Chronic Obstructive Pulmonary Disease: A View on Comorbidity Phenotypes. A literature review

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Abstract

Objective: This review's purpose is to summarize the current state of knowledge on the systemic implication of chronic pulmonary obstructive disease

Background: The 'systemic repercussions' of COPD are of great importance. These include accidental weight loss, skeletal muscle dysfunction, and a higher risk of cardiovascular disease, osteoporosis, and depression. Frequently affecting the patient's health and prognosis, these extrapulmonary COPD characteristics demand thorough screening and proper management to give the most effective medical care.

Methods: We conducted a search of papers describing COPD as a systematic disease on the MEDLINE database.

Discussion: Local and systemic inflammation, oxidative stress, and changes in the neuro-humoral states are some of the likely candidate pathways by which these extrapulmonary complications of COPD are affected, even though the mechanisms for the association of COPD with systemic disorders have not been fully clarified. The processes and mechanisms behind the extrapulmonary symptoms of COPD will likely become more transparent with further research.

Conclusion: COPD management should be based on a clear understanding of COPD-related comorbidities and their impact on COPD itself.

Keywords: *COPD, Phenotypes, Risk factors, Symptoms, Severity, Comorbidities, Cluster*

Introduction

Chronic obstructive pulmonary disease is a preventable and treatable disease with significant effects on the lungs. It is a progressive inflammatory condition with persistent respiratory symptoms and airflow limitation. More recently, Fabbri and Rabe have stated that COPD should be considered a chronic systemic inflammatory syndrome to encompass the effects of the generalized inflammatory processes related to COPD on hormones, metabolism, and the musculoskeletal system [1]. Although historically, COPD severity has been strongly associated with airway obstruction level, other severe diseases and chronic medical conditions can affect patients with COPD. These are known as COPD-related comorbidities, and they are not to be confused with conditions stemming from the systemic consequences of COPD, even though both influence the course of the disease. [2] Many comorbidities share the same risk factors, and their presence and quantity

have direct results in COPD progression, patient's quality of life, number of exacerbations, and mortality. One of the major mechanisms underpinning these systemic effects is low-grade, persistent systemic inflammation. [3]

COPD-related comorbidities are not exclusive to patients with severe COPD and can be present in any stage of airflow limitation. It is very likely for multiple comorbidities to exist simultaneously in the same patient. [4] They also affect many facets of COPD management strategies and rehabilitation. [5]

Discussion

COPD phenotypes

Several definitions of COPD exist and suggesting that one is a better fit than others would be inaccurate. In recent decades, these definitions have taken place over one another. However, tentatives to perfect COPD definitions have yet to narrow the gap between our understanding of COPD pathophysiology and the goal of personalized therapy. This is where the concept of COPD phenotype comes in handy. A phenotype is the physical appearance or biochemical characteristic resulting from an interaction between its genotype and the environment. [6] Patients can present with predominant emphysema or chronic bronchitis, which has treatment implications. Therefore, identifying individuals with the phenotype of chronic bronchitis and repeated exacerbations is important in clinical practice. Additional phenotypes with clinical or therapeutic relevance include overlap COPD-asthma and frequent exacerbator. Patients who experience two or more exacerbations a year are considered to have the COPD exacerbator phenotype. [7] This phenotype is based on clinical data and patient recall. The COPD exacerbator phenotype suggests a worse prognosis, emphasizes the significance of inquiring about and documenting exacerbations in the clinical record and identifies individuals who may need anti-inflammatory medication in addition to bronchodilators. [8] The complexity of COPD suggests the need to classify different COPD phenotypes based on clinical parameters, number of hospitalizations, comorbidities, and systemic inflammation. Epidemiological research on the incidence of COPD demonstrates that young smokers with asthma differ from those with a chronic airflow obstruction but no history of asthma. In the first instance, increased plasma concentrations of IgE are much more common, along with allergic rhinitis, bronchial hyperresponsiveness, and wheezing, demonstrating that this is an overlap phenotype between asthma and COPD [9]. The overlap COPD-asthma phenotype is described as an incompletely reversible airflow obstruction accompanied by symptoms or signs of greater obstruction reversibility [10] or as

the diagnosis of COPD in a patient with a history of previously diagnosed asthma before the age of 40. These phenotypes identify patients with different responses to the available treatments and allow a more personalised approach to treatment, which is modulated according to COPD severity.

Other COPD phenotypes have been proposed, but their importance when directing treatment is not established. Future research should concentrate on developing straightforward algorithms based on the most discriminating features for categorizing patients into particular phenotypes. Before they can be used in clinical practice, such algorithms must first be evaluated in validation cohorts.

COPD as a "cluster" disease

Several studies show that the cause of death in mild to moderate COPD patients differs from that in advanced COPD patients. While lung cancer and cardiovascular diseases are the main culprits in the first group, respiratory failure is a mortality factor in the second group. [11]

Cluster analysis is a collection of methods for defining groups of individuals based on measured characteristics so that they are grouped based on their differences, into clusters.[12]

Burgel et al.'s key finding is that COPD patients with identical airflow restriction belong to distinct phenotypes, have varied symptoms and outcomes, and vary in age and comorbidities. Comparing this study to the other two that have utilized cluster analysis to describe COPD is interesting[13]

Divo et al., in a prospective study in 2013, were able to significantly link twelve out of the seventy-nine comorbidities studied to mortality in COPD patients. They state that the most prevalent comorbidities in COPD patients, with a noticeable impact on overall morbidity and mortality, are cardiovascular, cerebrovascular diseases, lung cancer, and diabetes. The study developed a graphic depiction of this impact in the form of a "comorbidome." It validated using a simplified disease-specific comorbidities index to assess COPD mortality. [14]

Another prospective study was conducted in 2015 by Vanfleteren et al. [15] in a pulmonary rehabilitation center. 213 COPD patients were enrolled in this study, and five clusters were established based on 13 objectively diagnosed comorbidities in patients with COPD. The patients of each Cluster had the same level of airflow limitation, smoking, activity-related functional capacity, long term oxygen therapy, which illustrates that the prevalence of COPD-related comorbidities is independent of COPD severity.

1st Cluster - had fewer comorbidities than others
2nd Cluster - the cardiovascular Cluster

3rd Cluster - the cachectic Cluster; had the most significant prevalence of underweight-related conditions, osteoporosis, and conditions associated with muscle mass loss.
4th Cluster - the metabolic Cluster; patients with obesity, hyperglycemia, and dyslipidemia represented it.
5th Cluster - the psychological Cluster, had many patients suffering from depression and anxiety disorders. Surprisingly, the patients in this Cluster were affected by the greatest number of myocardial infarctions.

In 2018 one thousand, five hundred and eighty-four COPD patients were enrolled in a cohort study conducted by Raherison et al. [16]. Cluster analysis showed five phenotypes of comorbidities:

1st Cluster - included cardiac profile and was the most prevalent in groups B and D of COPD, according to GOLD classification.
2nd Cluster - included fewer comorbidities and had the greatest prevalence in groups A and C of COPD.
3rd Cluster - included metabolic syndrome, apnea, and anxiety depression. It had its most significant prevalence among groups C and D of COPD.
4th Cluster - denutrition and osteoporosis cluster. It was the most prevalent group B and D of COPD.
5th Cluster - bronchiectasis. It was most prominent in COPD patients of group D.

This Japanese study [17] evidenced that comorbidity profiles can be clustered into five categories:

1st Cluster – less comorbidity
2nd Cluster – Malignancy
3rd Cluster – Metabolic and cardiovascular diseases
4th Cluster – GERD and psychological diseases
5th Cluster – underweight and anemia

Each Cluster's patients have unique clinical characteristics, different in comorbidities, even for the patients with the same FEV1. There were no statistical differences in FEV1 between the 5 clusters because it involved all the COPD stages according to GOLD. It was noticed that there is no connection between the severity of airflow limitation and the type of comorbidity, therefore, the type of Cluster. All the patients in the malignancy cluster (the second one) had one or more extra pulmonary malignancies, and only 19% of them had lung cancer. The patients in

the 4th Cluster with GERD and psychological diseases had higher SGRQ scores and CAT scores, matching previous studies showing that anxiety, depression, and GERD worsen CAT and SGRQ scores. Knowing this fact, carefully treating these conditions is fundamental.

The study reported a connection between emphysema and osteoporosis and between muscle weakness and low BMI. The patients in the 5th Cluster, the underweight and anemia category, had a lower BMI and higher prevalence of osteoporosis, and low DLCO/VA. This suggests common mechanisms between emphysema, osteoporosis, and low BMI.

Main COPD-related comorbidities

When we mention COPD-related comorbidities, we mainly discuss the following:

- Cardiovascular disease
- Skeletal muscle disease
- Psychiatric disorders
- Sleep-related breathing disorders
- Endocrine disorders
- Gastrointestinal disease
- Lung Cancer
- Infections

It is still unclear if COPD is a disease distinct from its comorbidities or whether these are part of the spectrum of COPD symptoms because more than 50% of COPD patients have four or more comorbidities, but their presence is one of the most significant modifying risk factors for COPD severity. [18]

Cardiovascular diseases

Cardiovascular diseases are the most frequent of COPD-related comorbidities. [19] Patients with COPD have a two to three-fold increased risk of developing cardiovascular diseases than non-COPD patients of the same age group and the same smoking habits,[20] and in some studies, the risk is estimated to be up to fivefold as much.[21]

The basic mechanism in the development of cardiovascular disease was once believed to be the establishment of atherosclerotic plaque: endothelial denudation and smooth muscle cell proliferation created an atheroma with lipid accumulation in its center. Later research has revealed that particular inflammatory cells and

their signaling pathways are crucial for the development of atherosclerotic plaques, plaque rupture, and atherothrombosis, all of which result in cardiac events. It is now established that circulating inflammatory markers can predict cardiac events. Future cardiac events can be strongly predicted by CRP, an acute-phase reactant produced in response to acute injury, infection, or inflammation. Baseline CRP independently of conventional risk variables, predicted cardiovascular events in two prospective investigations of healthy males and females. [22] [23]. A combination of systemic inflammation, oxidative stress, and physiological stresses may bring on subendocardial myocardial injury. [24]

A high body mass index, extremely high rates of diabetes, congestive heart failure, and ischemic heart disease are all indicators of groups of people who have "systemic COPD," according to cluster analysis. They experienced higher rates of dyspnea, a worse quality of life, more frequent medical visits, and a higher risk of death than those with equivalent airflow limitation but without a heavy comorbid load. [25] According to two separate research, cardiovascular comorbidities are likely to play a major role in this phenotype's poor health outcomes and quality of life scores. [26] The ARIC population study had a 15-year follow-up period for COPD patients. The incidence of cardiovascular events was more common in subjects with a lower FEV1 regardless of smoking status or the presence of cardiovascular disease at baseline. [27] The prevalence of COPD is also high among patients with Coronary Artery Disease (CAD), and it ranges in literature from 7% to 33.6%. [28] [29] [30] [31] While CAD patients are not at greater risk of developing COPD exacerbations, the duration of exacerbations may be prolonged by cardiovascular illness.[32]

Heart failure

The overall prevalence of heart failure in COPD patients with moderate-to-severe airflow limitation in different cohort studies ranges from 7% to 39%, and impairment of left ventricle fraction ejection does not play a role. [33] [34] [35] As in most cases with COPD-related comorbidities, COPD and heart failure are clinically interrelated: while airflow limitation itself major risk factor of heart failure, the latter may result in airflow limitation. [36] [37]

Hypertension

Across all GOLD stages, hypertension appears to be the cardiovascular comorbidity that is most common. [38]

The link between hypertension and COPD is not well understood. According to recent research, increasing loss of elastic connective tissue may be linked to

increased arterial stiffness in COPD. The likelihood of hospitalization within 5 years and the mortality risk increases in COPD patients with hypertension. Patients with COPD are more likely than healthy people to have carotid plaques with higher lipid contents, which are more likely to burst and cause strokes. [39]

Research shows that targeting aggressive disease management of comorbidities in COPD patients with persisting symptoms who are receiving optimum respiratory therapy and have a large burden of cardiovascular comorbidities may help improve symptoms and health outcomes.

Skeletal muscle dysfunctions

Both ventilatory and non-ventilatory muscle groups in COPD patients are affected by skeletal muscle dysfunction in terms of quality of life and survival. An increasingly sedentary lifestyle is a major factor in muscle dysfunction, which leads to a loss of mobility and independence and, eventually, mortality in chronic obstructive pulmonary disease. [40] The reReducedtal muscle strength associated with severe exacerbations can be effectively avoided by preventing and treating them quickly and aggressively. Individuals who receive repeated doses of oral corticosteroids should be closely monitored for skeletal muscular strength, or corticosteroids should be avoided altogether. Oral corticosteroids should be used sparingly when muscle force starts to diminish. Exercises involving the entire body, like walking or cycling, improve the aerobic capacity of skeletal muscles. According to some studies, specific skeletal muscle growth and differentiation factors were upregulated after exercise training. [41]

Metabolic syndrome and diabetes

Type 2 diabetes and metabolic syndrome are 1.5–3 times more prevalent in COPD patients than in the general population. Circulatory markers of systemic inflammation were increased in patients with chronic bronchitis and COPD when metabolic syndrome was detected, irrespective of the degree of lung function impairment. [42] A person with diabetes has a lower quality of life and a shorter life expectancy. The microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular consequences (ischemic heart disease, stroke, and peripheral vascular disease) are primarily to blame for this increased morbidity and mortality. [43] Additionally, diabetes has been linked to a higher risk of infection and sepsis. By decreasing neutrophil activity and humoral immunity, hyperglycemia alters the host's response to infection. [44] The growth and pathogenicity of invading

bacteria are both arated by elevated glucose levels in tissues and secretions [45]. Increased systemic inflammation increases COPD mortality as well as COPD exacerbations, which become more frequent. By lowering insulin resistance and cardiovascular risk, modifications to COPD patients' routine exercise regimens, dietary recommendations, and drug therapy may improve their outcomes. The shared risk factors and pathogenic processes between metabolic syndrome, type 2 diabetes, and COPD can explain their high correlation. [46] The intensity and impact of each illness are exacerbated by the presence of the others, decreasing patient outcomes. In order to improve respiratory disease, lower cardiovascular risk, and maybe improve other systemic manifestations, best clinical management should therefore encompass both optimizing respiratory disease to reduce insulin resistance and controlling blood glucose and other metabolic variables. [47] The combined effects of quitting smoking and pulmonary rehabilitation are already beneficial for both respiratory and metabolic diseases. All COPD patients' results could be further enhanced by modifying exercise routines, nutritional guidance, and medicines to lower risk or improve control of metabolic syndrome and diabetes.

Depression and anxiety disorder

Between 2% and more than 50% of COPD patients report anxiety symptoms. Accordingly, the frequency of depression symptoms varies. These wildly divergent results can have a number of causes. Anxiety, despair, and fear of being out of breath are signs of emotional fragility and can help identify it because they are linked to a well-documented rise in mortality, morbidity, hospitalizations, length of stay, and readmissions. [48] Several physiological, psychological, and social elements have a role in the complex link between COPD and neuropsychiatric diseases. Before a psychiatric diagnosis is determined, the physical symptoms of the patient should be evaluated very carefully. It is feasible to treat comorbid psychiatric disorders, and effective therapy results in an enhanced quality of life.

Obstructive sleep apnea syndrome

Changes in central respiratory control, lung mechanics, and muscle contractility are just a few of the ways that sleep affects breathing. Healthy people are not adversely affected by these effects, but patients with COPD may experience substantial hypoxemia and hypercapnia, especially during rapid eye movement (REM) sleep.[49] Due to the frequent inability of clinical practice to consider

potential concurrent SDB among specific COPD patients, overlap syndrome is quite common yet frequently goes unrecognized. Greater more significant hypoxemia and hypercapnia are associated with overlap syndrome than with COPD or OSAS alone, which may have important cardiovascular effects. Morbidity and mortality will be decreased with early diagnosis and CPAP therapy. Despite overlap syndrome's great frequency, there is a dearth of information on its pathophysiology and clinical effects. Although several clinical outcome studies in this field have started, long-term follow-up research on the path overlap syndrome's pathophysiology and clinical effects ed. Future research should focus on defining the extent and effects of inflammation, oxidative stress, and leukocyte dysfunction in the overlapping processes of overlap syndrome. [50] [51]

Lung Cancer

COPD and lung cancer are closely related and frequently coexist in patients. Smoking continues to be a serious public health concern despite public health interventions and is still a major cause of lung cancer and COPD. Pulmonologists face a clinical problem when treating patients with severe COPD who have lung cancer, which calls for a multidisciplinary approach.

There have been conflicting findings regarding the incidence of lung cancer among COPD patients in various stages, with some studies finding an increased incidence with COPD severity and others reporting the opposite.[52] If a patient has genetic or epigenetic risk factors common to both diseases, lung cancer may be more common at less severe COPD stages and patients in the more severe stages would not have the predisposing risk factors; on the other hand, if chronic inflammation is to blame, the worse the COPD severity, the higher the risk of developing lung cancer. This could explain why the results are contradictory. Further research is necessary to determine the real cause of these disparate results. [53]

Gastro-oesophageal reflux disease

In multiple datasets, Gastro-oesophageal reflux disease (GORD) symptoms have been linked to more frequent exacerbations in COPD patients. The underlying mechanisms are not well known and need further research. [54] There are several potential causes. One of them is the microaspiration of gaseous and liquid refluxate into the lower respiratory tract. [55] Another one brings up symptoms exacerbated by the vago-vagal reflex from the oesophagus to the airway. In addition, there are

also autonomic dysregulations of the Lower oesophageal sphincter to consider. [56] The widely held belief that GORD has adverse effects on people with COPD is unfounded; in fact, exacerbations of the disease can likely disturb the body's physiology and lead to higher GORD. The intriguing possibility that treating GORD may result in improved outcomes for COPD is still present. However, more randomized controlled trials of antireflux therapy are needed.

Infections

The natural history of COPD is complicated and multifaceted, with both pulmonary and extrapulmonary diseases having a substantial impact. An airway infection is an essential component of the disease pathophysiology. Deteriorating airway inflammation leads to increased systemic inflammation, which is linked to the elevated risk of cardiovascular disease in COPD patients. Not only are airway infections common during COPD exacerbations, but bacterial colonization during disease stability may also raise the risk of pneumonia, resulting in episodes with greater loads of potentially harmful microorganisms and, ultimately, structural alterations in the lung. This creates a vicious cycle of the airway and systemic inflammation, which raises the risk of both conventional and atypical infection. [57] Patients with COPD may experience abrupt cardiovascular events during infection because of increased inflammatory pathways and platelet activation. Recent findings have indicated that patients with stable COPD had greater circulating platelet-monocyte aggregates than well-matched controls [58], as platelet-monocyte aggregate formation is an early phase in atherothrombosis. Analysis of data from 25,857 COPD patients in The Health Improvement Network database has produced additional proof that acute infectious exacerbations are associated with cardiovascular disease [59]. One in every 2,513 exacerbations was linked to an MI within 1–5 days, and there was a 2.27-fold higher risk of MI in those time frames. The bacteria Chlamydia pneumoniae and coronary heart disease have also been linked mechanistically, in addition to increased systemic inflammation. Up to 10% of all pneumonia cases are caused by C. pneumoniae, which may potentially exacerbate bronchial inflammation brought on by smoking. Up to 10% of cases of pneumonia are caused by C. pneumoniae, which may worsen smoking-related bronchial inflammation and it has been theorized to have a role in the pathological alterations associated with COPD [60].

Epidemiological studies have shown that COPD is one of the most common comorbidities associated with Community-acquired pneumonia (CAP) [61], and COPD patients are more likely to have worse clinical outcomes, contributing to the overall socioeconomic costs of CAP. Hospitalized COPD patients with CAP are more likely to be older, have additional concurrent comorbidities, have poorer

clinical outcome data, have a higher pneumonia severity score, and have a higher mortality rate. [62]

Conclusions

The complexity of COPD suggests the need to classify different COPD phenotypes based on clinical parameters, number of hospitalizations, comorbidities, and systemic inflammation. One of the major mechanisms underpinning these systemic effects is low-grade, persistent systemic inflammation.

COPD patients can present with predominant emphysema or chronic bronchitis, which has treatment implications. Therefore, identifying individuals with the phenotype of chronic bronchitis and repeated exacerbations is important in clinical practice. Additional phenotypes with clinical or therapeutic relevance include overlap COPD-asthma and frequent exacerbator. Patients who experience two or more exacerbations a year are considered to have the COPD exacerbator phenotype. Cluster analysis is a collection of methods for defining groups of individuals based on measured characteristics so that they are grouped based on their differences, into clusters. Several studies show that the cause of death in mild to moderate COPD patients differs from that in advanced COPD patients. While lung cancer and cardiovascular diseases are the main culprits in the first group, respiratory failure is a mortality factor in the second group.

It is still unclear if COPD is a disease distinct from its comorbidities or whether these are part of the spectrum of COPD symptoms because more than 50% of COPD patients have four or more comorbidities, but their presence is one of the most significant modifying risk factors for COPD severity.

A high body mass index, extremely high rates of diabetes, congestive heart failure, and ischemic heart disease are all indicators of groups of people who have "systemic COPD," according to cluster analysis. They experienced higher rates of dyspnea, worse quality of life, more frequent medical visits, and a higher risk of death than those with equivalent airflow limitation but without a heavy comorbid load. Combined diagnosis of COPD and heart failure entails a higher level of care burden, complicated polypharmacy, and a higher chance of misunderstandings among various healthcare professionals.

Preventing exacerbations and treating them early and aggressively can successfully reduce the decrease in skeletal muscular strength associated with severe exacerbations. Oral corticosteroids should either not be used at all in people who get them on a regular basis if skeletal muscle strength is to be regularly evaluated. When muscle force starts to decline, oral corticosteroids should be taken with caution.

The optimum clinical care should include both optimizing respiratory disease to reduce insulin resistance and regulating blood glucose and other metabolic variables in order to reduce cardiovascular risk, improve respiratory disease, and maybe improve other systemic symptoms. Modifications to COPD patients' regular exercise routines, nutritional advice, and medication management may improve their results by reducing insulin resistance and cardiovascular risk.

Several physiological, psychological, and social elements have a role in the complex link between COPD and neuropsychiatric diseases. Before a psychiatric diagnosis is determined, the physical symptoms of the patient should be evaluated very carefully. It is feasible to treat comorbid psychiatric disorders, and effective therapy results in an enhanced quality of life.

In terms of public health, it appears necessary to identify smokers who are most at risk of developing COPD and/or lung cancer. Doing so would also usher in a new era of preventative medicine. In this manner, a potential application offering intriguing potential for the future would be to target smokers for low-dose CT screening for early identification of lung cancer.

The widely held belief that GORD has adverse effects on people with COPD is unfounded; in fact, exacerbations of the disease can likely disturb the body's physiology and lead to higher GORD. The intriguing possibility that treating GORD may result in improved outcomes for COPD is still present. However, more randomized controlled trials of antireflux therapy are needed.

The disease's pathogenesis includes airway infection and is associated with a higher-than-normal risk of cardiovascular disease in COPD patients. Exacerbations play a significant role in the vicious cycle of systemic and airway inflammation, which increases the risk of both common and uncommon infections.

Hospitalized COPD patients with CAP are more likely to be older, have additional concurrent comorbidities, have poorer clinical outcome data, have a higher pneumonia severity score, and have a higher mortality rate.

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