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OVERVIEW OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract:

Background: *Chronic Obstructive Pulmonary Disease (COPD) is a complex disease influenced by both genetic and environmental factors, leading to irreversible lung damage, systemic complications, and a significant global health burden. Effective diagnosis, management, and adherence to treatment guidelines are essential to alleviate the burden on patients and improve outcomes.*

Aim: *The present study aims to review the update on Chronic Obstructive Pulmonary Disease.*

Methods: *Comprehensive research of COPD. PUBMED and Google Scholar search engines were the databases used for the search process, and articles were collected from 2013 to 2023. The terms used in the search were COPD, risk factors, Pathophysiology, Manifestations, Diagnosis, treatment, and Exacerbation.*

Conclusion: *COPD is a prevalent and progressive lung condition characterized by irreversible airflow obstruction, inflammation, and damage to lung tissue. The main subtypes are chronic bronchitis and emphysema. COPD is influenced by both genetic and environmental factors, with cigarette smoke being a primary risk factor. It is associated with systemic inflammation and comorbidities like cardiovascular diseases, diabetes, and muscle weakness. Viral infections, particularly influenza A viruses, can trigger acute exacerbations. The pathophysiology involves oxidative stress, altered immune response, and inflammation, leading to chronic bronchitis, emphysema, and small airway disease. Diagnosis includes spirometry, pulmonary function tests, and clinical factors, with various laboratory and imaging tools aiding in confirmation. Treatment strategies encompass pulmonary rehabilitation, pharmacologic therapies (bronchodilators, corticosteroids), surgical interventions, and oxygen therapy. Vaccinations are recommended, and careful management of exacerbations involves oxygen therapy, inhaled antibiotics, and corticosteroids. Smoking cessation is crucial, and newer therapies like stem cell-based treatments show promise.*

Keywords: *COPD, risk factors, Pathophysiology, Manifestations, Diagnosis, treatment, Exacerbation.*

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INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is a common and progressive lung condition characterized by irreversible airflow obstruction, inflammation, and damage to lung tissue due to chronic bronchitis and emphysema as the most frequently occurring subtypes (1). It is also associated with systemic inflammation and comorbidities such as cardiovascular and cerebrovascular disease, lung cancer, diabetes, cachexia, muscle weakness, osteoporosis, anxiety and depression, pulmonary infections, anemia, gastroesophageal reflux disease, and pulmonary embolism (2). Moreover, it is influenced by both genetic and environmental factors [figure1](3). Genetic susceptibility plays a role in COPD development, with genes such as FAM13A, AHRR, HHIP, IL19, IL4, and PPBP associated with the disease (4). Environmental factors, particularly cigarette smoke and second-hand smoke, are the most common risk factors for it and account for approximately 50% of COPD deaths (4); however, not all COPD patients have a history of smoking, indicating that other factors, including genetic susceptibility, contribute to the disease (5). Other environmental factors like air pollution and occupational exposure, such as gases, vapors, dust, and fumes, are important risk factors for COPD. In particular, a study revealed that ambient air pollution and household particulate matter contribute to 20% and 10% of deaths, respectively. On top of that, many studies have shown that individuals exposed to occupational hazards have a higher prevalence of respiratory symptoms, severity of airflow restriction, and clinical symptoms of COPD (6-8). Overall, The interaction between genetic susceptibility and environmental exposures, such as smoking, further increases the risk of COPD (4, 5). In addition, Viral infections, particularly influenza A viruses, can also trigger acute exacerbations of COPD (9). Over and above that, risk factors for re-hospitalization due to worsening of symptoms include being male, age over 70 years, smoking experience over 40 years, COPD duration over 10 years, and the presence of three or more comorbid pathologies (10). Additionally, factors such as recurrent admissions, non-invasive ventilation during admission, and long-term oxygen therapy are associated with readmission or mortality in COPD patients.

The disease is associated with chronic inflammation, corticosteroid resistance, and accelerated lung aging. Besides, It is a major cause of morbidity and mortality worldwide, leading to significant healthcare utilization and cost. It is often underdiagnosed and undertreated, resulting in a high burden on patients and their families. Better evaluation, diagnosis, and management of chronic symptoms are needed to reduce the burden of COPD (1).

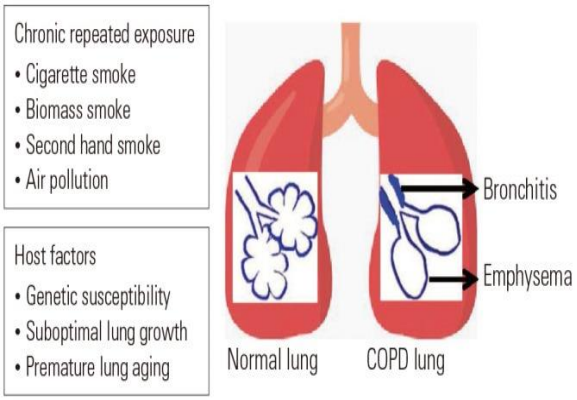


Figure [1]: Causes and risk factors for COPD.

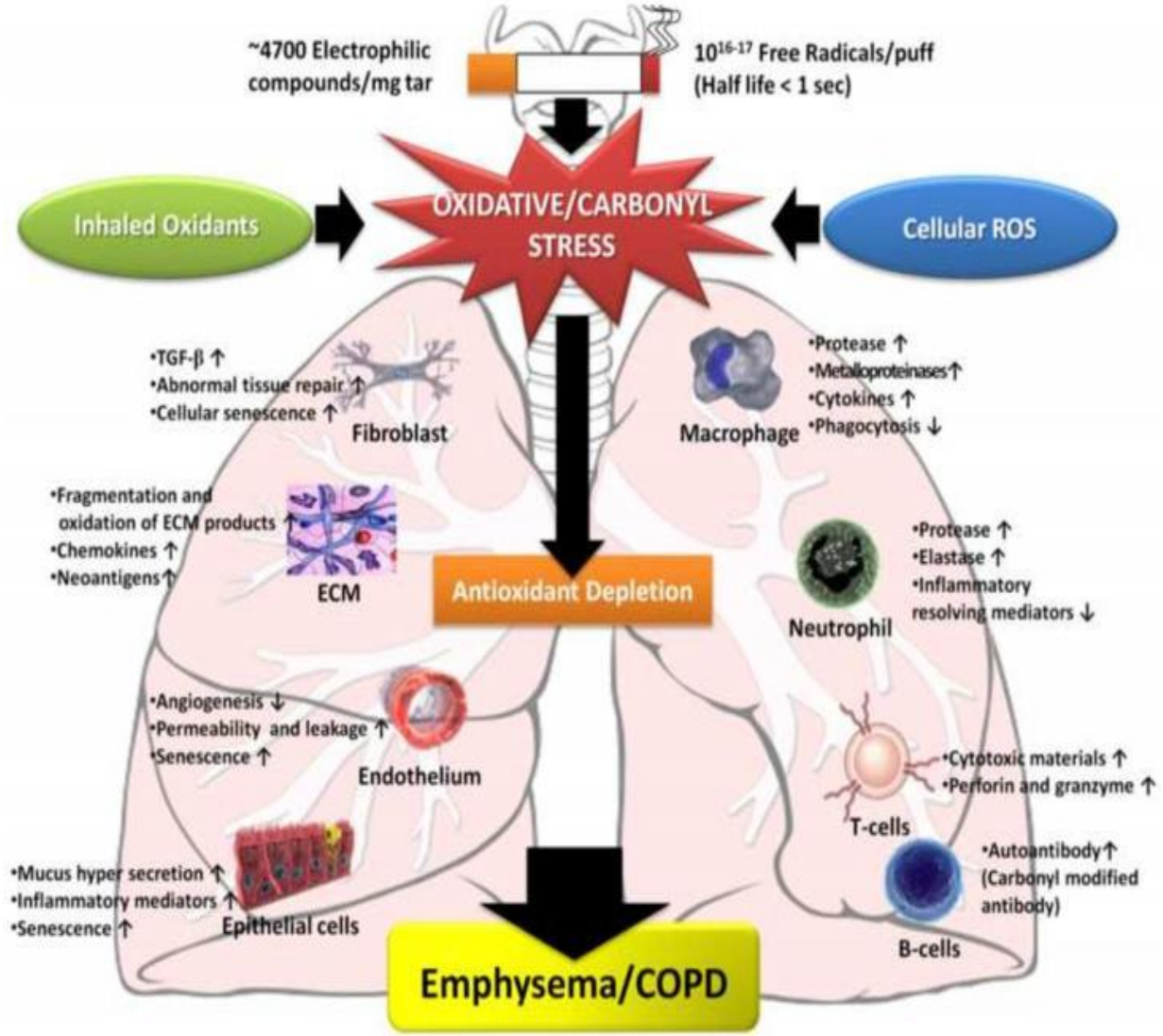
Pathophysiology

COPD is a complex and heterogeneous disease with a diverse underlying lung pathology involving chronic bronchitis, emphysema, and small airway disease due to oxidative stress, altered immune response, and inflammation, each with distinct anatomical, pathological, and clinical characteristics that cause permanent damage and irreversible (11). COPD patients exhibit elevated levels of oxidative stress in their peripheral blood leukocytes and increased plasma levels of malondialdehyde (MDA), which are associated with impaired cardiac autonomic control and inversely correlated with pulmonary function(12). The lungs of COPD patients are exposed to both exogenous and endogenous oxidative stress [Figure 2], which leads to chronic inflammation, cellular senescence, impaired DNA repair, and increased mucus secretion. On the other hand, different clinical and functional phenotypes of COPD exhibit distinct immune response patterns. In the bronchitic phenotype, the inflammatory process is activated with the differentiation of naive T lymphocytes along the Th1-dependent pathway. In contrast, the immune response develops along the Th17 pathway in the emphysematous phenotype. The Th1 pathway predominates in the early stages of the disease, while the Th17 pathway becomes more prevalent with increasing severity. The type of immune response is associated with the severity of the disease and the clinical and functional phenotype of COPD. There are also relationships between systemic inflammation indexes and functional parameters of external respiration. Understanding the immune response in COPD can help predict disease progression and guide phenotype-oriented therapy (13). Bacterial and viral infections play a role in worsening lung function in COPD and can modulate the inflammatory state of the lung. The combined response of macrophages,

autophagy, and NETosis may impact lung homeostasis and lung function decline (14). In COPD patients with rapid functional decline, an impaired humoral immune response is characterized by reduced secretory IgA and plasma cell numbers in the bronchial lamina propria (15). IL-6, a systemic inflammatory marker, acts on CD4+ T-helper cells and impacts the formation of the Th immune response in COPD. The expression level of the IL-6 receptor on CD4+ cells is increased in severe COPD, potentially enhancing the Th17 immune response (16).

Several inflammatory mediators play a role in the disease. These include IL-6, HGF, OPG, and various chemokines such as CXCL9, CXCL10, CXCL11, CX3CL1, CXCL1, MCP-3, MCP-4, CCL3, CCL4, and CCL11 (17). Additionally, matrix metalloproteinase-9 (MMP-9), matrix metalloproteinase-12 (MMP-12), tissue inhibitor of metalloproteinase-1 (TIMP-1), and tissue inhibitor of metalloproteinase-4 (TIMP-4) are increased in the exhaled breath condensate (EBC) of COPD patients(18). Specialized pro-resolving lipid mediators (SPMs) have been implicated in the pathophysiology of COPD and other respiratory diseases, as they are involved in the resolution of inflammation. Furthermore, Phosphodiesterase-4 (PDE4) is overexpressed in COPD patients, leading to decreased cAMP hydrolysis and inactivation, activating downstream inflammatory signaling pathways (19).

Figure [2]: Consequences of oxidative stress in COPD (20)



Manifestations and Differential Diagnosis

Chronic obstructive pulmonary disease (COPD) is a complex multisystem disease with various manifestations. These include systemic inflammation, cardiovascular diseases, impaired physical function and activity, increased frailty, skeletal muscle dysfunction, depression and anxiety, obstructive sleep apnea, osteoporosis, gastroesophageal reflux disease, anemia, lung cancer, cognitive impairment, diabetes, renal insufficiency, and chronic infections (21). Additionally, Systemic manifestations of COPD affect respiratory symptoms such as progressive dyspnea, cough, expectoration, wheezing, and shortness of breath(1, 22). Other common symptoms include decreased expiratory volumes, sputum production, and abnormal respiration rate. The key sign of COPD is Dahl's sign, characterized by areas of thickened and darkened skin on the lower thighs and/or elbows. This sign can also be seen in patients with interstitial lung disease, congestive heart failure, and chronic moderate to severe persistent asthma. Other physical signs of COPD include purse-lip breathing, breath sound intensity, forced expiratory time, abdominal paradox, Hoover's sign, barrel-shaped chest, and accessory muscle use. COPD can be misdiagnosed with other diseases such as coronary artery disease (CHD), arrhythmias, interstitial lung diseases, bronchiectasis, asthma, anxiety, depression, pneumonia, pulmonary embolism, and pneumothorax (23). Generally, COPD exacerbation frequency can lead to reduced quality of life, functional status, increased healthcare utilization, and accelerated disease progression and mortality rate (24).

How to diagnose COPD?

Chronic obstructive pulmonary disease (COPD) can be diagnosed using various techniques. Spirometry is the basic test for suspicion of COPD, allowing noninvasive assessment of lung function by the criteria that have been proposed for early COPD in young smokers, including FEV1/FVC < LLN and FEV1 decline ≥60 ml/year (25). Pulmonary function tests (PFTs) provide valuable information for diagnosing COPD and determining the severity of the case, but they are underutilized in clinical practice; they include post-bronchodilator FEV1/FVC quotient below the fixed threshold of 0.7 or the lower limit of normal (LLN) according to the GLI reference values (26). Capnography data collected by the N-Tidal™ device can be analyzed using machine learning techniques to distinguish CO2 recordings of patients with COPD from those without (27). In addition, Clinical factors such as productive sputum, body mass index, and hyperinflation by chest X-ray can also be used as diagnostic tools for further testing (28). These techniques provide non-invasive, cost-effective, and accurate methods for diagnosing COPD, facilitating early screening, and improving patient outcomes.

Moreover, Other tests such as blood gas measurement, computed tomography, electrocardiography, echocardiography, morphology, and sputum culture can also be helpful in the diagnosis of COPD (29). Additionally, surface electromyographical (EMG) analysis of the sternomastoid muscle can be used for early diagnosis of COPD. A mathematical model incorporating EMG analysis results, physiological parameters, daily routine, and habits has been developed and tested with a high accuracy of 93.13% (30). Besides, Laboratory tests, including troponin, C-reactive protein (CRP), hemoglobin, and carbon dioxide, can provide predictive value and identify high-risk patients (31). Radiological diagnosis, particularly computed tomography (CT), is sensitive in detecting pathological changes in the lung parenchyma and respiratory tract, especially in the early stages of COPD, including bronchial wall thickening, nodules, bronchiectasis, apical fibrosis, and tree-on-bud patterns (32). In addition, Multi-omics panels of biomarkers, such as proteomics and metabolomics, have shown promise in diagnosing COPD and exploring molecular subtypes (33). These tests can provide valuable information for diagnosing COPD, assessing disease severity, and predicting clinical outcomes.

Treatment

The treatment plan includes various strategies such as pulmonary rehabilitation, pharmacologic and non-pharmacologic medical therapies, surgical treatments, inhaled bronchodilators, and interventional treatments delivered via a bronchoscopic approach. These options aim to manage the disease, improve quality of life, and decrease exacerbations(34).

Inhaled beta-agonists and anti-muscarinic bronchodilators are the mainstays of acute and chronic treatment, often combined with inhaled corticosteroids to reduce chronic inflammation (35). Also, long-acting bronchodilators such as β2-agonists (LABA) and long-acting antimuscarinic agents (LAMA) are considered the most effective treatment options. as well as inhaled glucocorticosteroids (ICS) in fixed/opened double and triple combinations. Triple therapy, which combines LABA, LAMA, and ICS, is particularly effective in preventing negative outcomes of the disease, reducing exacerbations, slowing down disease progression, improving quality of life, and reducing mortality in the long run (36). In addition, Single inhaler triple therapy (SITT) with an inhaled

corticosteroid, a long-acting β2-agonist, and a long-acting muscarinic antagonist is also an effective and attractive therapeutic option for COPD management (37). As well, a novel LAMA/LABA combination of umeclidinium/vilanterol (UMEC/VI) has shown efficacy and cost-effectiveness in the treatment of COPD, especially in patients who are not adequately controlled with dual ICS/LABA or LAMA/LABA therapy (38). Overall, The main classes of drugs for treatment are LABA, LAMA, and ICS, and the evolution of therapeutic approaches has led to the creation of new fixed inhalation combinations of these drugs. Moreover, PDE4 inhibitors are used in the treatment by preventing the metabolism of cyclic adenosine monophosphate (cAMP), thereby reducing inflammation, which helps regulate metabolism and suppress inflammatory responses(19). Long-term oxygen therapy (LTOT) is the most studied form of oxygen therapy in COPD, with evidence based on trials conducted several decades ago. However, there are still questions about which patients benefit the most from LTOT and how to define that benefit. Additionally, challenges exist in training clinicians and patients on best practices for LTOT and providing optimal therapy. Short-term oxygen therapy (STOT) is often prescribed to allow COPD patients to be safely discharged from the hospital following an acute illness. Persistent hypoxemia requiring STOT is a marker of disease progression toward the requirement for LTOT. However, high-concentration oxygen therapy in hypercapnic COPD patients is associated with increased mortality. Overall, High-flow oxygen therapy (HFT) is an alternative to conventional oxygen therapy in patients with acute respiratory failure due to COPD exacerbation (39-41).

The current guidelines for managing COPD exacerbation recommend a syndromic approach to diagnosis, assessing the severity of the episode, identifying the trigger, and addressing treatable traits (TTs)(42). Vaccinations are important; Influenza, pneumococcal, and shingles vaccinations are recommended in COPD. Studies have shown that consecutive immunization with pneumococcal conjugate and polysaccharide vaccines leads to a decrease in the isolation rate of pneumococcus in sputum and a reduction in exacerbations, antibiotic use, and hospitalizations (43). Additionally, influenza vaccination has been associated with a reduced risk of ischemic heart disease, acute coronary syndrome, ventricular arrhythmia, lung cancer, dementia, and death in COPD patients. Besides, The best methods for managing COPD exacerbation include targeted oxygen therapy, assessment of gas exchange using arterial blood gases, and inhaled bronchodilators (44). Inhaled antibiotics are effective and safe in COPD patients with multiple exacerbations and/or chronic bronchial infection (CBI) by any potentially pathogenic microorganisms (PPM), especially Pseudomonas aeruginosa (PA) (45). Corticosteroids have been found to alter the phenotype and function of COPD lung macrophages, reducing iron availability for bacterial growth and enhancing efferocytosis, which may provide short-term benefits in managing exacerbations, their long-term use should be carefully considered due to the associated adverse outcomes such as pneumonia, osteoporosis, sleep disorders, and anxiety/depression (46).

Also, Surgical or Interventional treatments, either through surgery or bronchoscopy, such as lung volume reduction treatment using endobronchial valves lung transplantation, which targets structural abnormalities of the airway and lung parenchyma, have been shown to improve dyspnea, exercise tolerance, and quality of life in patients with severe COPD and hyperinflation (34, 47-49). Stem cell-based therapy using autologous bone marrow-mononuclear stem cells has also shown promise in reducing major symptoms (50). In addition, Smoking cessation is also crucial in the treatment plan, as smoking is the most important preventable risk factor for exacerbation and deterioration of the disease. Overall, it is important to ensure that the treatment delivered aligns with the current recommendations in the guidelines to avoid suboptimal outcomes and medication side effects (51).

CONCLUSION:

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent and progressive lung condition characterized by irreversible airflow obstruction, inflammation, and damage to lung tissue. The main subtypes are chronic bronchitis and emphysema. COPD is influenced by both genetic and environmental factors, with cigarette smoke being a primary risk factor. It is associated with systemic inflammation and comorbidities like cardiovascular diseases, diabetes, and muscle weakness. Viral infections, particularly influenza A viruses, can trigger acute exacerbations. The pathophysiology involves oxidative stress, altered immune response, and inflammation, leading to chronic bronchitis, emphysema, and small airway disease. Diagnosis includes spirometry, pulmonary function tests, and clinical factors, with various laboratory and imaging tools aiding in confirmation. Treatment strategies encompass pulmonary rehabilitation, pharmacologic therapies (bronchodilators, corticosteroids), surgical interventions, and oxygen therapy. Vaccinations are

recommended, and careful management of exacerbations involves oxygen therapy, inhaled antibiotics, and corticosteroids. Smoking cessation is crucial, and newer therapies like stem cell-based treatments show promise.

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