REVIEW ARTICLE

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND ASSOCIATED COMORBIDITIES: THE ROLE OF PAIN

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Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD is characterized by chronic respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused mainly by excessive exposure to cigarette smoke and occupational pollutants and influenced by gene-environment interactions throughout life. It is one of the top ten causes of death worldwide. An epidemiological feature of the disease is the occurrence of acute flares or exacerbations, which are associated with existing comorbidities. Comorbidities increase the risk of exacerbations, which in turn increase several mechanisms that can cause pain in COPD patients and reduce their quality of life.

Aim: The aim of this review was to investigate the association of chronic obstructive pulmonary disease (COPD) with comorbidities and pain and their impact on the lives of patients with COPD.

Methodology: A comprehensive review of the relevant literature was carried out through electronic databases (Google Scholar, Mednet, Pubmed, Medline, Cinahl, the Hellenic Academic Libraries Association -HEAL-Link) and scientific journals (English and Greek) using the appropriate key words.

Results: The presence of comorbidities in patients with COPD is associated with the worst prognosis, but there is considerable variation in the impact of different comorbidities on outcomes. The clinical profile of COPD is further complicated by the presence of pain. Although the cause-and-effect relationship is unclear, there is some evidence that the pain experienced by people with COPD might be related to comorbidities. The most common comorbidities in COPD are cardiovascular diseases (heart failure, peripheral vascular disease and atrial fibrillation), psychological disorders (anxiety and depression), metabolic diseases (diabetes, arterial hypertension and abdominal obesity), sleep disorders, anemia and gastroesophageal reflux & ulcer.

Conclusions: The heterogeneity and complexity of COPD can be better understood through comprehensive clinical assessment of severity, pathophysiology and relationship with other comorbidities. Appropriate recognition and management of pain can improve patients' quality of life.

Keywords: COPD, pain, chronic pain, comorbidities.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as a common, preventable and treatable disease. It is characterized by chronic respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused mainly by excessive exposure to cigarette smoke (CS) and occupational pollutants and influenced by gene-environment interactions throughout life.[1,2]

According to the World Health Organization (WHO), COPD was the third leading cause of death globally in 2019, causing 3.23 million deaths, and according to the CDC, COPD was the sixth leading cause of death overall and the fifth disease-related cause of death in the US in 2021, responsible for the majority of deaths from chronic lower respiratory diseases. Even today COPD is still one of the top ten causes of death worldwide.[3,4]

In Greece, the prevalence of COPD has been estimated to be 8.4-10.6% in previous studies. The prevalence was higher in men (11.6%) compared to women (4.8%), in the population aged >70 years (23%) and in rural areas. Smoking intensity and age were significantly associated with a higher prevalence of COPD in both men and women. According to the Hellenic Thoracic Society, mild COPD was the most common manifestation of the disease (57.4% mild, 25.3% moderate and 16% severe), while 81.4% of COPD patients were unaware that they had the disease. [5-7]

A very important epidemiological feature of the disease is the occurrence of acute flares or exacerbations, which are associated with increased mortality, morbidity (ICU or hospital admission) and disease worsening after each event. Exacerbations of COPD increase several mechanisms that can cause pain (dyspnoea, hyperinflation and inflammation) with a reported prevalence ranging from 44% to 88% and reduce the quality of life of those affected. They also contribute significantly to the economic and social costs of the disease. [8-10]

Furthermore, patients with COPD very often have other chronic diseases at the time of diagnosis, but COPD itself is an important factor in the development of comorbidities. In clinical practice, the term “comorbidity” refers to the presence of one or more additional conditions often co-occurring (that is, concomitant or concurrent) with a primary condition. The term was initially introduced by Feinstein in 1970 and is derived from the Latin words “co” meaning together and “morbus” meaning sickness.[11] It is estimated that about 2/3 of COPD patients have one or two comorbidities. Identifying the type of comorbidity and the potential clinical impact on the risk of exacerbations can help healthcare professionals to improve the care of patients with COPD.

The aim of this review was to investigate the association of chronic obstructive pulmonary disease (COPD) with comorbidities and pain and their impact on the lives of patients with COPD.

METHODOLOGY

A comprehensive review of the relevant literature was carried out through electronic databases (Google Scholar, Mednet, Pubmed, Medline, Cinahl, the Hellenic Academic Libraries Association -HEAL-Link) and scientific journals (English and Greek) using the appropriate key words: COPD, pain, chronic pain, comorbidities.

Chronic obstructive pulmonary disease

COPD represents a spectrum of pathological conditions with chronic bronchitis (CF) at one end and emphysema at the other, with most people having some features of both. It is clear that all of these complex and intricate processes manifest themselves in different phenotypes. Historically, patients with the predominant type of chronic bronchitis associated with generalised cyanosis and cardiac pathology secondary to COPD were referred to as 'blue bloaters', whereas patients with the predominant type of emphysema associated with late stage cyanosis were referred to as 'pink puffers', although this classification was abandoned over time.[12]

Long-term exposure to harmful particles such as cigarette smoke induces pathological changes characteristic of COPD, affecting the central large airways, peripheral small airways, lung parenchyma and pulmonary vasculature. The combination of these pathological changes is heterogeneous from patient to patient, making it difficult to predict the course of the disease. In COPD patients, destruction of the lung parenchyma usually results in centrilobular emphysema. This is associated with dilation and destruction of the airway bronchioles.[13]

In COPD patients, the combination of pathological anatomical changes in the lungs, chronic hypoxaemia, systemic inflammation and chronic cortisone use leads to effects on the musculoskeletal system and bones.[14] Significant structural and functional changes occur in

peripheral skeletal and respiratory muscles. The diaphragm and intercostal muscles follow adaptive mechanisms due to the increased demands on their continuous function against the chronically increased respiratory workload.[15]

Dyspnoea is one of the most characteristic symptoms of COPD. It is a major cause of disability and anxiety associated with the disease, as many patients adopt a sedentary lifestyle to avoid exertional dyspnoea. This predictably leads to extensive skeletal muscle deconditioning, social isolation and negative psychological consequences. [2,16]

Cough is also an important symptom and may or may not be accompanied by sputum. Chronic cough and mucus hypersecretion have been reported to be associated with an accelerated decline in lung function, more frequent exacerbations and hospital admissions, all of which affect the quality of life of patients. [17]

Other symptoms of COPD include chest tightness and the presence of wheezing, which is one of the major findings on clinical examination. Symptoms may vary throughout the day or week. Some people report more severe symptoms in the morning, with coughing and sputum production being the most troublesome. Morning symptoms of COPD are also known to adversely affect daily physical activity.[18,19]

Other symptoms of COPD include fatigue, anorexia and weight loss.[20] The extrapulmonary manifestations of COPD, such as changes in body composition, have been recognized for a long time and are a treatable aspect of the disease.[21] In patients with COPD, extreme weight loss or underweight increases the risk of gasolysis, decreased diffusing capacity and reduced exercise tolerance.[22] A reduction in the mass of the diaphragm and respiratory muscles is common in COPD, suggesting a loss of cellular mass in the body, which ultimately leads to a reduction in strength and endurance.[23]

These effects lead to deterioration in the patient's respiratory capacity and consequently their functional capacity. To manage the musculoskeletal disorders and functional limitations resulting from these respiratory conditions, novel therapeutic modalities focused on thoracic and soft tissue joints may be beneficial, with the potential to address joint dyskinesia, subsequent postural, musculoskeletal adjustments, and pain.[24]

In stable COPD, medications can reduce symptoms, exacerbation frequency and severity, and improve exercise tolerance and health status. The choice of appropriate drug therapy depends on the availability and cost of medications and the balance between clinical benefit and adverse effects.[2]

Comorbidities

The presence of comorbidities in patients with COPD is associated with the worst prognosis, but there is considerable variation in the impact of different comorbidities on outcomes. Some of the possible causes of comorbidities include older age, physical inactivity, poor diet, smoking, hypoxia and systemic inflammation.[25]

The most common comorbidities in COPD are cardiovascular diseases (heart failure, peripheral vascular disease and atrial fibrillation), psychological disorders (anxiety and depression), metabolic diseases (diabetes, arterial hypertension and abdominal obesity), sleep disorders, anemia and gastroesophageal reflux & ulcer. Others include bronchial cancer, respiratory infections, thromboembolic disease associated with asthma, osteoporosis - osteopenia, musculoskeletal dysfunction, arthritic pain, weight loss and malnutrition.[26,27]

COPD and Cardiovascular Diseases

Cardiovascular disease (CVD) is generally one of the most common comorbidities in COPD and is also associated with an increased risk of mortality. One of the most important pathophysiological markers of COPD—lung hyperinflation—plays a significant role in the appearance of functional limitations of the pumping function of the heart, creating unfavorable conditions by exerting a compression effect on the heart muscle.[28] In fact, in the typical COPD patient, death from cardiovascular causes is as likely as death from respiratory causes.[29]

Smoking and several common systemic conditions such as diabetes mellitus, hypertension and obesity are risk factors in the development of both cardiovascular disease and COPD. In addition, chronic systemic inflammation, oxidative stress, chronic hypoxia, arterial stiffness and endothelial dysfunction appear to significantly influence the relationship between these two diseases.[30]

COPD leads to endothelial dysfunction, which may be a risk factor mechanism for cardiovascular disease.[31] It has recently been described as the pulmonary component of a systemic endothelial disease in which a number of 'inflammatory' processes affect multiple organs simultaneously, leading to a state of multimorbidity.[29]

Inflammation-induced endothelial dysfunction leads to increased permeability to lipoproteins and their subendothelial accumulation, leukocyte recruitment and platelet activation. It also plays a crucial role in atherosclerotic plaque formation. Through increased leukocyte clones in the peripheral blood, it is the link between ageing and cardiovascular disease. [32]

COPD and Psychological Disorders

There is evidence from many studies that people with COPD have an increased prevalence of psychological and cognitive problems. This is of concern because adherence to COPD treatment is affected by mental health complications, and symptoms are exacerbated in COPD patients with brain-related comorbidities.[33]

The mechanism of depression and anxiety in COPD is not fully understood, and because the relationship is complex, there has been debate about whether genetic causes should be considered for the observed association between COPD and depression or anxiety. The estimated genetic heritability for COPD is 25-37% and for major depressive disorder (MDD) [28-51]%.[34,35] A possible mechanism linking depression and COPD is the 'overspill' theory, which suggests that inflammatory markers diffuse into the general circulation and cause systemic inflammation. For instance, markers such as sTNFR-1 (soluble tumour necrosis factor receptor alpha-1) have shown strong correlation with depression rates in COPD patients.[36]

In addition, the failure of patients and health professionals to recognize symptoms of anxiety or depression as psychological distress rather than symptoms of COPD, the lack of systematic screening for mental health problems as part of routine health care, the social isolation associated with COPD, and the perception of depression and anxiety as 'normal' reactions to living with a incurable chronic disease rather than indicators of poor psychosocial adjustment, all contribute to the difficulty in identifying psychological distress, diagnosing and appropriately treating mental health problems in people with COPD.[37]

COPD and metabolic diseases

The association between metabolic syndrome (MetS) and COPD is well documented in the literature and has been identified as an independent risk factor for exacerbations, impaired lung function, pulmonary hypertension and asthma.[38] MetS is a complex disorder recognized clinically by the presence of abdominal obesity, elevated triglycerides, atherogenic dyslipidaemia, hypertension and hyperglycaemia and/or insulin resistance.[39] The pathogenesis of both lung disease and the MetS is multifactorial. They have a number of risk factors in common, such as smoking, genetics, obesity, physical inactivity and airflow obstruction.[38,40]

It is also known that the concentrations of lipid metabolites in body fluids are altered in people with COPD. Disturbances in lipid metabolism in COPD lead to lipotoxicity via increased accumulation of metabolites. This accumulation of metabolites locally disrupts the structure of the lung parenchyma, impairs lung function and systemically causes cellular energy deficiency and fatigue through the mediation of mitochondrial damage.[41]

Osteoporosis is another significant metabolic comorbidity of COPD. It is a systemic bone disease characterized by low bone density and microstructure change that increase the risk of fractures. The prevalence of osteoporosis among COPD is higher than that among healthy subjects (osteoporosis, 14%–66% and osteopenia, 18%–65%) and osteoporotic fractures in COPD are associated with several adverse health outcomes, including decreased lung function, poor quality of life, increased hospital admissions and mortality.[42,43]

In addition, thyroid dysfunction is present in a significant proportion of patients with COPD, particularly in the severe form of COPD (GOLD stages C and D).[44] Blood gas abnormalities, including hypoxaemia and hypercapnia, are common in COPD due to impaired gas exchange. These disturbances can disrupt thyroid function, leading to hypothyroidism, hyperthyroidism and non-thyroid disease syndrome.[45] Thyroid dysfunction is a frequent cause of exacerbations in COPD, which can place an additional burden on patients.

Comorbidities and associated pain

Literature has shown that the clinical profile of COPD is further complicated by the presence of pain. Although the cause-and-effect relationship is unclear, there is some evidence that the pain experienced by people with COPD might be related to comorbidities.[46] As the sites of pain in people with moderate-to-severe COPD include the upper and lower back and lower limb joints, there is an impact of pain on physical activity and health related quality of life (HRQOL). Increased pain severity has been linked to poorer

HRQOL.[47,48] According to a previous study, people with COPD reported that pain had a negative effect on their breathing, walking ability, daily activities and sleep. It also contributed to the development of anxiety and depression.[49]

Several possible mechanisms that may cause or contribute to the maintenance of persistent pain in people with COPD have been suggested, including altered respiratory and musculoskeletal mechanics, postural deviations, compression fractures, vertebral deformities, costovertebral arthropathy, central sensitisation, adverse effects of prolonged steroid use, and personal characteristics (gender and socioeconomic factors).[50] In addition, systemic inflammatory processes inherent to COPD are likely to underlie pain sensitivity and may cause chronic and neuropathic pain. Musculoskeletal disorders and comorbidities (including mechanical limitations of chest wall motion due to hyperinflation and osteoporosis) are also considered potential causes of pain in COPD patients, and physical inactivity may exacerbate common age-related comorbidities such as osteoarthritis and low back pain. [51,52]

CONCLUSIONS

The heterogeneity and complexity of COPD is better understood through comprehensive clinical assessment of severity, pathophysiology and relationship with other comorbidities.

Appropriate recognition and management of pain can improve quality of life, exercise tolerance and exercise compliance throughout the lifetime of patients with COPD.

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