, engagement in a smoking cessation program and the use of drugs such as nicotine replacement therapy, bupropion and varenicline **(WHO, 2008).**

b) Occupational exposures:

Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases **(Oroczo-Levi et al., 2006).**

c) Air pollution:

A person who has COPD may experience fewer symptoms if they stay indoors on days when air quality is poor **(Rabe et al., 2007).**

2-Management of stable COPD

A) Pharmacologic treatment:

Recommendations for the pharmacological treatment **(GOLD 2009)**:

• Treatment tends to be cumulative with more medications being required as the disease state worsens.

• Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens.

• Individuals differ in their response to treatment and in the side effects they report during therapy.

(1)Bronchodilators

Bronchodilators are medicines that relax smooth muscle around the airways, increasing the caliber of the airways and improving air flow. They can reduce the symptoms of shortness of breath, wheeze and exercise limitation, resulting in an improved quality of life for people with COPD **(Liesker et al., 2002)**. They do not slow down the rate of progression of the underlying disease **(Rabe et al., 2007).**

There are three major types of bronchodilators, β2 agonists, anticholinergics and theophyllin. Anticholinergics appear to be superior to β2 agonists in COPD. Each type may be either long-acting (with an effect lasting 12 hours or more) or short-acting (with a rapid onset of effect that does not last as long) **(Salpeter et al., 2006).**

Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available **(GOLD 2009).**

(2) Corticosteroids

Corticosteroids act to reduce the inflammation in the airways, in theory reducing lung damage and airway narrowing caused by inflammation **(Pinto-Plata et al., 2006).**

Unlike bronchodilators, they do not act directly on the airway smooth muscle and do not provide immediate relief of symptoms. Some of the more common corticosteroids in use are prednisone, fluticasone, budesonide, mometasone, and beclomethasone. Corticosteroids are used in tablet or inhaled form to treat and prevent acute exacerbations of COPD. Well-inhaled corticosteroids (ICS) have not been shown to be of

benefit for people with mild COPD; however, they have been shown to decrease acute exacerbations in those with either moderate or severe COPD **(Gartlehner et al., 2006).**

(3)Other Pharmacologic Treatments:

a-Vaccines:

Influenza vaccines can reduce serious illness **(Wongsurakiat et al., 2004)** and death in COPD patients by about 50% **(Wongsurakiat et al., 2003).**

Vaccines containing killed or live, inactivated viruses are recommended **(Edwards et al., 1994)** as they are more effective in elderly patients with COPD **(Hak et al., 1998)**.

Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older **(Jackson et al., 2003).**

b-Alpha-1 antitrypsin augmentation therapy:

In young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema. However, this therapy is very expensive, is not available in most countries **(GOLD 2009).**

c-Antibiotics:

There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful **(Siakafas and Bouros, 1998).**

d-Mucolytic (mucokinetic, mucoregulator) agents:

(ambroxol, erdosteine, carbocysteine, iodinated glycerol).

Oral mucolytics are thought to reduce the viscosity of sputum in the airways and help patients expectorate. Their regular use reduces the frequency of exacerbations of COPD **(Poole and Black, 2001).**

e-Antioxidant agents:

N-acetylcysteine, have been reported to reduce the frequency of exacerbations, leading to speculation that these medications could have a

role in the treatment of patients with recurrent exacerbations **(Hansen et al., 1994).**

f-Immunoregulators (immunostimulators, immunomodulators):

Studies using an immunoregulator in COPD as phosphodiesterase 4 (PDE4) inhibitors (cilomilast and roflumilast) show a decrease in the severity and frequency of exacerbations **(Li et al., 2004).**

g-Antitussives.

Cough, although sometimes a troublesome symptom in COPD has a significant protective role. Thus the regular use of antitussives is not recommended in stable COPD. **(Irwin et al., 1998).**

h-Vasodilators:

Pulmonary hypertension in COPD is associated with a poorer prognosis. Hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt. Inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance **(Jones and Evans, 1997).** Therefore, nitric oxide is contraindicated in stable COPD.

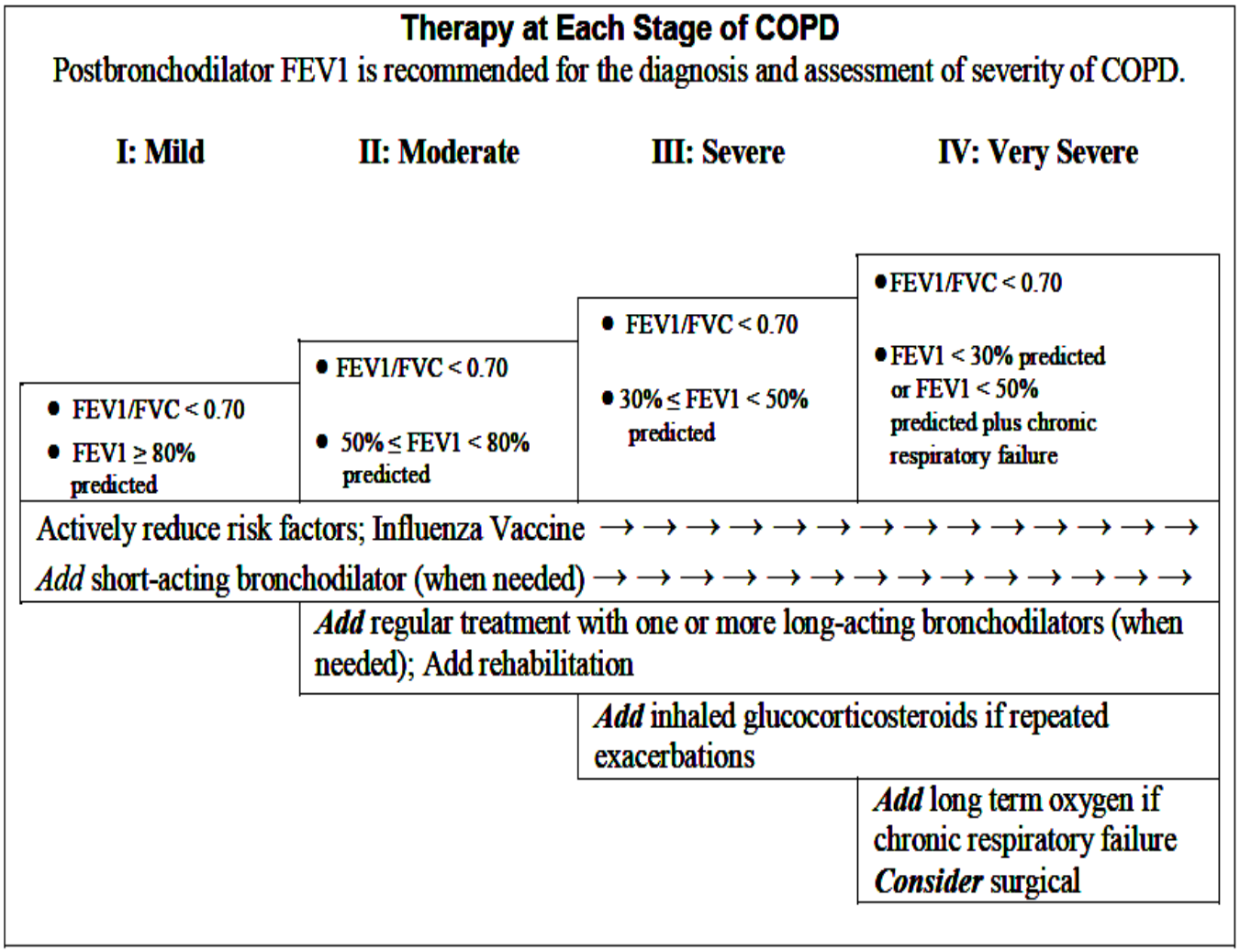
i-Narcotics (morphine):

Morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects **(Poole et al., 1998).**

j-Others:

Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupunture, homeopathy) cannot be recommended **(ATS/ERS 2004).**

Figure 1: Pharmacologic Therapy by Disease Severity (Gold 2009):



Postbronchodilator FEV1 is recommended for the diagnosis and assessment of severity of COPD.

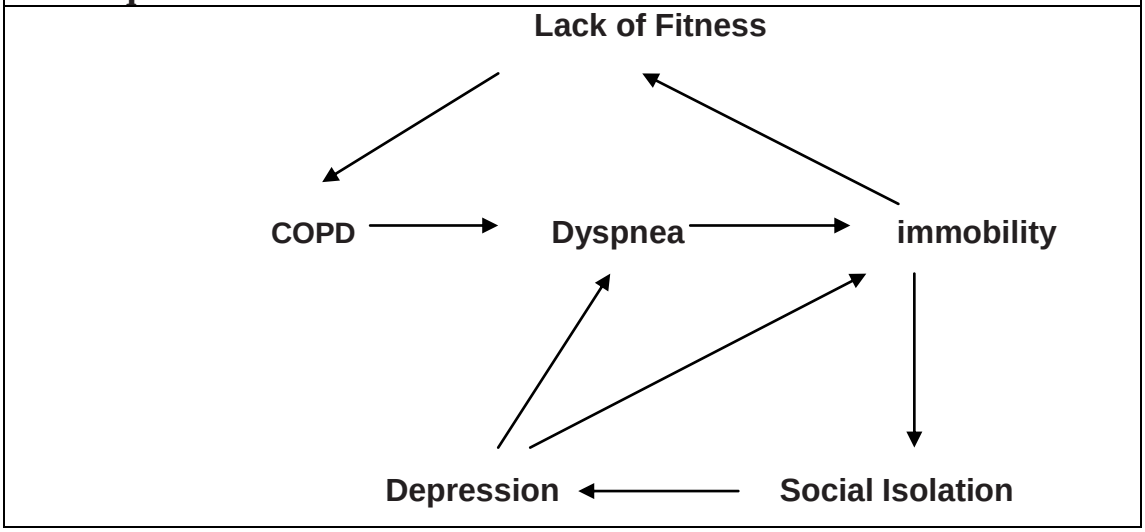
B) Non- pharmacologic treatment

1) Rehabilitation

Pulmonary rehabilitation is a program of exercise, disease management and counseling coordinated to benefit the individual. Pulmonary rehabilitation has been shown to improve shortness of breath and exercise capacity. Pulmonary rehabilitation covers a range of non-pulmonary problems including exercise de-conditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. These problems have complex interrelationships and

improvement in any one of these interlinked processes can interrupt the "vicious circle" in COPD (Fig. 2). A comprehensive statement on pulmonary rehabilitation has been prepared by the ATS/ERS **(Nici et al., 2006).**

Figure 2: The Cycle of Physical, Social, and Psychosocial Consequences of COPD



The cycle of physical, social, and psychosocial consequences of COPD **(GOLD 2009)**

The components of pulmonary rehabilitation program include exercise training, nutrition counseling, and education **(Lacasse et al., 2002).**

2) Oxygen Therapy:

One of the principal non pharmacologic treatments for patients with Stage IV: Very Severe COPD **(ATS 1995).**

The primary goal of oxygen therapy is to increase the baseline PaO2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO2 at least 90%, which will preserve vital organ function.

Long-term oxygen therapy is generally introduced in Stage IV: Very Severe COPD for patients who have:

• PaO2 at or below 7.3 kPa (55 mm Hg) or SaO2 at or below 88%, with or without hypercapnia

• PaO2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival **(Report of the Medical Research Council Working Party, 1981).**

Oxygen is usually delivered by:

- Facemask, with appropriate inspiratory flow rates varying between 24% and 35%.
- Nasal cannulae but requires additional blood gas monitoring
- Fixed oxygen Concentrator with plastic piping allowing the patient to use oxygen in their living area and bedroom. Treatment should be for at least 15 hours per day and preferably longer **(Currie and Douglas, 2007)**.

3) Ventilatory Support:

Noninvasive ventilation is now widely used to treat acute exacerbations of COPD **(Lightowler et al., 2003).**

4) Surgical Treatments:

Bullectomy:

Removal of a large bulla that does not contribute to gas exchange decompresses the adjacent lung parenchyma. This procedure is effective in reducing dyspnea and improving lung function **(Mehran and Deslauriers, 1995).**

Some investigators have recommended that the bulla must occupy 50% or more of the hemithorax and produce definite displacement of the adjacent lung before surgery is performed **(Laross et al., 1986).**

Lung volume reduction surgery (LVRS):

Lung volume reduction surgery involves removal of segments of inefficient emphysematous lung parenchyma in order to promote better gas exchange in the remaining, less affected part **(Fishman et al., 2008)**.

LVRS reduces hyperinflation and improves muscle mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition) **(Criner et al., 1998).**

In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates **(Fessler and Permutt, 1998).**

Interest has been growing in bronchoscopic lung volume reduction in patients with COPD. This involves obstructing emphysematous areas of lung with, for example, an endobronchial valve, therefore avoiding the risks associated with major surgery **(Hopkinson et al., 2005).**

Lung transplantation:

In patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Trulock, 1997).** Criteria for lung transplantation include FEV1 < 35% predicted, PaO2 < 7.3-8.0 kPa (55-60 mm Hg), PaCO2 > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension **(Hosenpud et al., 1998).**

Special Considerations:

Surgery in COPD:

The risk of postoperative respiratory failure appears to be in patients undergoing pneumonectomy with a preoperative FEV1 < 2 L or 50% predicted and/or a DLCO < 50% predicted **(Schuurmans et al., 2002).**

COPD patients at high risk due to poor lung function should undergo further lung function assessment as tests of regional distribution of perfusion and exercise capacity **(Celli et al., 2004).**

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Definition:

(Anthonisen et al., 1987) defined **AECOPD** clinically by the presence of one or more of the following findings:

1. Worsening of dyspnea.
2. Increase in sputum volume.
3. Increase in sputum purulence.

Classified it into:

- **Level I** (severe) has all the three symptoms.
- **Level II** (moderate) has two of them.
- **Level III** (mild) has one symptom plus at least one of the followings:

    A. Upper respiratory infection in the past 5 days.

    B. Fever without another apparent cause.

    C. Increased wheezing.

    D. Increased cough.

    E. Increased respiratory rate > 25 breaths/minute.

    F. Increased heart rate by 20% above baseline.

Rodriguez-Roisin (2000): proposed the following definition of AECOPD as "it is a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates change in regular medication in a patient with underlying COPD"**.**

He also proposed a staging classification system based on health care utilization**:**

Mild: patient has an increased need for medications, which can be managed in patient's normal environment**.**

Moderate: patient has an increased need for medications and feels the need to seek additional medical assistance.

Severe: patient/caregiver recognizes deterioration in condition requiring hospitalization.

An exacerbation of chronic obstructive pulmonary disease (COPD) is a sustained worsening of respiratory symptoms that is acute in onset and usually requires a patient to seek medical help or alter treatment. The deterioration must be more severe than the usual daily variation experienced. Exacerbations are characterised by increased breathlessness, cough, sputum volume or purulence, wheeze, and chest tightness **(Currie and Wedzicha, 2007).**

Causes and risk factors of AECOPD:

The most common causes of an exacerbation are infection of the tracheobronchial tree by virus (Rhinovirus spp., influenza); bacteria (Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Enterobacteriaceae spp., Pseudomonas spp.) and air pollution **(White et al., 2003).**

Pathology of AECOPD

Although it has been assumed that exacerbations are associated with increased airway inflammation, there has been little information available on the nature of inflammatory markers, because of the difficulty in performing invasive maneuvers such as brushing, lavage or biopsies during an acute exacerbation of COPD. However, the technique of sputum induction allows the study of these patients during exacerbations, and it has been shown that it is safe and well tolerated in COPD patients. There were more increase in neutrophils, T. lymphocytes (CD3+) and tumor necrosis factor-alpha- positive cells, while there were no changes

in the number of CD4+ or CD8+ T cells, macrophages or mast cells **(Wedzicha, 2002)**.

Pathogenesis of AECOPD

Many exacerbations are infectious in origin (either bacterial or viral). However, many patients with COPD are colonized by bacteria when clinically stable. Thus, there are a substantial percentage of exacerbation episodes of unclear cause. Potential mechanisms include air pollution, changes in ambient temperature and pulmonary emboli, among others (smoking and cessation of medication) **(Wedzicha, 2001).**

Pathophysiology of AECOPD:

Airflow obstruction is almost unchanged during mild exacerbations and only slightly reduced during severe exacerbations **(Seemungal et al., 2000).** Severe exacerbations are accompanied by a significant worsening of pulmonary gas exchange (due mostly to increased ventilation-perfusion inequality**)** and, potentially, by respiratory muscle fatigue. Worsening ventilation-perfusion relationships in exacerbations of COPD are multifactorial and relate to airway inflammation and oedema, mucus hypersecretion and bronchoconstriction, which affects ventilation and causes hypoxic vasoconstriction of pulmonary arterioles, which reduces perfusion. Alveolar hypoventilation and respiratory muscle fatigue also contribute to hypoxaemia, hypercapnia and respiratory acidosis leading to severe respiratory failure and death. Hypoxia and respiratory acidosis produce pulmonary vasoconstriction imposing an additional load on the right ventricle and, together with renal and hormonal changes, can result in peripheral oedema **(Barbera et al., 1997).**

Diagnosis and assessment of severity*:*

1-Clinically:

In 2004, the UK National Institute for Clinical Excellence (NICE) developed consensus statements**.** Stated the following**:**

A): Symptoms of an exacerbation:

Exacerbations of COPD can be associated with the following symptoms:

- increased dyspnoea
- increased sputum purulence
- increased sputum volume
- increased cough
- upper airway symptoms (e.g. colds and sore throats)
- increased wheeze
- chest tightness
- reduced exercise tolerance
- fluid retention
- increased fatigue
- Acute confusion.
- Chest pain and fever are uncommon features of COPD exacerbations and should prompt a search for other etiologies.

B) Assessment of the severity of an exacerbation (signs of severity):

Some exacerbations are mild and self-limiting. These are frequently managed by patients at home without consulting healthcare professionals. Other exacerbations are severe, carry a risk of death and require hospitalization. A number of factors can be used to assess the severity of an exacerbation. Not all will be present, but the occurrence of any of these should alert the clinician as shown in table (3) **(Celli et al., 2004)**.

Table (3): **Clinical history, physical findings and diagnostic procedures in patients with exacerbation of chronic obstructive pulmonary disease (COPD). (Celli et al., 2004):**

	Level I	Level II	Level III
*** Clinical history**			
Co-morbid conditions(1)	+	+++	+++
History of frequent exacerbations	+	+++	+++
Severity of COPD	Mild/moderate	Moderate/Severe	Severe
*** Physical findings**			
Haemodynamic evaluation	Stable	Stable	Stable/unstable
Use accessory respiratory muscles, tachypnoea	Not present	++	+++
Persistent symptoms after initial therapy	No	++	+++
*** Diagnostic procedures**			
Oxygen saturation	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Chest radiograph	No	Yes	Yes
Blood tests(2)	No	Yes	Yes
Serum drug concentrations(3)	If applicable	If applicable	If applicable
Sputum gram stain and culture	No(4)	Yes	Yes
Electrocardiogram	No	Yes	Yes

+: Unlikely to be presen ++: likely to be present +++: very likely to be present

(1) The more common co-morbid conditions associated with poor prognosis in exacerbations are congestive heart failure, coronary artery disease, diabetes mellitus, renal and liver failure.

(2) Blood tests include cell blood count, serum electrolytes, renal and liver function.

(3) Serum drug concentrations, consider if patients are using theophylline, warfarin, carbamezepine, digoxin.

(4) Consider if patient has recently been on antibiotics.

2-Laboratory:

a) Pulse oximetry and arterial blood gas measurement:

Can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. Moderate-to-severe acidosis (pH < 7.36) plus hypercapnia (PaCO2 > 6-8 kPa, 45-60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation **(Celli et al., 2004).**

b) Chest X-ray and ECG:

Chest radiographs both postero-anterior, laterally views are useful in identifying alternative diagnosis that can mimic the symptoms of an exacerbation **(Pauwel et al., 2001).**

An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes especially if a previously normal ECG is available. **(postma et al., 1999).**

c) Spirometry and PEF:

. Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended**.** In general, PEF < 100 L/min. or an FEV1 < 1 L indicates a sever exacerbation **(Neiwoehner et al., 2000**).

d) Bio- chemical test:

Abnormalities can be associated with an exacerbation and include electrolyte disturbance (s) (e.g., hyponatremia, hypokalemia), poor glucose control and metabolic acid-base disorder**. (Pauwel et al., 2001).**

Differential diagnosis of an exacerbation:

Other conditions may present with similar symptoms in patients with COPD. These must be considered and excluded when making a diagnosis of an exacerbation, other causes of similar symptoms in patients with

COPD are **(Currie and Wedzicha 2007):**

- pneumonia
- pneumothorax
- left ventricular failure/pulmonary oedema
- pulmonary embolus
- lung cancer
- upper airway obstruction
- pleural effusion
- Recurrent aspiration.

Treatment:

1) HOME MANAGEMENT

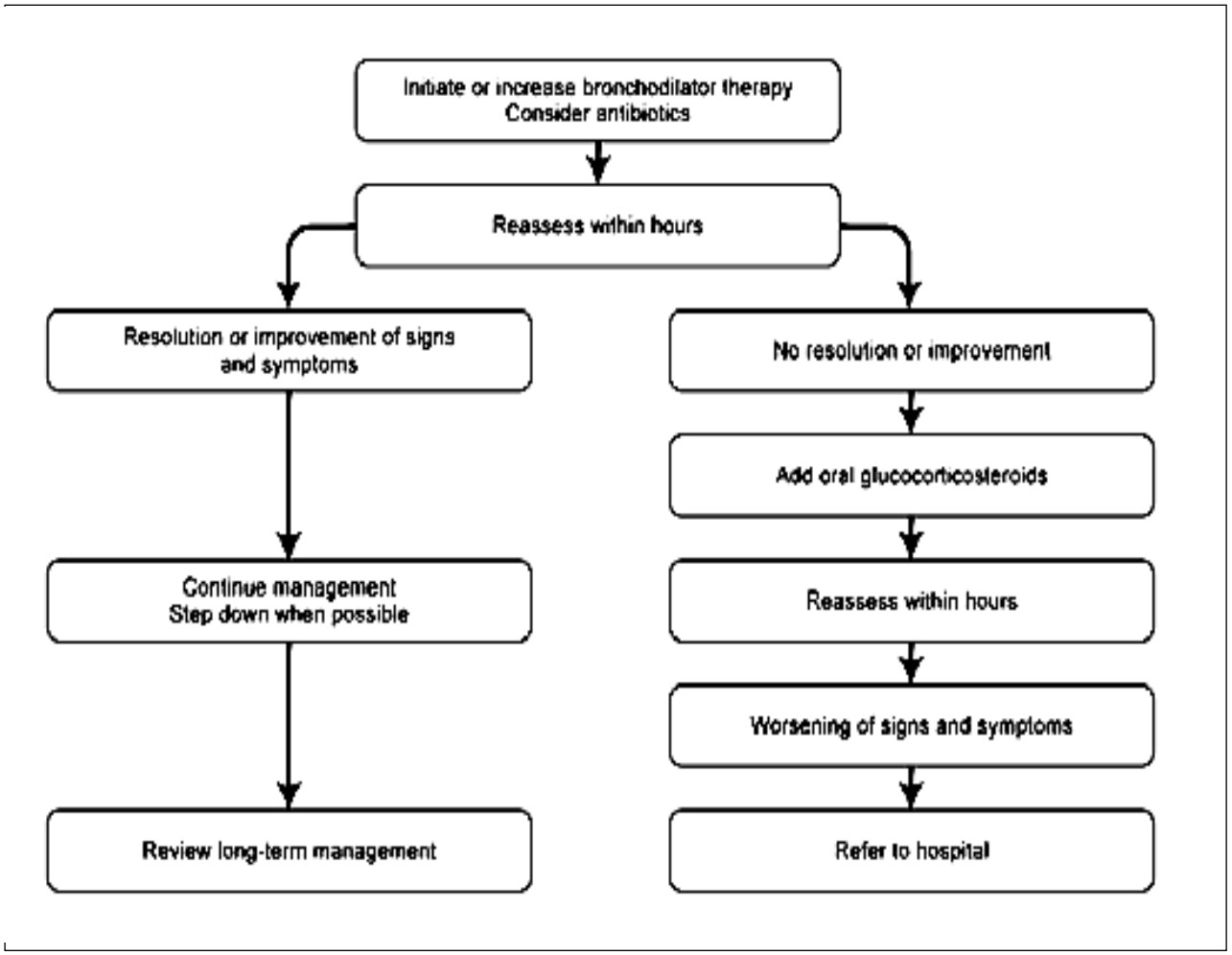


Figure 3: Algorithm for the Management of an Exacerbation of COPD at Home **(Rodriguez-Roisin, 2006)**

Home management includes:

a) Patient education

By checking inhalation technique and consider use of spacer devices **(ATS/ERS, 2004)**.

b) Bronchodilators

Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short acting bronchodilator therapy including short-acting β2-agonist (albuterol, salbutamol, terbutaline) and/or ipratropium MDI with spacer or hand-held nebuliser as needed, also consider adding long-acting bronchodilator if patient is not using it **(Turner et al., 1997)**.

c) Corticosteroids

Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV1) and hypoxemia (PaO2). A dose of 30–40 mg prednisone per day for 10 days **(O'Donnell et al., 2007)** in addition to use inhaled corticosteroid **(Maltais et al., 2004)**.

d) Antibiotics

May be initiated in patients with altered sputum characteristics. There choice should be based on local bacteria resistance patterns. Including the use of amoxicillin/ampicillin, cephalosporins (cefpodoxime, cefprozil), doxycycline **(Adams and Anzueto, 2000)** and macrolides (azithromycin, clarithromycin) **(Swanson et al., 2002).** If the patient has failed prior antibiotic therapy consider: amoxicillin/clavulanate moxifloxacin) **(Wilson et al., 2002)**.

e) Mucolytics:

There is no evidence of shortening in the duration of the exacerbations or improvement of the FEV1 values when using mucolytics in AECOPD.

In the non acute COPD setting, systematic reviews have found a reduction in the number of acute exacerbation and days of illness when mucolytics were routinely used **(Poole and Black, 2001).**

f) Anticoagulants:

Subcutaneous heparin administration could be of promising beneficial therapeutic value in exacerbated COPD patients **(Talat, 2002).**

g) Diuretics:

Diuretics are indicated if there is peripheral oedema and a raised jugular venous pressure **(BTS, 1997).**

2) HOSPITAL MANAGEMENT

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support **(Connors et al., 1996).**

Indications for Hospital Assessment or Admission for Exacerbations of COPD (GOLD 2009):

• Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
• Severe underlying COPD
• Onset of new physical signs (e.g., cyanosis, peripheral edema)
• Failure of exacerbation to respond to initial medical management
• Significant comorbidities
• Frequent exacerbations
• Newly occurring arrhythmias
• Diagnostic uncertainty
• Older age
• Insufficient home support

Treatment for hospitalized patient:

a) Bronchodilators

Short acting β2 agonist (Albuterol, salbutamol) and/or Ipratropium MDI with spacer or hand-held nebuliser as needed **(Turner et al., 1997)**

b) Supplemental oxygen (if saturation <90 %)

Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 > 8.0 kPa, 60 mm Hg, or SaO_2 > 90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient **(Celli et al., 2004).**

c) Corticosteroids

If not contraindicated, prednisone 30–40 mg per day for 10-14 days unless the patient can not tolerate oral intake, equivalent dose intravenous for up to 14 days **(O'Donnell et al., 2007)** and also consider the use of inhaled corticosteroids by MDI or hand-held nebulizer **(Maltais et al., 2004).**

d) Antibiotics (based on local bacteria resistance patterns)

May be initiated in patients that have a change in their sputum characteristics (purulence and/or volume) .The Choice of antibiotics should be based on local bacteria resistance patterns such as Amoxicillin/clavulanate **(Anzueto et al., 2001)** and respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin) **(Gotfried et al., 2001)**

If Pseudomonas spp. and/or other Enterobactereaces spp. are suspected, consider combination therapy **(ATS/ERS, 2004).**

Indications for ICU Admission of Patients with Exacerbations of COPD (GOLD 2009)

• Severe dyspnea that responds inadequately to initial emergency therapy

• Changes in mental status (confusion, lethargy, coma)

• Persistent or worsening hypoxemia ($PaO_2 < 5.3$ kPa, 40 mmHg), and/or severe/worsening hypercapnia ($PaCO_2 > 8.0$ kPa, 60 mmHg), and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation

• Need for invasive mechanical ventilation

Treatment in patients requiring ICU (Celli et al., 2004):

a) Supplemental oxygen

b) Ventilatory support

The primary objectives of mechanical ventilatory support in patients with COPD exacerbations are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive intermittent ventilation using either negative or positive pressure devices and invasive (conventional) mechanical ventilation by oro-tracheal tube or tracheostomy **(GOLD, 2009).**

Noninvasive positive pressure ventilation (NPPV) should be offered to patients with exacerbations when, after optimal medical therapy and oxygenation, respiratory acidosis (pH <7.36) and/or excessive breathlessness persist.

If pH <7.30, NPPV should be delivered under controlled environments such as intermediate intensive care units (ICUs) and/or high-dependency units.

If pH <7.25, NPPV should be administered in the ICU and intubation should be readily available.

c) Bronchodilators

• Short acting β2 agonist (Albuterol, salbutamol) and ipratropium MDI with spacer, two puffs every 2–4 h.

• If the patient is on the ventilator, consider MDI administration.

• Consider long-acting β agonist.

d) Corticosteroids

• If patient tolerates oral medications, prednisone 30–40 mg per day for 10 days.

• If patient can not tolerate, give the equivalent dose I.V. for up 14 days.

• Consider use inhaled corticosteroids by MDI or hand-held nebuliser.

e) Antibiotics

• Choice should be based on local bacteria resistance pattern.

• Amoxicillin/clavulanate.

• Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin)

• If Pseudomonas spp. and or other Enterobactereaces spp. are suspected consider combination therapy

C-reactive protein

CRP is a member of an ancient family of molecules called the pentraxins, which have been highly conserved in both invertebrates and vertebrates for >400 million years. Tillet and Frrancis reported that it was discovered in humans in 1930 as a serum component that binds the C polysaccharide of Streptococcus pneumoniae (hence CRP). **(Anderson, 2006).**

Structure:

CRP is composed of five identical subunits (hence pentraxin), each ~ 23 kDa in mass, which are linked noncovalently to form a disc-like pentagonal ring. **(Carlson et al., 2005).**

CRP is also a member of a diverse class of defense molecules called the acute-phase proteins, which includes structurally unrelated mannose-binding protein and fibrinogen. Levels of acute-phase proteins rise rapidly, and often dramatically, during infection and after injury **(Anderson, 2006).**

Initially it was thought that CRP might be a pathogenic secretion, as it was elevated in people with a variety of illnesses, including carcinomas. Discovery of hepatic synthesis and secretion of CRP closed that debate. It binds to phosphocholine, thus initiating recognition and phagocytosis of damaged cells **(Lau et al., 2005)**

Triggering:

CRP levels can be increased over 1,000-fold in serious infection when spill-over of inflammatory mediators into the blood, especially interleukin (IL)-6 and IL-1ß, triggers its production in the liver. It should also be noted that nonhepatic production of CRP by monocytes and lymphocytes has been demonstrated and it is possible (as with leptin) that

some CRP is made locally in the inflamed lung **(Broekhuizen et al. 2005)**.

In biology, when a molecule like CRP is both ancient and highly conserved across species, it almost invariably points to function(s) that are essential to preserve life rather than cause disease **(Anderson and Bozinovski, 2003).**

Function:

-As an opsin to agglutinate bacteria and promote phagocytosis and is directly bactericidal**.** Exogenous CRP protects mice, which oddly are naturally deficient in CRP, from diverse lethal infections **(Husebekk and Hansson, 1996).**

-CRP is an excellent scavenger of chromatin from damaged cells, such as those that are bound in the apoptosis-prone COPD lung, which would otherwise cause severe damage to nearby tissue **(Gershov et al., 2000)**.

-CRP has been shown to induce anti-inflammatory IL-1 receptors, blunt the shedding of L-selectin that precedes the movement of neutrophils from blood to tissue and to dampen leukocyte oxidative burst. CRP can trigger anti-inflammatory immunoglobulin crystallisable fragments gamma (Fcγ) inhibitory receptors bearing a cytoplasmic immunoreceptor tyrosine-based inhibitory motif **(Ballou and Lozanski, 1992).**

-CRP can also act as a potent pro-inflammatory agent. CRP activates the classical complement cascade, which can be intensely pro-inflammatory, by binding directly to the complement fragment C1q **(Anderson, 2006).**

-CRP also activates NF-κB in endothelial cells and mononuclear cells to induce proteases and pro-inflammatory cytokines, such as IL-1ß, IL-6, IL-8 and IL-18 **(Ballou and Lozanski, 1992).**

-CRP represses the repair potential of endothelial stem cells **(Suh et al., 2004).**

Stimulation of CRP production in clinically stable COPD:

CRP is classically induced on infection:

-Bacterial colonization occurs in about 30% of stable COPD patients and COPD patients might have Chlamydia or mycoplasma infection **(De Torres et al., 2006).**

-Air pollutants particulate may contribute **(van Eden et al., 2005).**

-Non hepatic production of CRP by monocytes and lymphocytes is made locally in the inflamed lung **(Anderson, 2006).**

Elevated CRP concentration can be detected within 6-12 hours of the onset of an inflammatory stimulus **(Melbye and Stocks, 2006),** and the concentration peak within 24-48 hours **(WeitKamp and Achner, 2005).**The elevation can even be more than 1000 fold **(Black et al., 2004).**

CRP has been found to reflect closely the extent, activity and severity of disease. With resolution of infection or inflammatory process, CRP levels decline rapidly owing to the short half–life (19 hours) of CRP in the bloodstream **(Pepys, 2003).**

Although elevated CRP concentration is not specific to any particular disease, quantitative measurement of CRP adds valuable information to the diagnosis, treatment and monitoring of an inflammatory process and the associated disease. In a primary care setting, CRP can assist doctors in distinguishing between bacterial and viral infections and also in monitoring the efficacy of antibiotic therapy **(Philip and Mills, 2000).**

CRP levels are increased markedly by invasive bacterial infection. 50-85% of patients with a CRP concentration exceeding 100 mg/l will have a bacterial infection **(Gabay and Kushner, 1999).**

Acute Gram-positive bacterial infections are among the most potent stimuli for CRP production also uncomplicated viral infection usually has little effect on CRP concentration. **(Pepys, 2003).**

CRP concentrations drop rapidly, about 50% a day, in response to effective treatment. So, it is of great value in monitoring the effect of antibiotic therapy, and antibiotics can be stopped upon normalization of CRP value **(Weitkamp and Achner, 2005).**

CRP in various clinical situations:

-Serious bacterial infection:

Septicemia, endocarditis, osteomyelitis, septic arthritis, bacterial pneumonia and meningitis as well as pyelnephritis are usually associated with markedly elevated CRP concentrations **(Stolz et al., 2006).**

Measurement of CRP is also useful in the management of feverish conditions without localizing signs. Fever is also a common symptom in self-limiting, benign viral illness. However, some febrile patients without apparent source of infection may have an occult severe bacterial infection **(Maheshwari, 2006).**

-Cardiovascular diseases:

CRP is a stronger predictor of risk for incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death than is low-density lipoprotein (LDL) cholesterol. The additive value of CRP to lipid screening in terms of coronary risk prediction has been demonstrated in several settings **(Ridker et al., 2002).**

CRP levels predict early and late mortality in acute coronary ischemia and add to the predictive value of cardiac troponin **(Mueller et al., 2002).**

-CRP and pathogenesis of atherosclerosis:

Binding of CRP to lipids, especially lecithin (phosphatidyl choline), and to plasma lipoproteins has been known for over years, but the first suggestion of a possible relationship to atherosclosis came when demonstrated that aggregated, but not native, CRP selectively bound only LDL and some VLDL from whole serum **(pepys et al., 1985).**

Native CRP dose bind to oxidized LDL (Chang et al., 2002) and to partly degraded LDL, as found in atheromatous plaques, and then activates complement **(Bhakdi et al., 1999).**

Addition of CRP to LDL in cell culture systems has been reported to stimulate formation of foam cells, which are a typical feature of atherosclerotic plaque **(Zwaka et al., 2001).**

-Role in cancer:

Blood samples of persons with colon cancer have an average CRP concentration of 2.69 milligrams per liter. Persons without colon cancer average 1.97 milligrams per liter. The difference was statistically significant **(Erlinger et al., 2004).**

-CRP in relation to Body Mass Index (BMI):

CRP is made by the liver in response to inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) **(Gabay and Kushner, 1999).**

Adipose tissue is a major source of these inflammatory cytokines **(Yudkin et al., 1999).**

Consequently, a strong positive association has been found between measures of obesity, such as waist circumference (WC) and body mass index (BMI), with CRP **(Huffman et al., 2010)**

CRP, erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and procalcitonin (PCT):

-CRP versus ESR:

ESR is a nonspecific inflammation marker and a commonly performed laboratory analysis **(Pepys, 2003).**

CRP has many advantages over ESR. ESR is greatly influenced by the size, shape and number of erythrocytes, gender and age of the patient, as well as serum proteins such as fibrinogen and immunoglobulins. Therefore, ESR results can vary and sometimes mislead. As a patient's

condition worsens or improves, ESR changes rather slowly, whereas plasma CRP concentration reacts rapidly. **(Gabay and Kushner, 1999).**

ESR is also greatly affected by technical factors, such as assay temperature, sample dilution and tilting of the ESR tube **(Bridgen, 1999).**

-CRP versus WBC:

CRP has been found to be more sensitive and specific than WBC for differentiation between bacterial and viral infection **(Stolz et al., 2006).**

In young febrile children, CRP is superior to WBC in predicting which febrile children have occult severe bacterial infection requiring antibiotic therapy **(Pratt and Attia, 2007).**

WBC values are also not consistent enough to be used in monitoring the effect of antibiotic treatment in bacterial infection **(Roine et al., 1995).**

-CRP versus Procalcitonin:

Similarly to CRP, PCT is a general marker of bacterial infection **(Tang et al., 2007).** However, PCT measured at central laboratory is not ideal for routine primary care **(Briel et al., 2005).**

The impact of C-Reactive Protein on COPD

There is increasing evidence that chronic obstructive pulmonary disease (COPD) is a multiorgan systemic disease. Skeletal muscle weakness and wasting and impaired exercise performance have been well described as frequently occurring symptoms in advanced COPD **(Wouters, 2002).** These features are poorly related to the severity of airflow limitation but appear to be linked to a systemic inflammatory response **(ATS/ERS, 1999).**

Several systemic inflammatory mediators such as tumour necrosis factor α (TNF-α), some interleukins (ILs), acute phase proteins (C-reactive protein (CRP), fibrinogen, lipopolysaccharide binding protein (LBP)) and leucocytes are increased in COPD. One of the markers of systemic inflammation that is consistently shown to be slightly increased in patients with COPD compared with healthy controls is CRP **(Gan et al., 2004).**

CRP seems to increase with increasing severity of COPD. **(Mannino et al., 2003)**.

Although the exact origin of systemic inflammation is unknown, lung biopsy examination clearly shows that local inflammation is more pronounced with worse lung function**. (Hogg et al., 2004).**

CRP is principally induced by IL-6 and this is amplified by IL-1. Both IL-6 and IL-1ß have been found in asthma and COPD **(Broekhuizen et al., 2006).**

The highest CRP levels were found in current smokers, as cigarette smoking induces IL-6 in lung tissue **(Vlahos et al., 2005).**

Previously, IL-6 was identified as an ‘‘exercise factor’’, being produced by contracting muscle and subsequently released into the blood. Under normal circumstances the IL-6 gene is rapidly activated during exercise.

It has been shown that IL-6 gene transcription is mediated by the glycogen content and that increased IL-6 expression is associated with increased glucose uptake during exercise. **(Pedersen , et al., 2004)**

When contracting muscles are low in glycogen, IL-6 is released to increase glucose uptake and induce lipolysis and gene transcription in abdominal subcutaneous fat. However, it has also been shown that murine myotubes express IL-6 when exposed to oxidative stress**, (Kosmidou et al., 2002)**.

In COPD several changes have been reported that can influence the above mentioned process. Firstly, decreases in oxidative enzymes involved in carbohydrate and fatty acid oxidation have been reported in some patients with COPD**. (Maltais et al, 2000).**

Furthermore, it has been shown that some COPD patients have impaired muscle glycogen content due to inactivity and hypoxia, and have enhanced lactic acid production during cycling compared with healthy control subjects**. (Maltais et al,. 1996).**

Systemically, patients with COPD also have an imbalance between oxidants and antioxidants at rest and also after exercise, suggestive of increased oxidative stress. Moreover, patients with COPD cannot adapt their muscle redox status to training**. (Koechlin et al, 2004)**

Imbalances between oxidants and antioxidants could increase the release of IL-6 independently of muscle intrinsic changes. Because IL-6 is a strong inducer of acute phase proteins, the exacerbated increase in IL-6 production of muscle could induce CRP, as illustrated by the strong correlation between CRP and IL-6. (**Kishimoto, 1989)**

Studies have also shown an inverse relation between CRP and exercise capacity in healthy elderly subjects as well as in those with COPD**. (Koechlin et al, 2004)**

The increased demand for specific amino acid to generate CRP may increase muscle protein breakdown, increasing resting energy expenditure (REE) and inducing a vicious cycle of intrinsic muscle changes leading to decreased exercise capacity leading to more muscle impairment. CRP may thus be a marker of a repetitive supraphysiological increase in IL-6 production of muscle in a subgroup of COPD patients**. (Reeds et al, 1994)**

. CRP analysis has already been recommended for clinical application in the detection and prevention of cardiovascular disease**. (Ridker, 2003).**

Since cardiovascular disease is a major cause of mortality in COPD, and CRP is a predictor of acute exacerbations of COPD, hospital admissions, and mortality in chronic respiratory failure **(Cano et al, 2004).**

Subjects and Methods

This study was performed on 40 male patients with COPD admitted in chest department at Benha University Hospital in the period between March 2009 and March 2010, 40 healthy male of the same age and sex were included as a control group, 20 smokers and 20 non smokers with no history of ischemic heart diseases and with normal ventilatory function tests.

All subjects were submitted to the following:

1. History taking:

   -History of smoking (current, Ex. and non smoking)

   -History of chest symptoms (cough, expectoration, dyspnea and wheeze).

   -History of any other co-morbidities that may raise the C-reactive protein as ischemic heart diseases, hypertension, diabetes mellitus, tuberculosis, malignancy, hepatic cirrhosis, end-stage renal disease, rheumatoid arthritis and any systemic infection or inflammation that could be associated with increased CRP values **(Anderson, 2006).**

2. Clinical examination general and local with special regards to manifestations of right sided heart failure, cardiac examination and blood pressure measurement.

3. Body mass index (BMI) was calculated as the weight in Kg divided by height^2.

4. Radiological examination: Plain postero-anterior and Lt. lateral chest x-rays was done to exclude any chest lesion if present.

5.Pulmonary function tests (spirometry) before and after bronchodilatation. Ambient temperature and pressure were entered with

the patient data (age in years, weight in kilograms, height in centimeters and sex) so that all results were calculated as percent of predicted (% predicted) except for FEV_1/ FVC.

Pulmonary function tests were done using Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL.

-Spirometry (F⁄V loop):

1) Maneuver of flow volume loop **(Coates, 1988)**:

a. Calibration of the system was done.

b. Explaining the procedure to the patient.

c. The nose was clipped by nose clip and the patient was connected to the mouth piece.

d. The patient was instructed to breath tidally for several times then to inhale slowly till TLC was reached , then to exhale forcibly as much as he can till RV was reached , then the patient was instructed to inhale forcibly till TLC.

e. The patient was instructed to continue exhaling so that the tracing crosses the red dotted 6 second line.

f. The patient was instructed to continue exhaling until "End of Test Criteria Met".

g. The patient was instructed to forcefully inspire as deep as possible after the "End of Test Criteria Met", message is displayed and the test is ended.

h. This procedure was repeated three times and the best result was taken.

From the flow volume loop the following data were collected:

-Forced vital capacity (FVC).

- Forced expiratory volume in the first second (FEV1)

- Forced expiratory volume in the first second to the forced vital capacity percent (FEV1/FVC %)

- Peak inspiratory and expiratory flow rate were read directly from the F-V loop.

- The flow at any lung volume was measured directly from the F-V loop. Forced expiratory flow at 75%, 50% and 25% of FVC were reported as the $FEF_{75\%}$, FEF_{50} , $FEF_{25\%}$ respectively with the subscripts referring to the percentage of FVC already exhaled **(Gregg, 1998).**

Every patient performed 3 successive trials pre-bronchodilator; the one with the best performance was chosen. Also every patient performed the test three successive times 15 minutes post-bronchodilator to determine the reversibility of airway obstruction. Inhaled bronchodilator given by metered dose inhaler (MDI). B_2-adrenergic aerosol (Salbutamol 200 µg) was used because it has a rapid onset of action, usually within 5 minutes (**Miller et al., 2005).**

Patients were classified according to their post-bronchodilator FEV1 into mild (FEV1≥80% predicted), moderate (50%≤FEV1<80% predicted), severe (30%≤FEV1<50% predicted) and very severe (FEV1<30% predicted or FEV1<50% predicted plus chronic respiratory failure) COPD patients **(GOLD 2009).**

2) Maneuver of MVV **(Coates, 1988):**

a. The patient was instructed to begin with normal breathing.

b. The patient was instructed to begin breathing fast and deep.

c. The patient was instructed to continue deep rapid breathing until the end of the test. The test ended automatically.

6- Blood samples for C-reactive protein measurement were taken.

-Precautions: Components from human origin were tested and found to be negative for the presence of HBsAg, HCV and HIV. However, samples were handled cautiously as potentially infectious.

- Samples: Fresh serum (stable 7 days at 2-8°C or 3 months at-20°C). Samples with presence of fibrin were centrifuged before testing.

-Principles of the method: The CRP- latex agglutination test for the qualitative and semi-quantitative detection of the CRP in human

serum.

-Latex particles coated with IgG anti-human CRP were agglutinated when mixed with samples containing CRP.

- Calibration: The CRP-latex sensitivity was calibrated to the Reference Material CRM 470/RPPHS.

- Additional equipment: Mechanical rotator with adjustable speed at 80-100 r.p.m.

- Calculation: The approximate CRP concentration in the patient sample was calculated as follow:

6*CRP Titer= mg/L

-Reference values: Up to 6mg/L.

-Performance characteristics:

1. Analytical sensitivity: 6mg/L.
2. Diagnostic sensitivity: 95.6%.
3. Diagnostic specificity: 96.2%. **(Lars-Olof et al., 1997).**

7- Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar.

Selection criteria:

Patients should be stable COPD patients, not in acute exacerbations.

Exclusion criteria:

1-By history and examination any disease that may result in elevation of CRP level as follows **(Anderson, 2006)**:

-Cardiovascular co- morbidities like hypertension, ischemic heart diseases and cerebral vascular diseases.

-Diabetes mellitus.

-Inflammatory bowel diseases.

-Arthritis.

- Hepatic cirrhosis.

- End- stage renal disease.

- Any systemic infection or inflammation that could be associated with increased CRP values.

2-Patients were also excluded who had tuberculosis, bronchiectasis, malignancy or connective tissue disorders.

3- By spirometry: improvement of FEV1>12% or 200 ml after bronchodilators.

The results were tabulated and statistically analyzed.

Statistical Analysis

(Yadolah, 2003)

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, analysis of variance [ANOVA] test and chi-square test by SPSSV.11.

(1) Mean value [$\bar{X}$]

The sum of all observations divided by the number of observation:

$$\bar{X} = \frac{\sum X}{N}$$

Where $\sum X$= sum of all list &N= number of observations.

(2) Standard Deviation [SD]:

It measures the degree of scatter of individual varieties around their mean:

$$SD = \sqrt{\frac{Ex^2 - (Ex)^2}{N-1}}$$

(3) Analysis of variance [ANOVA] tests:

According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

(4) Chi-square:

The hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood –ratio chi-square.

Fisher's exact test and Yates' corrected chi-square were computed for 2x2 tables.

(5) Linear Correlation Coefficient [r]:

$$r = \frac{\sum (X - \bar{X})(y - \bar{y})}{\sqrt{\{\sum (X - \bar{x})2\}\{\sum (y - \bar{y})2\}}}$$

Where:

X= independent variable.

Y= Dependant variable.

Results

Table (4): Demographic data of the studied subjects as regards age, weight, height and body mass index:

	Mean ± SD			F-Test	P-Value
	Patients	Controls			
		Smokers	Non-Smokers		
No.	40	20	20		
Age/year	58.04±9.59 R:40 - 81	52±12.83 R: 41 - 75	49±10.14[a] R:39 - 62	5.5	<0.05
Wt/Kg	77.53±14.44 R:49 - 108	82.65±17.10 R:56 - 115	75.9±11.26 R:55 - 102	2.1	>0.05
Ht/cm	171.04±7.86 R:155 - 189	170.15±5.59 R:158 - 183	171.45±5.54 R:165 - 183	0.1	>0.05
BMI/Kg. m^2	26.63±5.27 R:15.68 – 39.67	28.68±6.49[c] R:19.58 - 45.26	25.76±3.19 R:20.20 – 33.05	2.4	>0.05

R: Range

a =compare between control non smokers and COPD cases.

c =compare between control smokers and control non smokers.

*P-value:

>0.05 insignificant, <0.05 significant, <0.001 highly significant

Table (5): Comparison between COPD cases and control smokers as regard the smoking index:

		No.	Range	Mean ± S.D	t	p
Smoking index	COPD cases	40	75-1500	481.59±325.433	1.1	>0.05
	Control smokers	20	40-1000	392.37±299.000		

Table (6): Spirometric data (pre and post bronchodilator) among COPD patients (% Pred.):

Parameter (% Pred.)	Mean ± SD		
	Pre bronchodilator	Post bronchodilator	% Change
FVC	51.15±13.38 R: 29 - 72	53.47±9.98 R:34 - 73	4.97±6.85
FEV1	39.68±10.25 R:23 - 64	41.75±11.03 R:17 - 72	5.65±6.52
FEV1/FVC	55.07±9.27 R:40 - 69	54.93±8.67 R:38 -68	
FEF25-75%	25.57±12.83 R:8- 59	25.27±12.57 R:10 -58	1.72±17.99
FEF50%	23.77±12.19 R:7 -56	23.25±11.95 R:8 - 57	-0.77±18.61
PEF	30.22±10.41 R:17 - 68	31.89±10.68 R:19- 58	7.26±15.84
MVV	31.65±11.7 R:12 - 61	32.93±10.93 R:14 -61	5.88±13.53

R: Range

Fig.(4): Spirometric data (pre and post) bronchodilator among COPD patients.

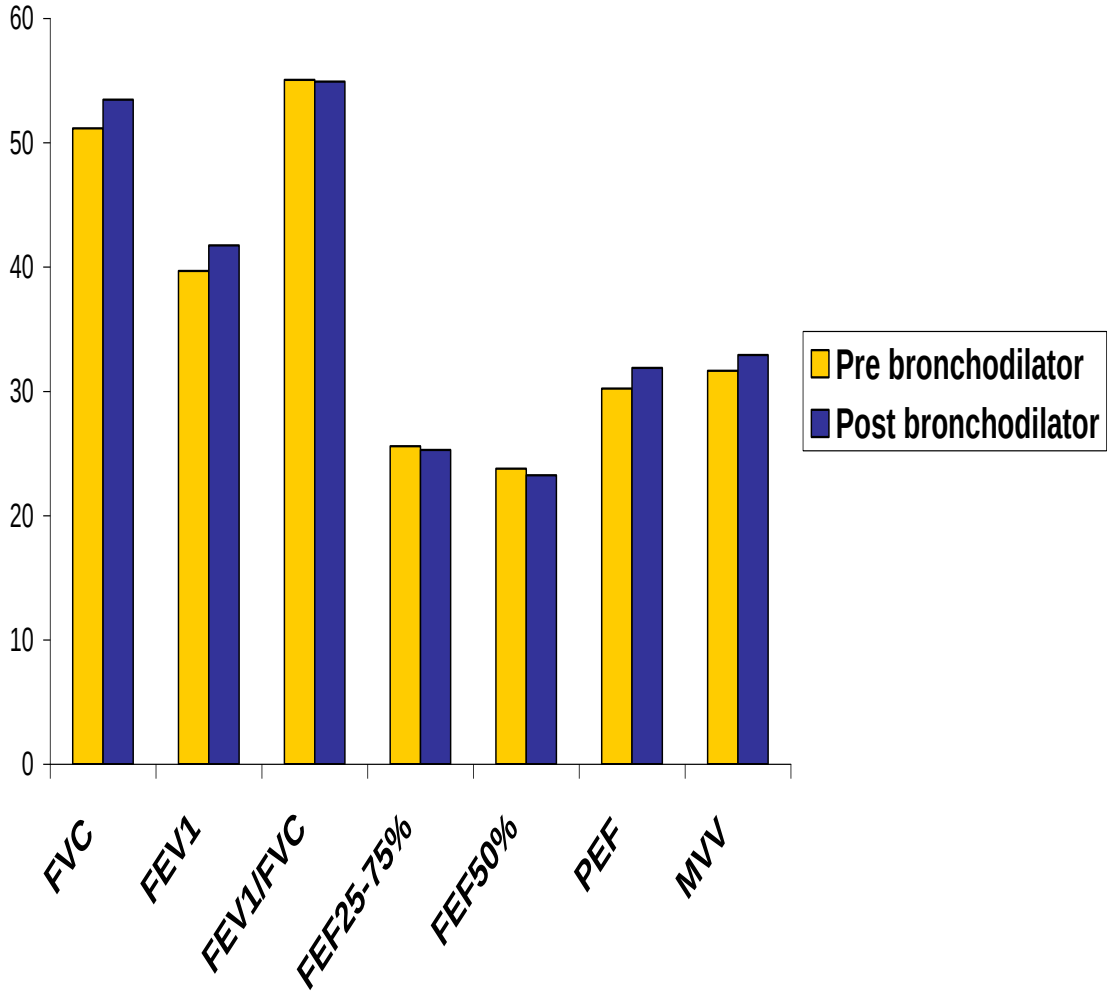


Table (7): Comparison between pre-bronchodilator spirometry in COPD patients and controls:

Parameter (% Pred.)	Mean ± SD			F-Test	P-Value
	Patients	Controls			
		Smokers	Non-Smokers		
FVC	51.15±13.38 R: 29 - 72	83.84±6.16[a] R:74 - 98	86.3±5.40[b] R: 80 - 95	103.9	<0.001
FEV1	39.68±10.25 R:23 - 64	85.32±7.26[a] R:80 - 115	89.9±7.58[b] R:82 - 115	261.6	<0.001
FEV1/FVC	55.07±9.27 R:40 - 69	74.26±7.46[a] R:55 - 97	76.95±6.01[b] R:72 - 97	63.4	<0.001
FEF25-75%	25.57±12.83 R:8- 59	59.37±26.99[a] R:30- 115	84.7±21.18[b,c] R:61 - 155	68.6	<0.001
FEF50%	23.77±12.19 R:7 -56	53.95±25.13[a] R:21 - 132	81.65±16.88[b,c] R: 60 -132	79.5	<0.001
PEF	30.22±10.41 R:17 - 68	49.32±15.96[a] R:24 - 90	73.6±14.24[b,c] R:58 -97	77.01	<0.001
MVV	31.65±11.7 R:12 - 61	58.47±16.15[a] R:27 – 93	74.8±11.63[b,c] R:58 - 93	82.4	<0.001

a =compare between control smokers and COPD cases.

b = compare between control non smokers and COPD cases

c = compare between control non smokers and control smokers.

Fig. (5): Comparison between pre-bronchodilator spirometry in COPD patients and controls (smokers and non-smokers):

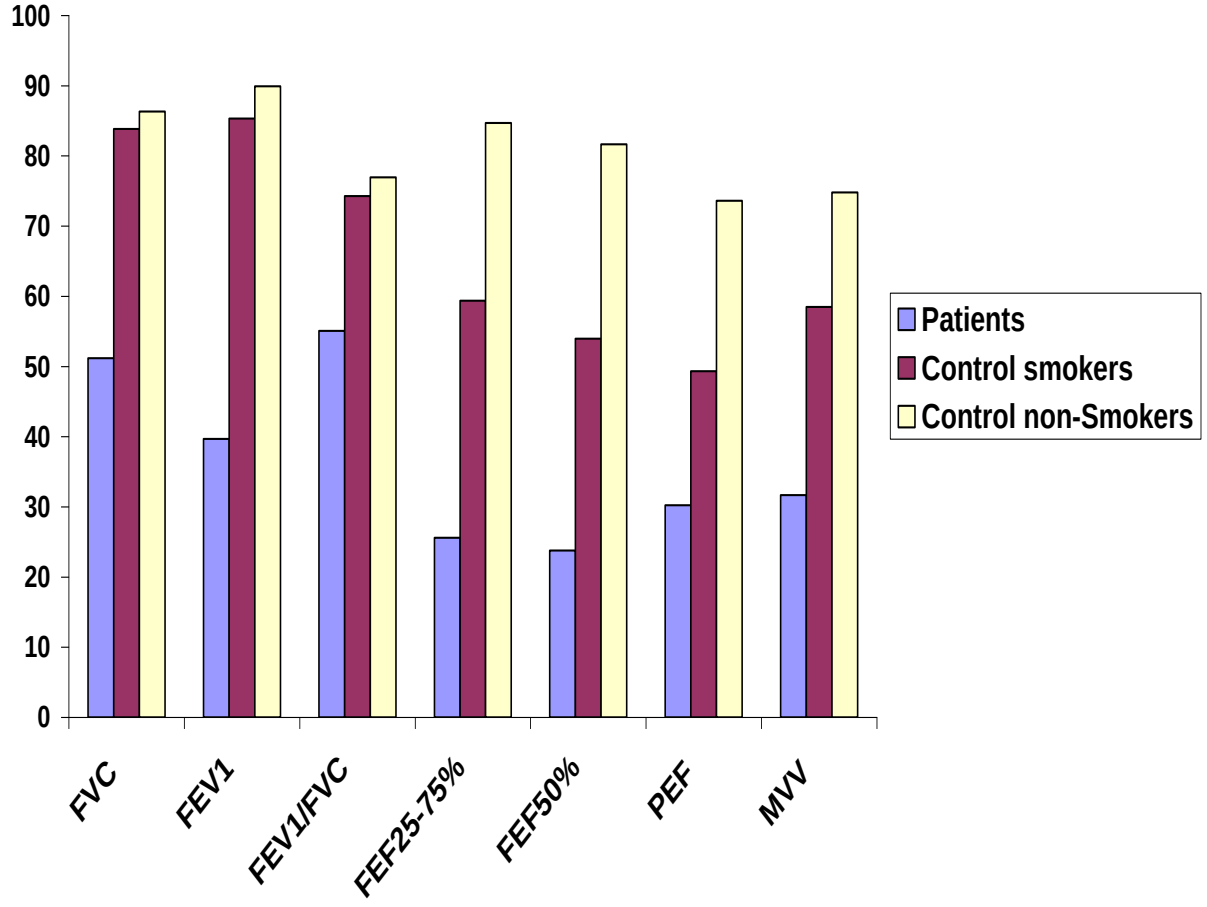


Table (8): Comparison between post-bronchodilator spirometry in COPD patients and controls:

Parameter (% Pred.)	Mean ± SD			F-Test	P-Value
	Patients	Controls			
		Smokers	Non-Smokers		
FVC	53.47±9.98 R:34-73	85.31±7.26[a] R:74-103	87.85±7.10[b] R:80-104	142.3	<0.001
FEV1	41.75±11.03 R:17-72	86±6.75[a] R:80-115	90.75±9.098[b] R:81-115	214.04	<0.001
FEV1/FVC	54.93±8.67 R:38-68	74.16±7.99[a] R:51-97	77.25±6.09[b] R:68-97	68.8	<0.001
FEF25-75%	25.27±12.57 R:10-58	60.53±27.43[a] R:30-155	84.3±20.46[b,c] R:63-155	70.3	<0.001
FEF50%	23.25±11.95 R:8-57	55.16±24.82[a] R:26-132	81.6±16.64[b,c] R:62-132	84.2	<0.001
PEF	31.89±10.68 R:19-58	50.15±16.29[a] R:25-90	75.15±14.49[b,c] R:58-97	73.1	<0.001
MVV	32.93±10.93 R:14-61	58.89±15.66[a] R:27-93	75.45±11.75[b,c] R:63-98	85.9	<0.001

a = compare between control smokers and COPD cases.

b = compare between control non smokers and COPD cases

c = compare between control non smokers and control smokers

Fig. (6): Comparison between post-bronchodilator spirometry in COPD patients and controls (smokers and non-smokers):

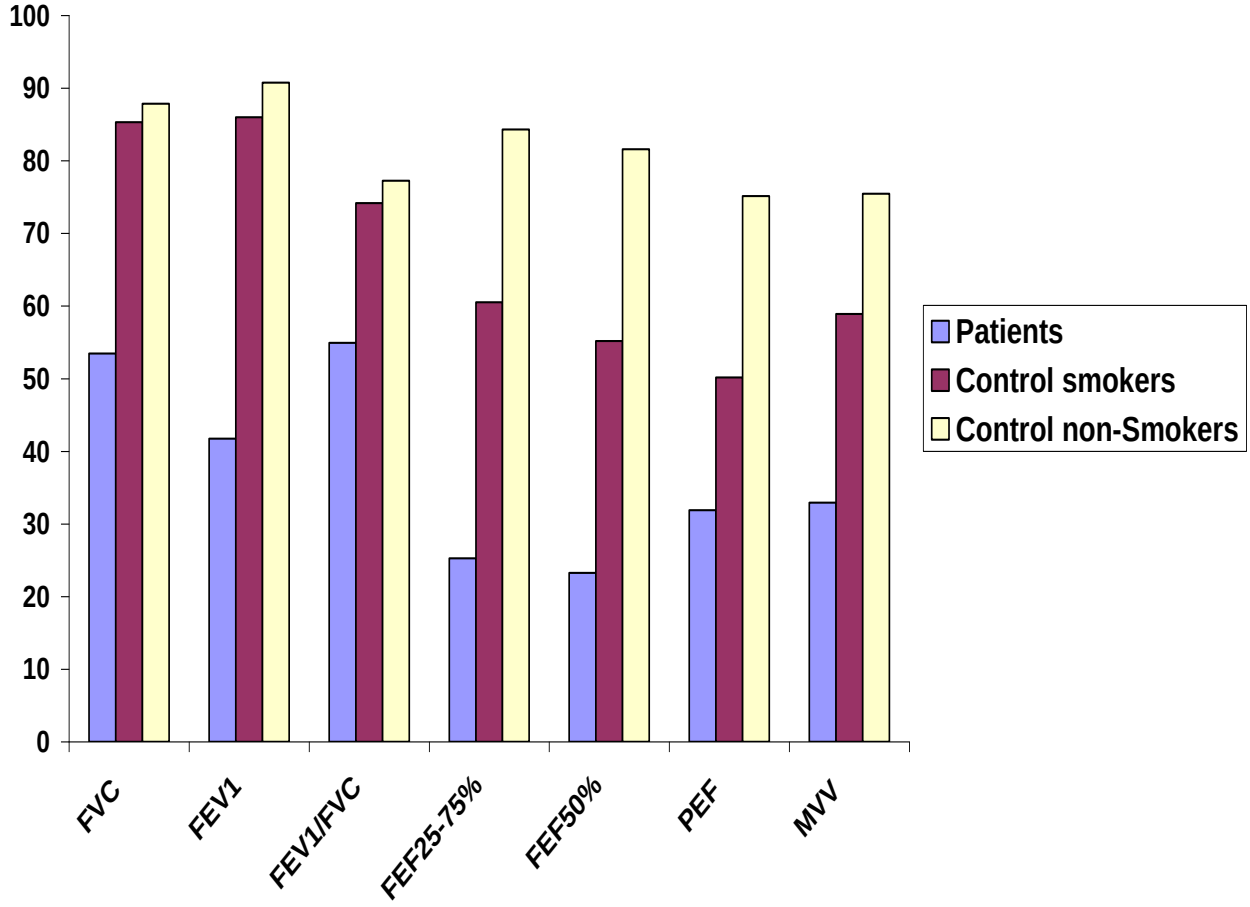


Table (9): Classification of COPD patients according to the stage of their disease **(Gold 2009):**

Stage	No.	%
Stage II (moderate) (FEV1 :50-70 % predicted)	**10**	**25**
Stage III (severe) (FEV1 :30- 47% predicted)	**24**	**60**
Stage IV (very severe) (FEV1 : 17-29 % predicted)	**6**	**15**
Total	**40**	**100**

Fig. (7): Classification of COPD patients according to the stage of their disease **(Gold 2009):**

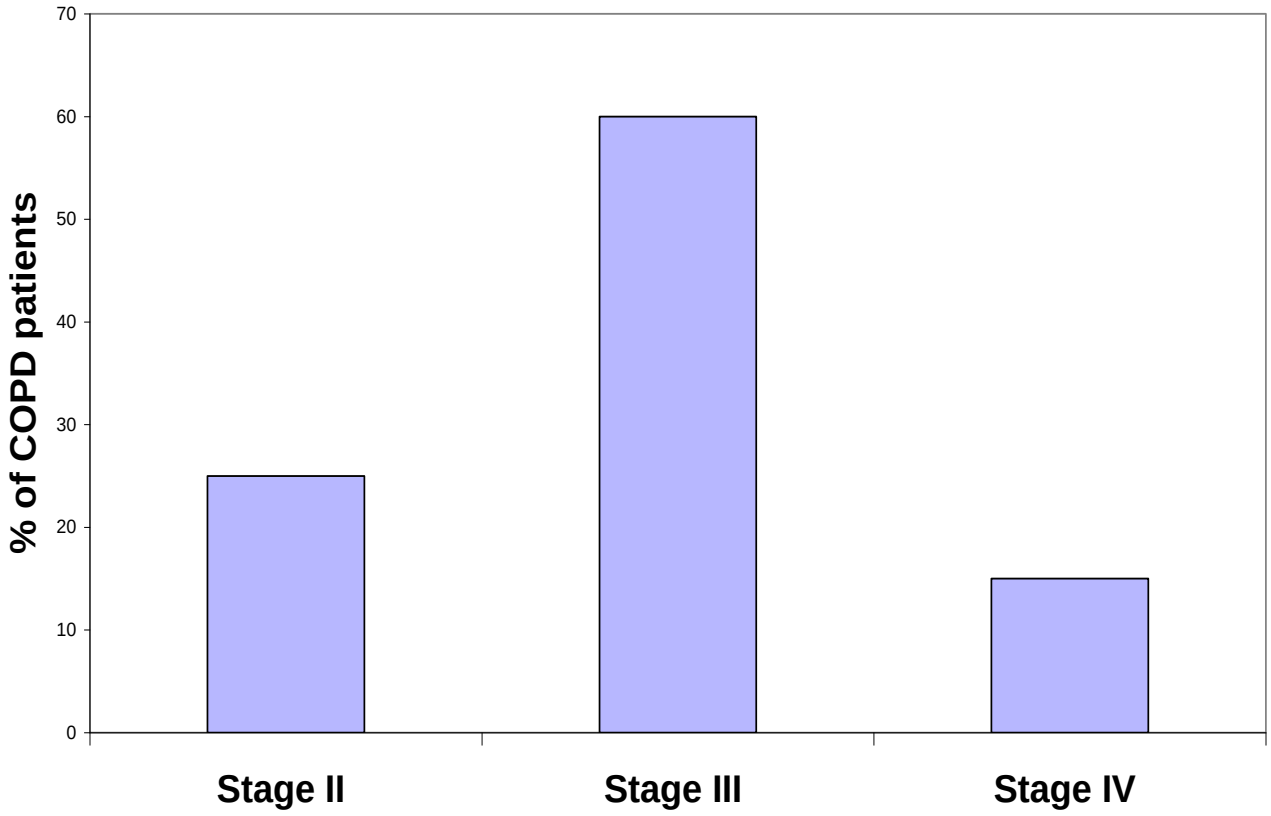


Table (10): Levels of serum CRP (mg/l) in patients and controls:

	CRP (mg/l)	
	Patients	Controls
Mean ± SD	31.09± 25.3 R: 6-96	<6

Table (11): Comparison of CRP levels (mg/l) according to the stage of the disease:

	No.	Range	Mean± S. D.	f	p
Stage 2	10	6-24	12.60± 6.603	12.7	<0.001
Stage 3	24	6-96	30.21±19.965[a,c]		
Stage 4	6	12-96	66.00±35.395[b]		
Total	40	6-96	31.09±25.596		

a = compare between stage 3 and stage 2.

b = compare between stage 4 and stage 2.

c = compare between stage 3 and stage 4.

Fig. (8): Comparison of CRP levels (mg/l) according to the stage of the disease:

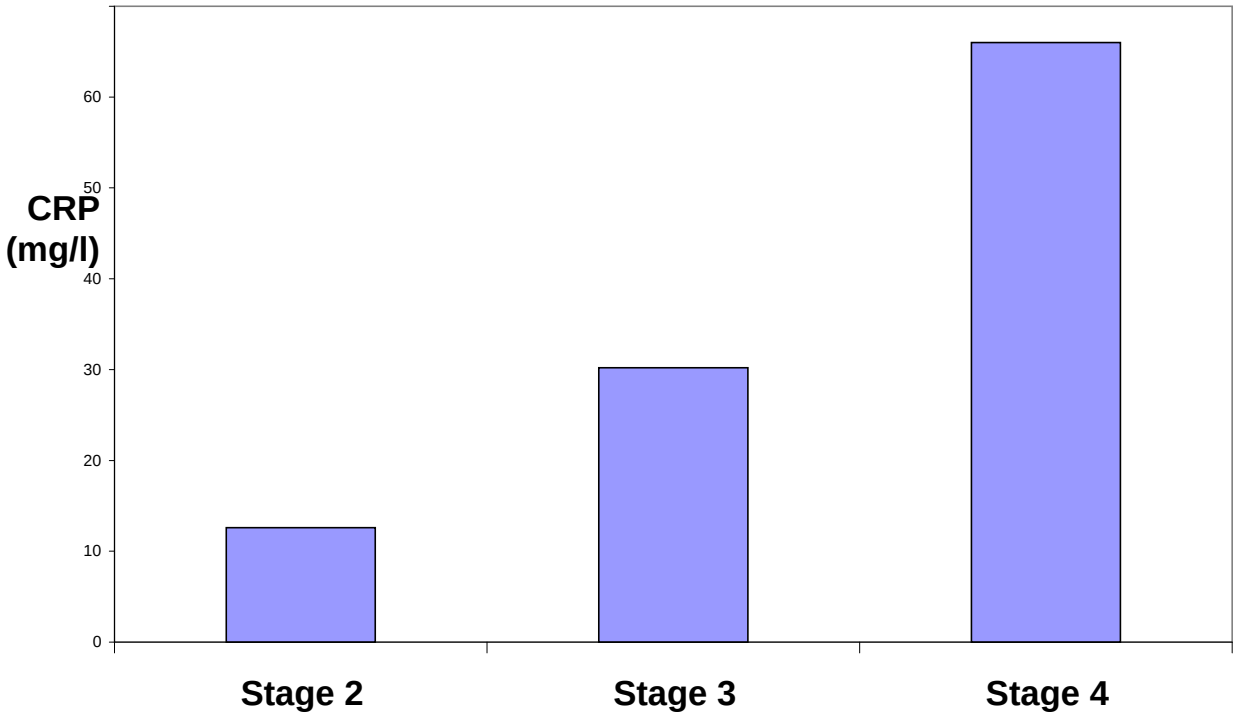
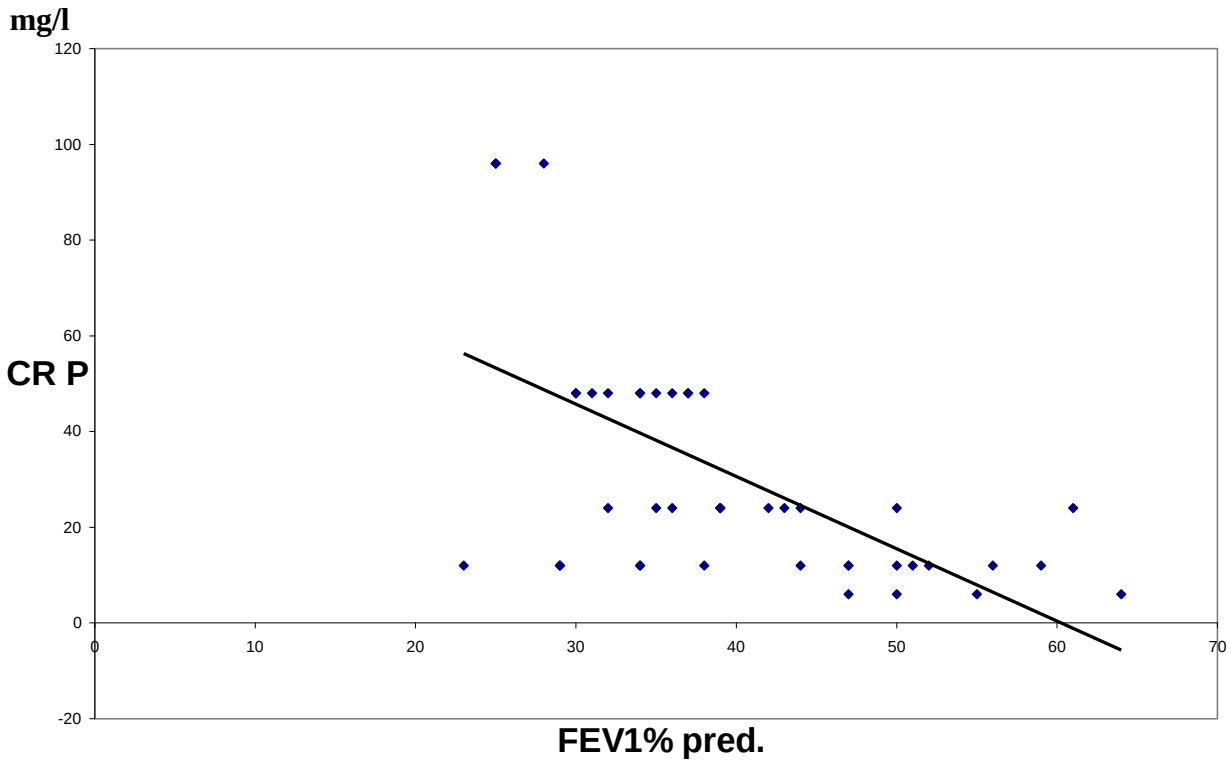


Table (12) Correlation between serum CRP level (mg/l) and pre-bronchodilator FEV1 (% pred.) of COPD cases:

	r	P
Pre FEV1%	-0.61	<0.001

Fig. (9): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEV1 (% pred.) of COPD cases:



Table(13) Correlation between serum CRP level (mg/l) and pre-bronchodilator FVC (% pred.) of COPD cases:

	r	P
PRE FVC%	-0.38	<0.05

Fig. (10): Correlation between serum CRP level (mg/l) and pre-bronchodilator FVC (% pred.) of COPD cases:

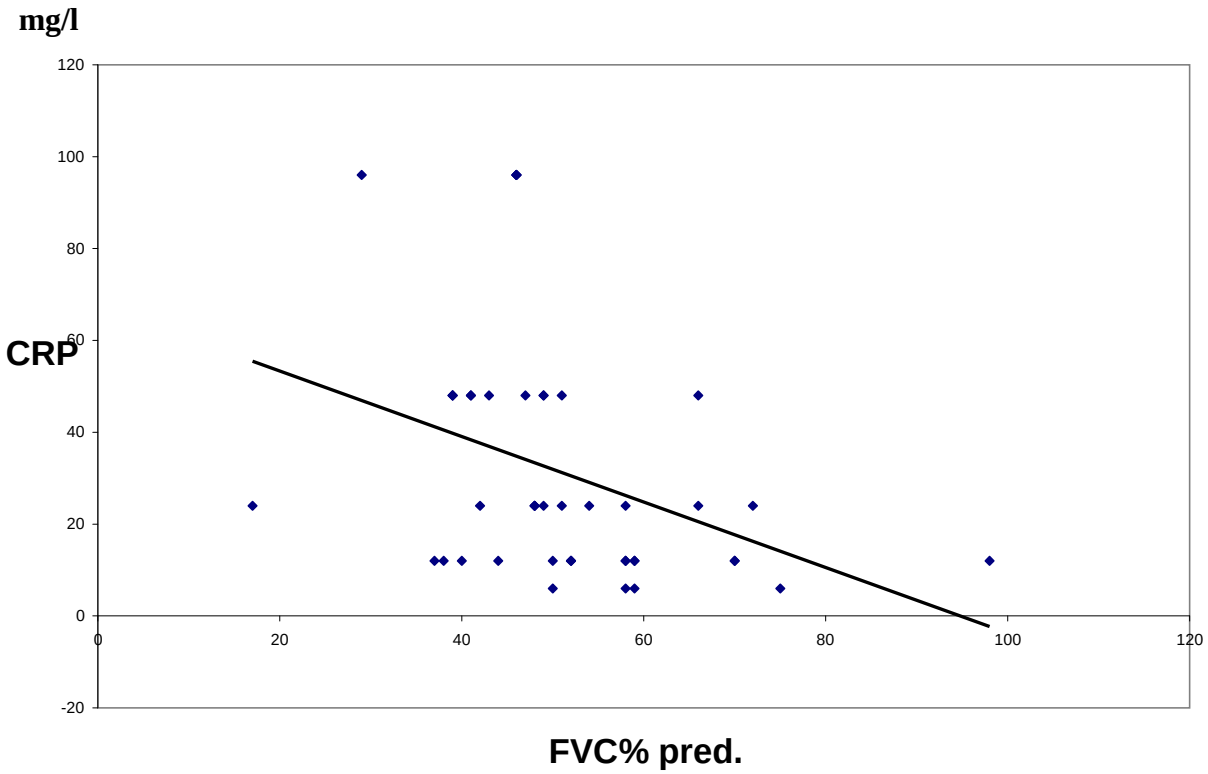


Table (14): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEV1/FVC%. of COPD cases:

	r	P
PreFEV1/FVC	-0.43	<0.05

Fig.(11): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEV1/FVC%. of COPD cases:

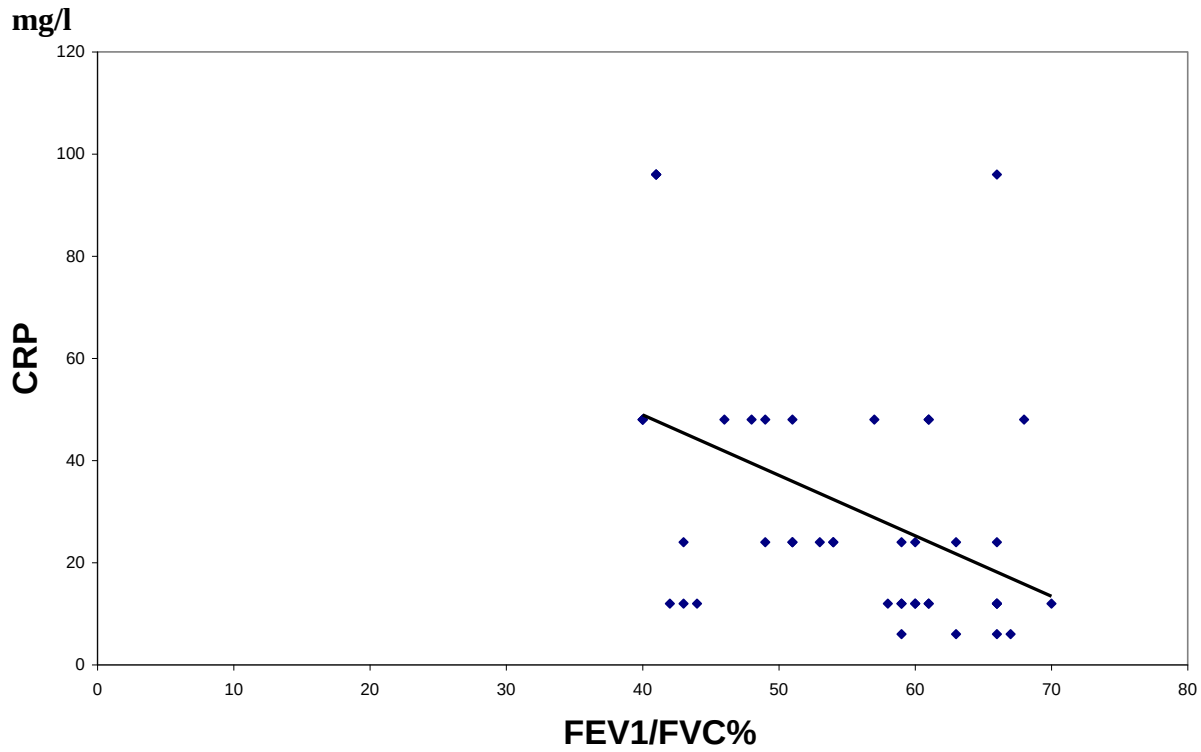


Table (15): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEF25-75% (% pred.) of COPD cases:

	r	P
PreFEF25-75%	-0.35	<0.05

Fig.(12): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEF25-75% (% pred.) of COPD cases:

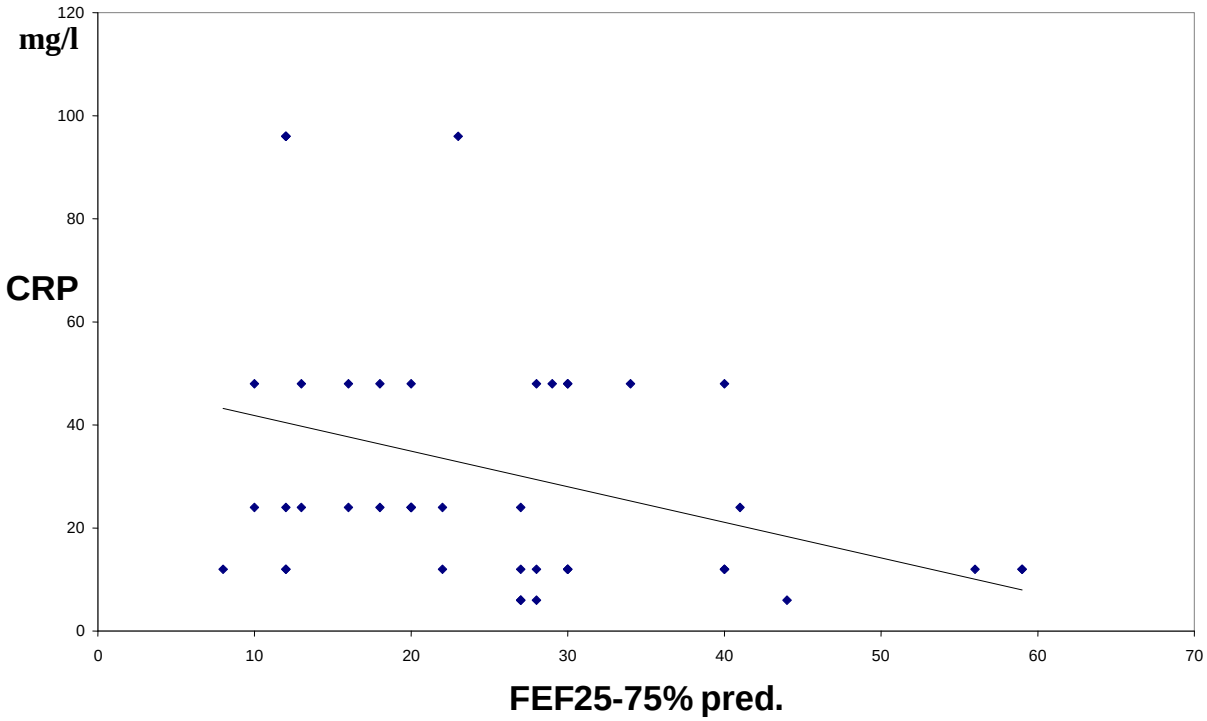


Table (16): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEF50% (% pred.) of COPD cases:

	r	P
Pre FEF 50%	-0.34	<0.05

Fig. (13): Correlation between serum CRP level (mg/l) and pre bronchodilator FEF50% (% pred.) of COPD cases:

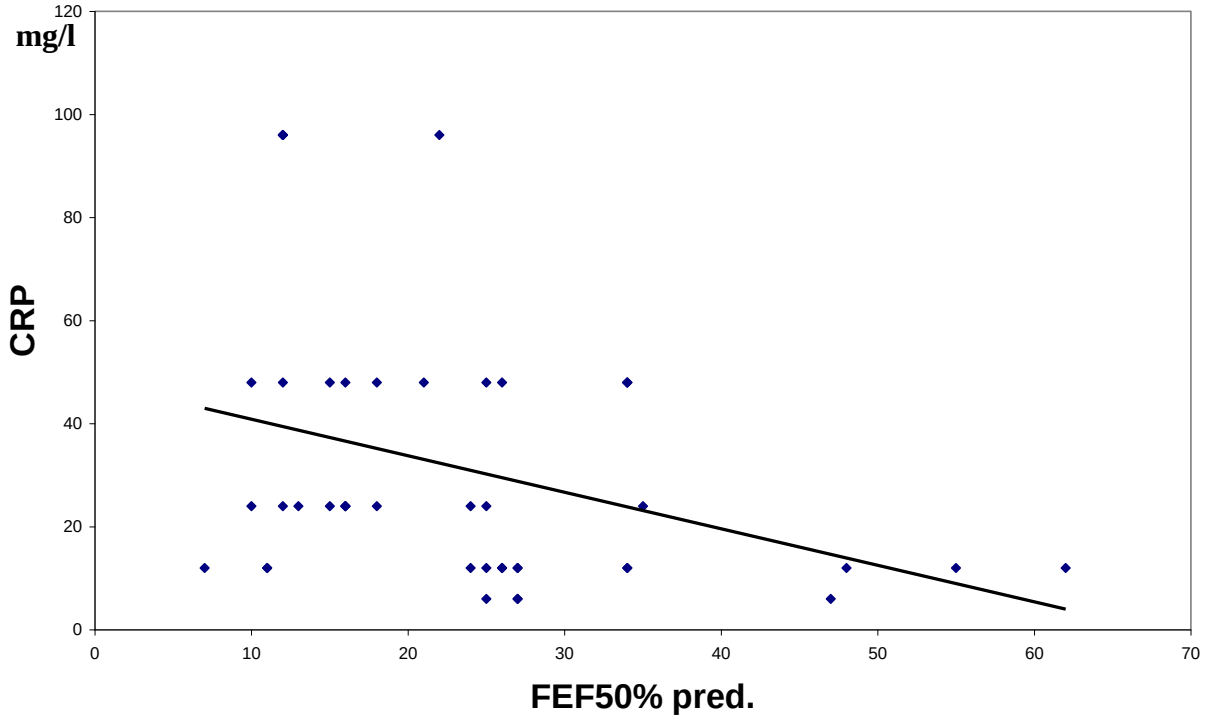


Table (17):Correlation between serum CRP level (mg/l) and pre-bronchodilator PEF (% pred.) of COPD cases:

	r	P
Pre PEF	-0.46	<0.05

Fig.(14): Correlation between serum CRP level (mg/l) and pre-bronchodilator PEF (% pred.) of COPD cases:

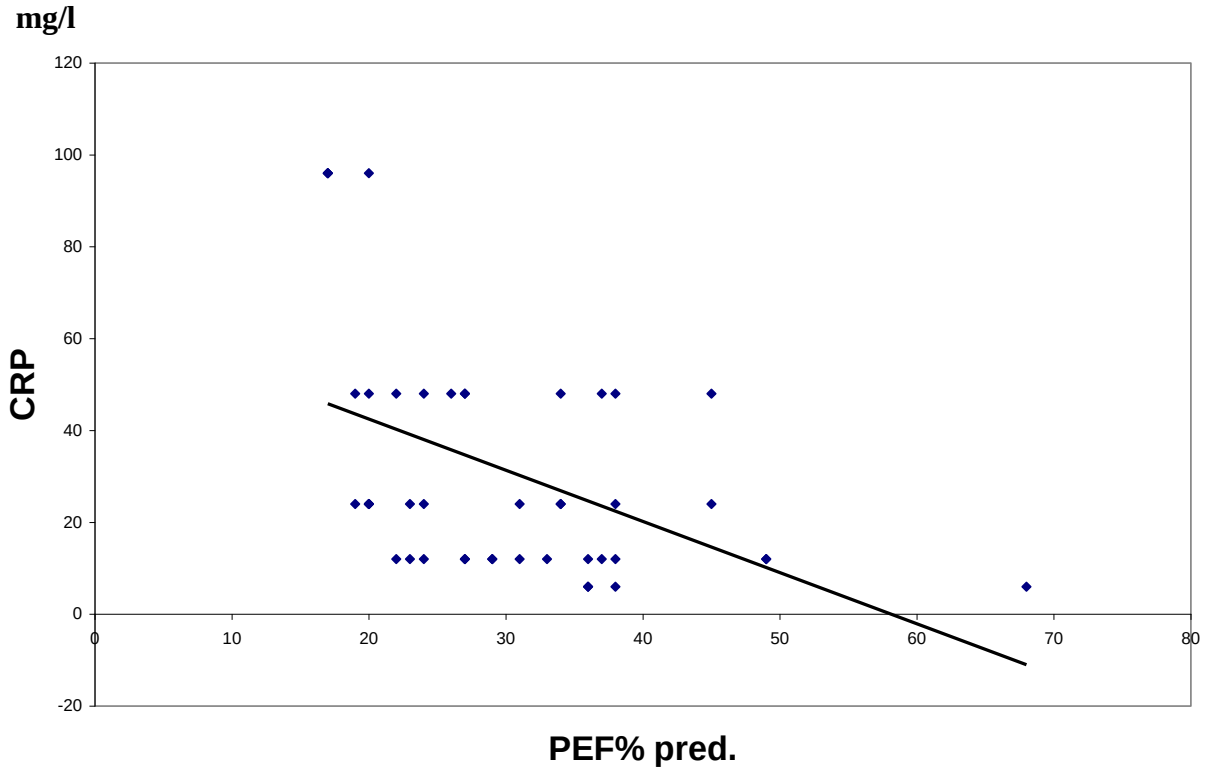


Table (18): Correlation between serum CRP level (mg/l) and pre-bronchodilator MVV (% pred.) of COPD cases:

	r	P
Pre MVV	-0.23	>0.05

Fig.(15): Correlation between serum CRP level (mg/l) and pre-bronchodilator MVV (% pred.) of COPD cases:

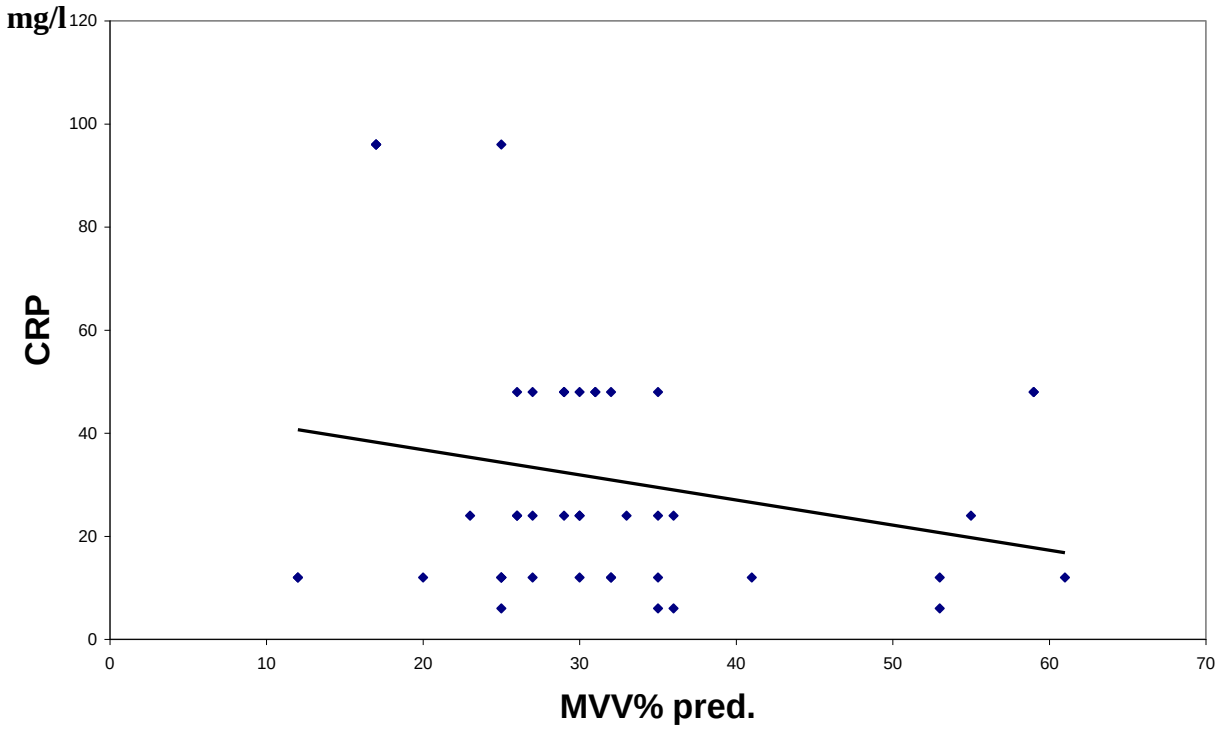


Table (19): correlation between serum CRP level (mg/l) and smoking index among COPD patients:

	r	P
Smoking Index	0.48	<0.05

Fig. (16): correlation between serum CRP level (mg/l) and Smoking Index among COPD patients:

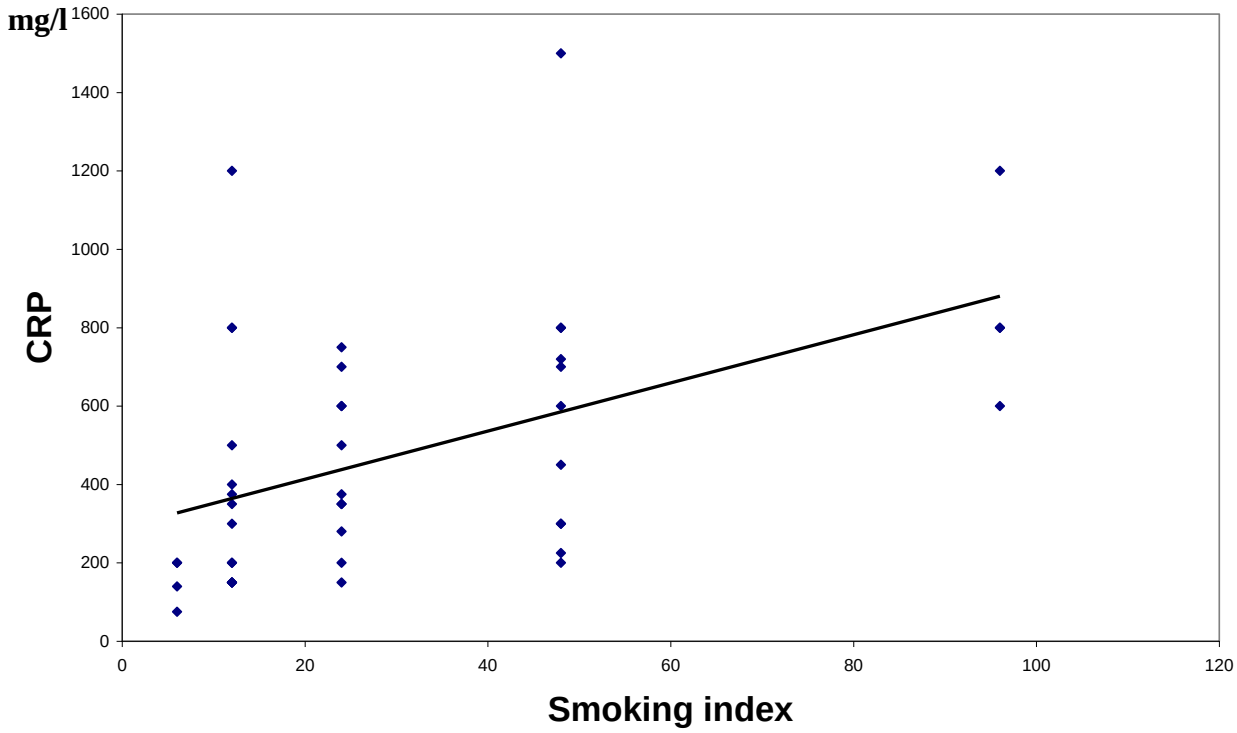


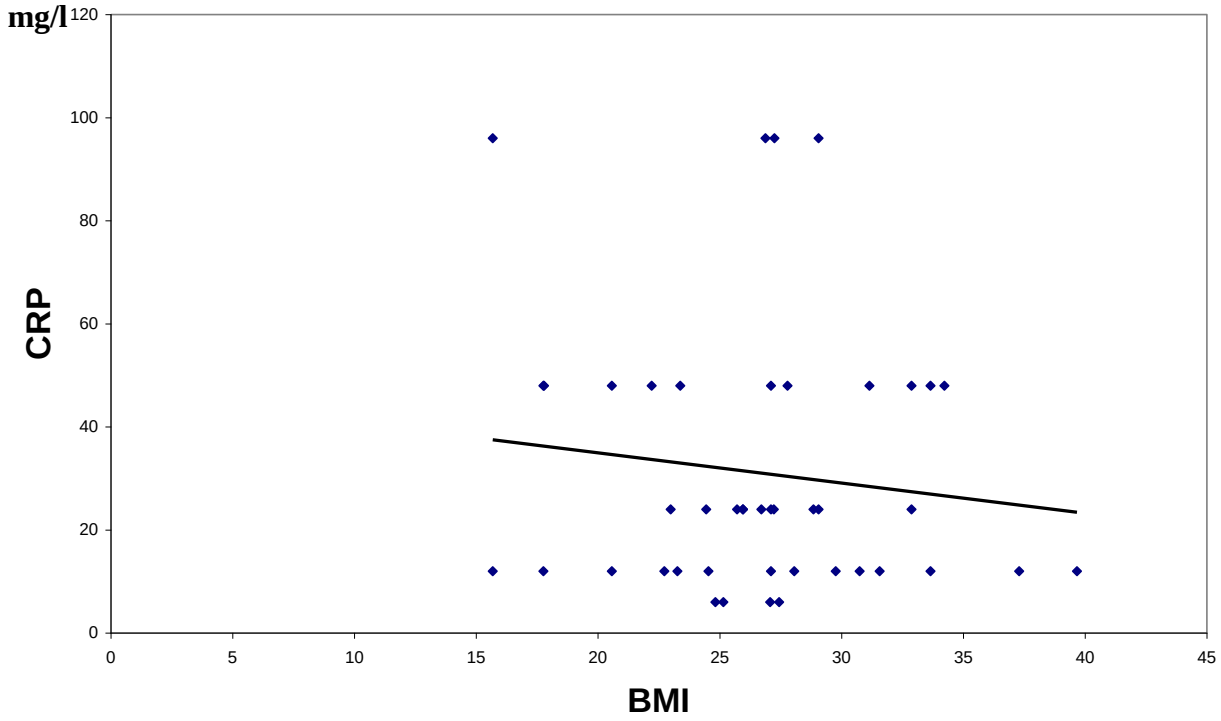
Table (20): Comparison in control groups as regarding smoking index and serum CRP level (mg/l):

	Control smokers	Control non-Smokers
Number	20	20
CRP	-ve (<6)	-ve (<6)
Smoking Index	391.5±287.95 R:50-1000	0

Table (21): correlation between serum CRP level (mg/l) and BMI of COPD patients:

	r	p
BMI	-0.12	<0.05

Fig.(17): correlation between serum CRP level (mg/l) and BMI of COPD patients:



Discussion

COPD is considered as multi component disease, including weight loss, nutritional abnormalities, skeletal muscle dysfunction, risk for myocardial infarction, angina, osteoporosis, bone fractures, depression and sleep disorders **(Van Weel and Schellevis, 2006).**

Several systemic inflammatory mediators such as tumour necrosis factor α (TNF-α), interleukins (ILs), acute phase proteins (C-reactive protein, fibrinogen, lipopolysaccharide binding protein (LBP)) and leucocytes are increased in COPD **(Gan et al., 2004).**

CRP is an acute phase protein synthesized mainly in the liver in response to tissue inflammation. Nonhepatic production of CRP by monocytes and lymphocytes has been demonstrated in the inflammed lung **(Anderson, 2006).**

The biomarker that provides the most significant correlation with COPD disease severity is C-reactive protein (CRP). Levels of CRP in the blood correlate well with future risk of morbidity and mortality in COPD **(Kim et al., 2008)**

To measure the level of CRP in COPD patients and determine its relationship to factors known to predict outcome in COPD, the present study was conducted in the chest department of Benha University Hospital. 80 subjects were included in this study, 40 patients known to

have COPD and 40 apparently healthy control subjects, 20 smokers and 20 non smokers.

The demographic data of the studied subjects included in this study are illustrated in **table (4)**. The mean age of COPD patients was 58.04±9.59 years, the mean weight was 77.53±14.44 Kg, the mean height was 171.04±7.86 cm and the mean BMI was 26.63±5.27. There was significant difference between control non smokers and COPD cases as regards age and significant difference between control smokers and control non smokers group as regard BMI.

There was non significant difference between COPD patients and controls smokers as regards the smoking index ($p > 0.05$) **(Table 5).**

In this study pre and post bronchodilator spirometry was done among 40 patients known to have COPD and showed partial reversibility in the FEV1% pred. (less than 12%) confirming the diagnosis of COPD cases **(Table 6 and Fig. 4)**.

In the current study pre and post bronchodilator spirometry was done for both patients and controls, there were significant difference in spirometric data between patients and controls ($p < 0.01$) ensuring that controls have normal pulmonary functions **(Tables 7, 8 and Fig.5, 6)**.

Based on the results of post bronchodilator spirometry 10 patients were classified as stage II (FEV1:50-70 % predicted), 24 patients as stage III **(**FEV1:30- 47% predicted) and 6 patients were classified as stage IV (FEV1: 17-29 % predicted) according to **GOLD (2009**) (**Table 9 and Fig. 7)**.

In the current study, the level of CRP was higher in COPD cases compared to normal controls (smokers and non smokers) and the difference between them was statistically significant **(Table 10).**

The increase in CRP level in COPD patients in comparison to control smokers means that CRP levels are raised in COPD patients independent of cigarette smoking denoting that the increase in CRP is secondary to systemic inflammatory processes associated with COPD as the level of CRP was normal in the control group even if they are smokers.

This result is in agreement with **Broekhuizen et al., (2005)**, who measured the level of systemic anti-inflammatory mediators (tumor necrosis factor α, interleukins, CRP, fibrinogen and lipopolysaccharide binding protein) in 102 patients with COPD and found that they were characterized by systemic inflammatory process indicated by raised CRP level.

Also this result is in agreement with **Pinto-plata et al., (2006)**, **Halvani et al., (2007)** and **Yanbaeva et al., (2009)** .

Pinto-plata et al., (2006) made a cross sectional analysis comparing cohorts of 88 patients with COPD, 35 smokers, and 38 non-smokers controls and found that CRP levels are raised in COPD patients without clinically relevant IHD and independent of cigarette smoking and that CRP is a systemic marker of the inflammatory process that occurs in patients with COPD.

Halvani et al., (2007) performed a comparative-descriptive study on 45 stable COPD patients in 2006. All understudy patients were males.

The exclusion criteria included ischemic heart disease and other causes of CRP increase. The control group consisted of 45 healthy men.

The samples were selected consecutively. Serum CRP was measured by ELISA (high sensitive).

The Results showed significant difference between serum CRP levels of COPD patients without ischemic heart disease (52.49 ng/ml) and healthy subjects (28.51 ng/ml) ($p<0.01$).Moreover, there was non significant correlation between serum CRP and cigarette smoking in COPD patients and healthy subjects.

Yanbaeva et al., (2009) performed a case-control study on 355 COPD patients and 195 healthy smokers. Plasma levels of CRP, IL-6 and fibrinogen were measured in the total study group.

They found that COPD patients had higher baseline median levels of circulating inflammatory markers. This difference was still significant after adjustment for age, sex, smoking status, BMI and pack-years smoked.

C-reactive protein (CRP) level had provided a reliable indicator of bacterial infection and some authors had reported CRP levels to be significantly elevated in patients with exacerbations of COPD and purulent sputum **(Soler, 2008)** .

This could be explained by the nature of COPD as a complex chronic inflammatory disease of the lungs involving several types of inflammatory cells and variety of inflammatory mediators. Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic repercussions **(Barnes et al., 2003).**

One of the inflammatory markers which are increasingly evaluated in COPD patients is CRP **(Yende et al., 2006).**

In our study, the level of CRP was related to the stage of the disease as there was a significant increase in CRP level with increasing the

severity of COPD; very severe COPD cases have higher level of CRP than severe and moderate cases, CRP was also raised in severe cases than moderate cases and the difference between them was highly statistically significant ($p<0.01$) **(Table 11 and Fig.8)**.

These results are in agreement with **Karadag et al., (2008), HE et al., (2010)** and **Corsonello et al., (2010).**

Karadag et al., (2008) made a study on thirty-five male patients with stable COPD and 30 age and sex-matched subjects with normal pulmonary functions. Serum CRP, Serum TNF-α and IL-6 concentrations were measured. They found that sixty percent of the patients had severe or very severe COPD and 40% moderate COPD patients. Serum CRP was significantly higher in stable COPD patients than control subjects ($p<0.001$), while TNF-α and IL-6 concentrations were not statistically different.

HE et al., (2010) performed an observational study on forty-four patients with stable COPD, 10 smoking controls and 10 non-smoking controls, induced sputum and peripheral blood samples were obtained simultaneously for measurement of inflammatory cell numbers and the concentrations of IL-6 and CRP.

They found that CRP levels in sputum were significantly higher in stage II, III and IV COPD patients than in smoking and non-smoking controls ($P < 0.01$) and as the disease stage progressed, airway inflammatory cells and IL-6 levels increased. Circulatory concentrations of IL-6 and CRP in stages III and IV COPD patients were significantly higher than in smoking and non-smoking controls ($P < 0.05$ and $P < 0.01$, respectively). Additionally, there were positive correlations between sputum and blood IL-6 and CRP levels ($r = 0.566$, $P < 0.01$ and $r = 0.443$, $P < 0.01$, respectively).

Corsonello et al., (2010) made an observational study on 223 consecutive outpatients aged 65 years or more with stable COPD. Patients were grouped according to normal/increased ESR/CRP values. They found that CRP was inversely correlated with the forced expiratory volume in the first second (FEV1%) and concluded that CRP, but not ESR, shows correlation with COPD severity.

This could be explained by the observation that CRP is one of the useful predictors for irreversible airway obstruction due to some kind of systemic inflammation and that CRP elevation in COPD followed a pattern of association with disease severity and morbidity **(Sin and Man, 2003).**

In the current work there was highly significant negative correlation between CRP level and FEV1% predicted in which CRP level is increased with decrease of FEV1% in COPD patients **(Table 12 and Fig. 9)**.

Our result is in agreement with **Mannio et al., (2003)** who examined the prevalence of increased CRP in COPD patients in the national health nutrition examination survey III. It was found that 41% of moderate COPD patients (FEV1 >50-80% predicted) had CRP level >3mg/l and 6% had level of >10mg/l, where as 52% of patients with severe COPD (FEV1 <50% predicted) had CRP level >3mg/l and 23% had level >10mg/l.

This result is also in agreement with **Shaabana et al., (2006)** who conducted a cross-sectional analysis based on 531 subjects (mean age at baseline: 37±7 years, 50% women and 42% non-smokers), Lung function was expressed as a percentage of predicted FEV1 and CRP was measured. They concluded that FEV1 as a % of predicted values was

negatively associated with serum CRP concentration ($P<0.02$) and in longitudinal analysis; changes in CRP levels during follow-up were associated with annual FEV1 decline.

This could be explained by the fact that subjects with lower FEV_1 may have higher exposure to tobacco smoke or to environmental insults that lead to a subtle decline in lung function and, in parallel, induce a low-grade inflammatory response **(Maestrelli et al., 2001).**

The result of the current study showed significant negative correlation between CRP level and FVC% predicted in which CRP level is increased with decrease of FVC% in COPD patients (**Table 13 and Fig. 10)**. It also showed significant negative correlation between CRP level and FEV1/FVC% in which CRP level is increased with decrease of FEV1/FVC in COPD patients **(Table 14 and Fig. 11)**.

This result is in agreement with **De Torres et al., (2006)** who studied 130 stable COPD patients with: spirometry, lung volumes, PaO2, dyspnea, 6 minute walk distance (6MWD), body mass index, free fat mass index, BODE index, health related quality of life, smoking status, the presence of cardiovascular risk factors or disease, corticosteroids use and number of exacerbations in the previous year. CRP levels were measured in these patients and in 65 control and they found that CRP levels were higher in COPD patients than in controls and negative correlation was found with the following variables: FEV1, FEV1% predicted, FVC and FVC% predicted.

This could be explained by the concept that severe and very severe cases of COPD are always associated with increased inflammatory response so that pulmonary functions are decreased and impaired , at the

same time this increased inflammatory response in severe and very severe cases lead to increased level of CRP.

The result of this study showed significant negative correlation between circulatory CRP level in blood and FEF25-75% of COPD cases **(Table 15 and Fig. 12)**. It also showed significant negative correlation between circulatory CRP level in blood and FEF50% of COPD cases **(Table 16 and Fig. 13)**.

This result is in agreement with **Verbanck et al., (2004)** who studied one hundred seventy two smokers, 47 of them were COPD patients with overt chronic obstructive pulmonary disease.
Lung function and multiple-breath washout (MBW) testing were performed. Lung function indices included FEV_1, PEF, FVC, mean forced mid-expiratory flow ($FEF_{25–75}$), forced expiratory flow after exhalation of 75% FVC (FEF_{75}), single-breath carbon monoxide transfer factor (DL_{CO}),
The results showed diminished $FEF_{25–75}$, FEF_{75} of both groups with no significant differences between healthy smokers and COPD patients.

Our results are in agreement with **Hylkema et al., (2007)** who reported that COPD is increasingly regarded as a systemic disorder and elevated CRP levels were found in ex-smokers with COPD. They also reported that Smokers with and without COPD show inflammation and fibrosis in the small airways and there is significant abnormalities in small airways function in smokers assessed by multiple-breath nitrogen washout test.

Also **Sunyer et al., (2008)** measured C-reactive protein (CRP), interleukin (IL)-6 and fibrinogen levels in peripheral blood and

spirometry was conducted at baseline in 134 post-myocardial infarction patients (2.7 years after the last MI).

Their results showed that CRP and IL-6 levels were negatively associated with forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and mean forced expiratory flow between 25 and 75% of FVC (FEF25–75%) and a stronger effect on FEF25–75% than on FVC or FEV1 was observed.

Cakmak et al., (2009) obtained blood samples for ESR, CRP, leukocyte and platelet counts from 964 smoker patients without any concomitant disease who were divided into groups as COPD and non-COPD according to spirometric values**.**

They found that ESR, CRP levels and platelet counts were significantly higher in COPD group than control group and a negative correlation was determined between these parameters and spirometric variables including FVC, FVC%, FEV1, FEV1%, FEV1/FVC, FEF 25-75 and FEF 25-75%

This could be explained by the effect of smoking which induces structural changes in small and large airways, and is considered a major factor in the development of airflow obstruction in chronic obstructive pulmonary disease **(Battaglia et al., 2007).**

Smoking is a common factor for inducing inflammatory changes in the small and large airways so affect the ventilatory functions of the lung especially the small airways and at the same time increasing the level of CRP.

The result of this study showed significant negative correlation between circulatory CRP level in blood and PEF of COPD cases **(Table 17 and Fig. 14)**.

This result is in agreement with **Hurst et al., (2006)** who assessed 36 biomarkers in 90 paired baseline and exacerbation plasma samples from 90 patients with COPD. They found that decline in PEF during exacerbation associated with increases in the concentration of systemic biomarkers especially CRP.

This was explained by (**Gompertz et al., 2001)** who stated that there is further up-regulation of systemic inflammation at the time of exacerbations and markers reported to be higher in blood during exacerbations compared with the baseline state

In the present study, there is non significant negative correlation between circulatory CRP level in the blood and MVV of COPD cases **(Table 18 and Fig. 15)**.

Pittaa et al., (2008) disagreed with the current study as they studied forty patients with COPD who performed spirometry and assessment of the physical activity level in daily life.

The results showed that MVV was significantly correlated to total energy expenditure and that MVV better reflects the physical activity level in daily life than FEV1 and IC in COPD patients.

The non significant result of this study may be due to different characteristics of our patients as regards weight, height and BMI.

Koechlin et al., (2004) found an inverse relationship between baseline CRP levels and muscle endurance in the COPD patients.

van Helvoort et al., (2005) concluded that COPD patients are exposed to systemic inflammation that is intensified by exhaustive exercise.

This could be explained by that systemic inflammation exists in stable COPD and that the intensity of the inflammatory process relates to the severity of the underlying disease .The systemic inflammatory process has been linked with adverse cardiovascular outcomes. Therefore, systemic inflammation in COPD is a risk factor for peripheral muscle weakness, diminished workload, and reduced exercise tolerance**. (Sin and Man, 2006)**

The result of this study showed significant positive correlation between smoking index and serum CRP level ($p<0.05$) **(Table 19 and Fig. 16)**.

The level of circulating CRP among control group, including smokers and non smokers, was less than 6 mg/l **(Table 20)**.

This result is in agreement with **Gan et al., (2004)** who noticed the importance of CRP level in COPD patients and demonstrated that CRP is elevated in patients who actively smoked and had reduced lung function.

Also in agreement with this study **Gan et al., (2005)** carried cross sectional survey on 7685 participant aged more than 40 years, to determine the independent contributors of active cigarette smoking and reduced FEV1 as well as their potential interaction on systemic inflammation. The participants were stratified into 4 equal groups based on FEV1 %, each group is further categorized as active smoker or non smoker according to serum nicotine level. Serum level of CRP was

compared across predicted FEV1%. They found that there is an additive effect of active smoking and reduced FEV1 on CRP level.

Tanni et al., (2010) performed a cross-sectional analysis comparing 53 COPD ex-smokers, 24 COPD current smokers, 24 current smokers controls and 34 never-smoker controls. Assessments included medical history, body composition, spirometry, and plasma concentration of tumor necrosis factor-alpha (TNF-α), interleukins (IL)-6, IL-8, and C-reactive protein (CRP).

They found that IL-6 and CRP were significantly higher in COPD patients when compared to smoker and never-smoker controls and the multiple regression analysis confirmed the association of these mediators with disease, but not with smoking status ($p < 0.001$).

This could be explained by the fact that cigarette smoking has a role in initiation of inflammatory process in COPD patients but it is not the leading cause of increased inflammatory markers and it should be noticed that not all cases develop inflammatory reaction following cigarette smoking and only some of them will show. This reaction can be due to genetic differences **(Pinto-Plata et al., 2006)**

In this study, there was significant negative correlation between CRP level in blood and BMI in which CRP level is increased with decrease of BMI in COPD patients **(Table 21 and Fig. 17)**.

This results is in agreement with **Schols et al., (1996)** who observed high CRP level in a special subset of 16 COPD patients with high resting energy expenditure and low fat free mass (FFM)

It agreed also with **Sarioglu et al., (2007)** who investigated the relationship between BODE index, quality of life, CRP, TNF-α, and IL-8. In their study 88 males, 15 females (103 stable COPD) were evaluated by pulmonary function tests, arterial blood gas analysis, body mass index, dyspnea scale and serum levels of CRP, TNF-α, IL-8. There was a significant relationship between BODE index and COPD stage ($p<0.01$); duration ($p<0.013$); number of exacerbations ($p<0.01$) and annual hospitalization rates ($p<0.01$).A negatively significant relationship was observed between BODE and PO2 ($p<0.01$)while there was a positively significant relationship with PCO2 ($p<0.01$).CRP was also negatively correlated with BODE($p=0.019$) as BODE index has a strong correlation with various COPD follow-up and systemic inflammation.

Hallin et al., (2010) studied forty nine patients with moderate to severe COPD. Spirometry was preformed, physical capacity was determined by a progressive symptom limited cycle ergometer test, 12-minutes walk distance and hand grip strength test. Nutritional status was investigated by anthropometric measurements, (weight, height, arm and leg circumferences and skin fold thickness) and bioelectrical impedance assessment was performed. Blood samples were analyzed for C-reactive protein (CRP) and fibrinogen.

They found that working capacity was positively related to forced expiratory volume in 1 s (FEV1) ($p < 0.001$), body mass index and fat free mass index ($p = 0.01$) and negatively related to CRP ($p = 0.02$)

In contrary, this result disagreed with **De Torres et al., (2006)** who showed that BMI correlates directly with CRP. Also in disagreement with **Eagan et al., (2010)** who found that COPD patients with low FFMI

(Fat free mass index) had lower not higher plasma levels of CRP and TNF-R1, whereas higher fat mass was associated with higher CRP and TNF-R1.

This may reflect the fact that adipocytes are the source of a substantial portion of base line IL-6 production **(Yudkin et al., 1999)** which principally induce the production of CRP **(Broekhuizen et al., 2006).**

SUMMARY

Chronic Obstructive Pulmonary Disease **(COPD)** is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases.

CRP is a member of an ancient family of molecules called pentraxins. It was discovered in human in 1930 as serum component that binds the C- polysaccharide of streptococcus pneumonae and composed of five identical subunits which are linked non covalently to form a disk like pentagonal ring.

Although COPD primarily involves the lung, the chronic inflammatory process causes systemic manifestations. One of the inflammatory markers which are increasingly evaluated in COPD patients is CRP**.**

The present study was conducted in the chest department in Benha University Hospital in the period between March 2009 and March 2010.

The aim of this work was to study the usefulness of serum CRP as a systemic inflammatory marker for COPD patients and to evaluate IHD and smoking as potential causes of raised CRP levels in COPD.

Eighty subjects were included in this study,40 male patients with COPD and 40 healthy control subjects of the same age and sex, 20 subjects with history of smoking and 20 non-smokers with no history of ischemic heart diseases and with normal ventilatory function tests.

COPD patients were stable with no exacerbation.

All subjects were submitted to:

1. Full history taking, including smoking history.
2. Full clinical examination.
3. Plain x-ray chest (postero-anterior and left lateral views).
4. Spirometry pre and post bronchodilator.
5. Electrocardiography.
6. Measurement of serum CRP by Latex agglutination test.

Exclusion criteria included:

1- Ischemic heart diseases(myocardial infarction or angina).

2- Tuberculosis.

3- Congestive heart failure.

4- Malignancy.

5-Hepatic cirrhosis.

6-End- stage renal disease.

7-Rheumatoid arthritis.

8-Diabetes Mellitus.

9-Any systemic infection or inflammation that could be associated with increased CRP values.

Results were tabulated and statistically analyzed:

It was found that CRP level was higher in COPD patients compared to control group.

There was negative correlation between CRP and FEV1%, FVC% and FEV1/FVC.

Also CRP showed negative correlation between with $FEF_{50\%,}$ $FEF_{25-75\%}$, MVV and PEF.

CRP showed a negative correlation with BMI.

CRP showed highly significant positive correlation with smoking index.

CONCLUSIONS

From this study, we concluded that:

1. CRP levels are raised in COPD patients without clinically relevant IHD and independent of cigarette smoking.
2. Increase in CRP levels was associated with a steeper FEV1 decline and impaired other pulmonary functions parameters.
3. Low BMI is associated with the degree of severity of COPD and systemic inflammation reflected by elevated CRP level.

RECOMMENDATIONS

From this study, it is recommended that:

- CRP may be used as a systemic marker of the inflammatory process that occurs in patients with COPD.
- CRP level may be used to assess the severity of the disease and response to treatment.
- CRP level may be used as a predictor for the development of exacerbation in COPD.
- Further studies should be performed on wide scale in stable COPD patients to assess CRP level in such patients.
- Subsequent studies are needed to assess the level of CRP in other inflammatory airway diseases as bronchial asthma.
- Subsequent studies are needed to assess the level of CRP level in sputum as a marker of exacerbation in COPD.

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