Chronic Obstructive Pulmonary Disease (COPD)☆

JM Antonini, National Institute for Occupational Safety and Health, Morgantown, WV, USA

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health issue. It is one of the most common causes of morbidity and mortality in the world, and is increasing in prevalence. COPD combines two lung diseases, emphysema and chronic bronchitis (American Lung Association, 2014). Both lung conditions exist together and cause obstruction of airflow that interferes with normal breathing. COPD is characterized by a slow, progressive airflow limitation that is mostly irreversible. Chronic inflammation, most often caused by cigarette smoking, leads to fixed narrowing of the small airways and alveolar wall destruction and remodeling. Although COPD lung damage is irreversible, there are treatments that can improve a patient's quality of life. Pharmacologic and non-pharmacologic therapy can improve respiratory symptoms and exercise capacity, and through their effects on reducing exacerbations of COPD, have the potential to modify disease progression (McDonald and Khor, 2013). Bronchodilators are the mainstay of pharmacotherapy, whereas smoking cessation is paramount in managing COPD with increased physical activity and pulmonary rehabilitation.

Definition

COPD has been defined by the Global Initiative on Obstructive Lung Disease (GOLD) as a disease state characterized by airflow limitation that is not fully reversible (Pauwels et al., 2001). The limitation in airflow is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.

Classification

COPD is classified as a chronic inflammatory lung disease. Most patients with COPD present with three pathological characteristics: (a) chronic obstructive bronchitis, (b) emphysema, and (c) mucus plugging (Barnes, 2002).

Consequences

Chronic obstruction of the small airways associated with COPD can lead to a significant reduction in lung function and gas exchange. This may lead to oxygen deprivation in cells and tissues throughout the body. Death may result from severe cases of COPD.

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Associated Disorders

COPD includes (a) chronic bronchitis with fibrosis and obstruction of small airways and (b) emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways (Barnes, 2003). Emphysema is defined as a chronic pulmonary disease characterized by increase in beyond the normal size of air spaces distal to the terminal bronchiole with destructive changes in their walls. Chronic bronchitis is defined by a productive cough of more than three months duration for more than two successive years caused by mucus hypersecretion. However, unlike COPD, chronic bronchitis is not usually associated with airflow limitation. COPD differs from asthma in that airflow limitation is mostly irreversible, whereas the airflow obstruction associated with asthma is usually reversible in early stages, either spontaneously or with treatment.

The airflow obstruction caused by COPD may have systemic consequences due to an adverse effect on cardiac function and gas exchange (Barnes and Celli, 2009). In addition, the 'spill-over' of inflammatory mediators from the pulmonary inflammation observed with COPD may result in systemic manifestations of disease, such as skeletal wasting and cachexia. Systemic inflammation also may initiate or worsen cormorbid diseases, such as heart failure, ischemic heart disease, hypertension, hyperlipidemia, lung cancer, osteoporosis, diabetes, anxiety, and depression (Barnes and Celli, 2009; McDonald and Khor, 2013).

Etiology

Long-term cigarette smoking is the most important risk factor for COPD. Smoking accounts for 85–90% of all cases (American Lung Association, 2014). Although it's been suggested that only a small percentage of smokers (10–20%) develop COPD (Weiss et al., 2003), studies indicate some degree of airflow obstruction is present in approximately 50% of smokers, with clinically significant COPD being present in 25% (Lundback et al., 2003). This variable response to cigarette smoking clearly suggests genetic susceptibility. The genetic factor, α1-antitrypsin, is deficient in 1–2% of individuals with COPD (McDonald and Khor, 2013). Other environmental factors may include air pollution, second hand smoke, occupational chemicals and dusts, a history of childhood respiratory infections, socioeconomic status, and exposure to biomass smoke for heating and cooking in developing countries (Hnizdo et al., 2002).

Epidemiology

COPD is a major cause of morbidity and disability and a leading cause of death worldwide, having a prevalence of 9–10% in adults over 40 years of age (Halbert et al., 2006). COPD is projected to increase as the population ages and smoking frequencies rise. By 2020, COPD is predicted to have become the third-leading cause of death worldwide, with 90% of those deaths occurring in low and middle income countries (Murray and Lopez, 1997). In 2011, 12.7 million U.S. adults were estimated to have COPD (Centers for Disease Control and Prevention, 2011). However, close to 24 million U.S. adults have evidence of impaired lung function, indicating an under diagnosis of COPD (Centers for Disease Control and Prevention, 2000).

Pathophysiology

COPD is characterized by acceleration in the normal decline of lung function that is associated with age. The pathological cellular and molecular mechanisms of COPD have been for the most part largely unknown. Evidence indicates that chronic inflammation of the small airways and lung parenchyma develops in response to inhalation exposure to cigarette smoke or other possible environmental stimuli (e.g., air pollution, occupational exposure, cooking and heating fumes) in susceptible individuals. The resulting inflammation develops into fibrosis with narrowing of the small airways (chronic obstructive bronchitis) and lung parenchymal destruction due to the action of various inflammatory cell-mediated proteases (Barnes, 2002). A variety of immune cells, including neutrophils, macrophages, and cytotoxic ($CD8^+$) T-lymphocytes, are recruited into the lungs and become activated. Increased numbers of neutrophils are found in the sputum and recovered bronchoalveolar lavage fluid (BALF) of COPD patients. Neutrophils secrete serine proteases (e.g., neutrophil elastase, cathepsin G, proteinase-3) which may contribute to alveolar destruction. A marked increase in macrophage number has been observed in the airways, lung parenchyma, BALF, and sputum of COPD patients. Macrophages may be activated by cigarette smoke to release inflammatory mediators (e.g., tumor necrosis factor-α, interleukin-8), initiating the development of cellular inflammation. Evidence suggests involvement of matrix metalloproteinases (MMPs) in COPD (Barnes, 2003). Expression of MMPs has been elevated in the BALF, and macrophages of COPD patients are likely involved in the destruction of exposed lung tissue. In addition, increased oxidative stress has been implicated as a possible mechanism by which the lungs become damaged in COPD. Cigarette smoke, as well as activated neutrophils and macrophages, expose lung cells and tissues to high concentrations of damaging reactive oxygen species.

Signs and Symptoms

Spirometry is needed for a diagnosis of COPD. A clinical examination and medical history may suggest a COPD diagnosis, but alone they are unreliable predictors of airflow obstruction. In the presence of symptoms, such as shortness of breath, cough, sputum production, and a history of cigarette smoking or other relevant exposures, a patient with a forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) of less than 70% of predicted normal lung function (an indication of irreversible airflow limitation) is considered to have COPD (McDonald and Khor, 2013). The clinical development of COPD has been described in different stages by GOLD (Pauwels et al., 2001): Stage 0- At Risk: chronic respiratory symptoms, smoking, and normal spirometry; Stage 1- Mild COPD: FEV1 is >80% predicted normal lung function and FEV1/FVC is <70% with a minimal impact on health-related quality of life issues. Symptoms may progress during this stage as patients begin to experience severe breathlessness; Stage 2- Moderate COPD: FEV_1 is 30–80% predicted normal lung function and FEV1/FVC is <70% with a significant impact on health-related quality of life issues; Stage 3- Severe COPD: FEV_1 is <30% of predicted normal lung function and FEV1/FVC is <70% with a profound impact on health-related quality of life issues. Respiratory symptoms of COPD include chronic cough, chest tightness, shortness of breath, an increased effort to breathe, increased mucus production, and frequent clearing of the throat.

Standard Therapies

Even though lung damage is irreversible and there is no cure for COPD, treatments are available that can improve a patient's health-related quality of life. The goals in management of stable COPD are to alleviate the symptoms, reduce the frequency and severity of exacerbations, improve exercise tolerance, slow disease progression, and reduce morality (McDonald and Khor, 2013). Cigarette smoking cessation is the most effective, as well as cost-effective, way to lower the risk of developing COPD and slow disease progression. Inhaled bronchodilators are the mainstay of pharmacotherapy for COPD. Bronchodilators include short-acting (e.g., albuterol, levalbuterol, metaproterenol, terbutaline) and long-acting (e.g., formoterol, arformoterol, salmeterol) beta-2 adrenergic receptor agonists. Short-acting beta-2 agonists are used to treat stable COPD in patients with intermittent symptoms, whereas long-acting beta-2 agonists are effective for preventing and treating persistent symptoms of COPD. Bronchodilators improve inspiratory capacity and end-expiratory volume to relieve breathlessness and improve exercise capacity in COPD patients (McDonald and Khor, 2013). Selective long-acting muscarinic receptor antagonists (e.g., aclidinium bromide) and anticholinergic drugs (e.g., ipratropium) also have been used in the management of COPD. Beta-2 adrenergic agonist and anticholinergic combinations (e.g., Combivent, DuoNeb) have been shown to improve lung function in COPD better than using either drug class alone. Inhaled corticosteroids can reduce lung inflammation. They can be used alone or in combination with bronchodilators (e.g., Symbicort, Advair) and are recommended in patients with moderate to severe COPD to help reduce recurrent exacerbations and improve quality of life. It is important to note that inhaled corticosteroids may cause local side effects and increase the risk of pneumonia and other types of respiratory infections. Non-drug treatments such as pulmonary rehabilitation, oxygen therapy, and surgery all have been shown to improve quality of life (American Lung Association, 2014). In addition, physical activity can protect against COPD development and slow its progression by actively working muscles which may help slow the decline in lung function.

Animal Models

Animal models that exactly mimic cigarette smoke-induced COPD for the development of possible treatment strategies of the disease have been disappointing. Most of the animal models have concentrated on emphysema and largely ignored small airway remodeling (Churg et al., 2011). Emphysema and small airway remodeling are independent responses of cigarette smoke-induced COPD, and small airway remodeling is an equally important cause of airflow obstruction. In addition, animal models only produce a mild form of COPD that never develops spontaneous exacerbations and progresses to the severe disease seen in humans after smoking cessation, making these models of little value in the development of potential treatments.

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Relevant Websites

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http://www.copdfoundation.org – COPD Foundation.