



doi • 10.5578/tt.2245
Tuberk Toraks 2016;64(4):289-298
Geliş Tarihi/Received: 18.02.2016 • Kabul Ediliş Tarihi/Accepted: 14.05.2016

DERLEME
REVIEW

Comorbidities and their impact on chronic obstructive pulmonary disease

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SUMMARY

Comorbidities and their impact on chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a complex disease that is associated with devastating outcomes resulting from lung involvement and several comorbidities. Comorbidities could impact on symptomology, quality of life, the complications, the management, economic burden and the mortality of the disease. The importance of comorbidities originates from their impact on the outcome of COPD. The most frequent comorbidities in COPD are cardiovascular, endocrinological, musculoskeletal, phycological disorders and lung cancer. Almost 50% of the COPD patients have 3 or more comorbidities. The recent Global Initiative of Obstructive Lung Disease (GOLD) Guideline suggested proactive search and the treatment of the comorbidities. However, there is no certain evidence demonstrating that active treatment of comorbidities improve the outcomes of COPD. However, it is well known that several comorbidities such as cardiovascular disease and lung cancer have greater impact on mortality caused by COPD. Several studies have shown that Charlson Comorbidity index or more recently COPD Specific Comorbidity Index (COTE) has been found to be related with mortality of COPD. This concise review intended to summarize the most frequent comorbidities in association with their impact on COPD.

Key words: COPD, comorbidity

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ÖZET

Kronik obstrüktif akciğer hastalığında komorbiditelerin hastalık üzerine etkileri

Kronik obstrüktif akciğer hastalığı (KOA), akciğer etkilenimi ve çeşitli komorbiditelerden kaynaklanan yıkıcı sonuçları olan kompleks bir hastalıktır. Komorbiditeler, semptomları, yaşam kalitesini, komplikasyonları, hastalığın yönetimini, ekonomik yükünü ve mortalitesini etkilemektedir. Komorbiditelerin önemi, KOA'nın sonuçları üzerine olan etkilerinden kaynaklanmaktadır. KOA'ta görülen en sık komorbiditeler, kardiyovasküler, endokrinolojik, muskuloskeletal ve psikolojik olanlar ve akciğer kanseridir. KOA olgularının en az %50'sinde üç veya daha fazla komorbidite bulunmaktadır. Yeni GOLD kılavuzu komorbiditelerin proaktif olarak araştırılmasını ve tedavisini önermektedir. Ancak bu komorbiditelerin aktif tedavisinin, KOA'nın sonuçlarını etkilediğine dair kesin bir kanıt yoktur. Öte yandan kardiyovasküler hastalıklar ve akciğer kanseri gibi komorbiditeler, KOA mortalitesi üzerinde önemli etkiye sahiptir. Çeşitli çalışmalar, Charlson komorbidite indeksinin veya KOA spesifik komorbidite indeksinin (COTE) KOA mortalitesi ile ilişkili olduğunu göstermiştir. Bu kısa derleme, KOA üzerindeki etkileri ile beraber en sık görülen komorbiditeleri özetlemeyi amaçlamıştır.

Anahtar kelimeler: KOA, komorbidite

INTRODUCTION

COPD is a complex disease that is associated with devastating outcomes resulting from lung involvement and several comorbidities (1,2). The medical dictionaries describe comorbidity as "the coexistence of concomitant but pathologically unrelated diseases". In practice the term of comorbidity is used for the coexistence of two or more diseases regardless of the pathogenic interlink". COPD has greater number (3.7) of comorbidities than non COPD subjects (1.8) (3-5). Studies showed that 94% of COPD patients had at least one comorbidity and up to 46% had three or more (3). The common etiological factors such as smoking, aging and reduced physical activities or shared inflammatory pathways can be the explanation of that relationship (1-3). The importance of comorbidities originates from their impact on the outcome of COPD. Comorbidities could cause additional impairment of patient's health quality of life, morbidity, health economy and mortality (1,3,6).

Gastroesophageal reflux disease (GERD), depression, anxiety, cardiovascular disease, and pulmonary embolism are associated with increased number of COPD exacerbations (6,7). The impact of comorbidities in exacerbations whether they mimic exacerbations or they precipitate the intensity of exacerbation is still a matter of debate (6). Comorbidities related with COPD Specific Comorbidiy Test (COTE) index revealed an increased risk of mortality (2.2 fold) (8). Toward a Revolution in COPD Health (TORCH) and Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) studies showed the almost 70% of causes of deaths in COPD were

non-respiratory and the major non-respiratory etiology of mortality was cancer and cardiovascular diseases particularly in mild to moderate disease (9,10). Recent guidelines recommend actively searching and effectively treating common comorbidities (1.) However, there is no enough evidence to suggest that treatment of COPD would reduce comorbidities, the treatment of comorbidities improves COPD and, that the presence of COPD alters the treatment modalities of comorbidities. The best suggested approach in reduction of comorbidities in COPD is reduction of common risk factors such as smoking, obesity and physical inactivity (Table 1).

COPD and RESPIRATORY SYSTEM

ACOPD can coexist with several respiratory disorders. Asthma, bronchiectasis, lung cancer and pulmonary fibrosis are among them.

Asthma

Distinguishing asthma from COPD could be problematic in adult patients especially in smokers. (11). Physician diagnosed Asthma COPD Overlap Syndrome (ACOS) has a prevalence of 20% of patients with obstructive lung diseases (asthma or COPD). The coexistence of both diseases has worse outcome than either disease alone. Those patients should not be put on either LABA or LAMA alone and inhaled steroids should be placed besides the bronchodilator therapy (11).

Lung Cancer

Ageing, smoking, family history and host susceptibility have been identified as key risk factors for both COPD and lung cancer (12). Several large

scale studies showed that emphysema and airflow obstruction increased the risk of lung cancer (Hazard Ratio: 2.8) (12-14). COPD has been found to coexist in 9% to 50% of lung cancer population (8,15). Lung cancer can be found incidentally in COPD patients while dealing with obstructive pneumonia or untractable COPD exacerbation. Lung cancer is a major comorbidity that can cause mortality in COPD patients (16). COPD may limit the chance of surgery in patients with lung cancer while increasing postoperative complications and finally increasing the likelihood of mortality due to COPD complications (3,6,17).

Lung Cancer Screening has been recommended in several guidelines. According to the National Lung Screening Trial, (NLST) current or former cigarette smokers within the past 15 years, 55 to 74 years of age, with at least 30 pack-years of smoking patients are the high risk criteria for the lung cancer. However, those criteria are still not sensitive enough and still can miss up to 39% of cancer patients. Therefore, several authors suggest adding emphysema to NLST is beneficial for improving detection rate (18).

Pulmonary Fibrosis

The combined appearance of pulmonary fibrosis and emphysema (CPFE) was first described in 2005 (19). This phenomenon would be a different entity than simple gathering two smoking associated diseases (20). There is upper lobes emphysema and lower lobe fibrosis with low carbon monoxide diffusion capacity (DLCO) and high risk of pulmonary hypertension and lung carcinoma (19). The symptoms of CPFE are more likely to resemble IPF showing progressive dyspnea and dry cough (21). Paraseptal emphysema is typical for CPFE (19,21). It is currently unknown whether pirfenidone or nintedanib are efficacious in CPFE (21). Lung transplantation is the only therapeutic option (6).

COPD and ENDOCRINOLOGY and METABOLISM

Weight loss and muscle wasting are present in 20%-70% of COPD patients (22). Aging, malnutrition, inactivity, smoking, hypoxemia, hypercapnia, administration of glucocorticoids and chronic comorbidities are associated with downregulation of anabolic states (22). This results in decreased testosterone levels, diminished bone density and muscle mass. COPD can cause late onset hypogonadism. However, replacing testosterone is no clear indication in COPD

(22). Studies showed that adrenal axis was also affected by COPD. The cortisol/DHEAS ratio was greater among patient with low muscle mass. However, there is no evidence that DHEA administration has a significant benefit in COPD (23-25).

Body Mass and COPD

Metabolic Syndrome and abdominal obesity is more prevalent in mild to moderate COPD (16-24%) than severe disease (6%) (26). In early COPD, obesity can induce cardiovascular mortality but in the late stages of disease, the cachexia takes place and associated with increased mortality (27).

Diabetes Mellitus

The prevalence of diabetes in patients with COPD is 10-18.7% (28). Glucose metabolism is more disturbed in COPD patients than non-COPD patients. Shared risk factors and common inflammatory pathophysiology could be reason behind that relation. TNF-alpha, IL-6, IL-1B, CRP and fibrinogen are most studied. Advanced age, hereditary factors, smoking, low birth weight are the shared risk factors of both diabetes and COPD (29). DM can cause pulmonary microangiopathy that results in reduced diffusion capacity of carbon monoxide (30). Hence, DM can cause phrenic neuropathy that results in diaphragm dysfunction (29). DM is also associated with increased risk of infectious exacerbations relating increased morbidity and mortality (31). Hyperglycemia can be induced by chronic systemic CS usage. DM can develop in 11% of those patients (32,33). There is evidence that particularly high dose inhaled steroids can increase the risk of type 2 diabetes and can worsen the glycemic control (33,34).

COPD and Vitamin D

Vitamin D hypovitaminosis is a common problem all over the world. There has been interest in a possible link between vitamin D hypovitaminosis and COPD pathogenesis, progression, exacerbations and associated comorbidities. The desired vitamin D level is above 30 ng/mL. Vitamin D deficiency is described as if the 25(OH) vitamin D level under 20 ng/mL. Insufficiency is between 20-29 ng/mL (35). COPD patients had significantly lower vitamin D levels when compared to controls (36). Low food intake, aging, staying indoors, increased vitamin D catabolism due to glucocorticosteroids, impaired activation by renal dysfunction, lower storage capacity in muscles or fat tissues due to wasting could be the etiology for

vitamin D hypovitaminosis in COPD (36,37). Vitamin D deficiency is related with osteoporosis, muscle weakness, infection and cardiovascular events in COPD. Several studies showed that Vitamin D deficiency is related with COPD onset, COPD progression and exacerbation.

Direct sun exposure without sunscreen is needed for skin to produce Vitamin D₃. The recent Endocrinology Guideline in vitamin D deficiency recommends that adults above age 50 require daily 600-800 IU vitamin D for bone and muscle health. However, in order to raise blood vitamin D level over 30 mg/dL 1500-2000 IU/d vitamin D will be needed (35).

COPD and MUSCULOSKELETAL DYSFUNCTIONS

Common musculoskeletal problems seen in patients with chronic obstructive pulmonary disease (COPD) are skeletal and respiratory muscle dysfunction, postural impairments, decreased flexibility and range of motion (38). Skeletal muscle dysfunction directly affects exercise performance, is associated with poor health status, and is an independent predictor of healthcare utilization and mortality (39,40). Skeletal muscle weakness is characterized by reduced muscle strength, reduced muscle endurance and the presence of muscle fatigue (41). The quadriceps muscle weakness is a common feature in patients within all stages of COPD and reduced quadriceps strength is found to be a useful predictor for mortality in patients with COPD (42,43). Also, postural abnormalities seen in patients with COPD are important due to negative impact on respiration and both components should be assessed individually. Changes in body and respiratory mechanics and acute/chronic cervical, thoracic or costal joint pains may occur with postural deviations (38,44).

There are several risk factors in COPD that may contribute to skeletal muscle weakness. These include smoking, corticosteroids, hypoxia, hypercapnia, inflammation, oxidative stress, reduced daily physical activity, vitamin D deficiency, nutritional deficit and age (45).

The estimated overall prevalence of skeletal muscle weakness in patients with COPD was shown to be 20%-30% (46,47).

Management of musculoskeletal dysfunction in COPD patients, pharmacological (testosterone replacement therapy and vitamin D and calcium supplementation) and non-pharmacological (exercise

training, prevention of falls and balance training and nutritional counseling) treatments are applied. (40,45). Their respective effects on limb muscles are summarized in Table 2.

COPD and OSTEOPOROSIS

Osteoporosis is defined a systemic disease by World Health Organization, characterized by a low bone mineral density and/or microarchitectural deterioration of bone tissue, leading to increased bone fragility and fracture risk (48). Osteoporosis prevalence increases with the severity of COPD (49-51).

Osteoporosis is common in both male and female patients with COPD (41). The prevalence of osteoporosis in COPD varies between 4% and 59%, depending on the diagnostic methods used and the severity of the COPD population (52). More than half of the patients with COPD recruited for the large TORCH trial had osteoporosis or osteopenia as determined by DEXA scan (53). Potential contributors to osteoporosis in COPD are corticosteroid use, inflammation, vitamin deficiency, anemia, smoking, and hypogonadism (41,43).

Prevention and treatment of osteoporosis involves both pharmacologic and nonpharmacologic interventions. Initially smoking cessation should be instituted into non-pharmacological interventions. Also overuse and overdose of ICS in COPD must be avoided (54). Pharmacological interventions consist of calcium and vitamin D supplementation and anti-resorptive therapy Oral or intravenous bisphosphonates are considered as the first line treatment for osteoporosis together with vitamin D and calcium supplementation. Also teriparatide and denosumab are the options.

COPD and GASTROESOPHAGEAL REFLUX DISEASE

The prevalence of gastroesophageal reflux disease (GERD) among COPD patients is significantly higher than in the normal population and a potential risk factor for exacerbation of COPD. The prevalence of GERD in COPD patients ranged between 7.7-30%. Also 58% of the COPD patients with GERD have asymptomatic reflux disease (55). In COPD patients with GERD associated risk factors are old age, female gender, many COPD medications except inhaled muscarinic antagonists (56).

Lifestyle modification and medical and surgical management have all been used to treat GERD.

Table 1. Summary of frequent comorbidities in COPD (6)

Comorbidity	Prevalence %	Shared risk factors
Respiratory system		
Asthma	20	Small airway obstruction, inflammation
Lung cancer	15-20	Systemic inflammation (NF-KB)
Pulmonary fibrosis	6	Systemic inflammation
PHT	10-91	Hypoxia, endothelial dysfunction, pulmonary arterial dysfunction
Endocrine system		
DM	10-19	Corticosteroid use, systemic inflammation, insülin resistance
Obesity	16-24	Hormones, systemic inflammation
Metabolic syndrome	25-57	Systemic inflammation, insülin resistance
Vitamin D deficiency	60	Aging, low food intake, corticosteroid use, immobilization
Musculoskeletal System		
Muscle dysfunction	36	Low physical activity, corticosteroid use, hypoxia, hypercapnia, inflammation, smoking
Osteoporosis	4-59	Corticosteroid use, systemic inflammation, vitamin D deficiency
Cardiovascular system		
IHD	16-53	Systemic inflammation, vascular endothelial dysfunction
HF	20-32	Systemic inflammation, dynamic hyperinflation
Systemic hypertension	40-60	Loss connective tissue, high arterial stiffness, aging
VTE	3-29	Endothelial dysfunction, immobilization, coagulopathy
Gastrointestinal system		
GERD	7.7-30	Decrease low esophageal sphincter relaxations
Malnutrition	10-15	Nutritional imbalance, systemic inflammation
Sleep disorders		
Overlap syndrome	0.5-3	Obesity, systemic inflammation
Hematologic system		
Anemia	7.5-33	Renal impairment, malnutrition, low testosterone levels, growth hormone level abnormalities
Urinary system		
CKD	16-39	
Anxiety-depression	8-80	Immobilization, hypoxia, increased number of comorbidities, poor quality of life, living alone

NK-KB: Nuclear factor KB, PHT: Pulmonary hypertension, DM: Diabetes mellitus, IHD: Ischemic heart disease, HF: Heart failure, VTE: Venous thromboembolism, CKD: Chronic kidney disease.

Treatment of the GERD in COPD, no alteration to standard acid suppression therapy is not required (56).

COPD and MALNUTRITION

In COPD, patients are usually said to be malnourished when their BMI is 20 kg/m². Malnutrition is present in 25-40% of severe COPD patients. Aging, tissue hypoxia, decreased physical activity, increased resting metabolic rate, chronic inflammatory processes, impaired anabolic mechanisms, increased work of breathing and energy expenditure, decreased appetite cause malnutrition in COPD patients (57). Decreased weight and muscle mass effect COPD patients undesirably and malnutrition is related with

increased mortality and morbidity. Energy consumption for respiration is 36-76 kkal in healthy individuals and 430-720 kkal in COPD patients respectively. Moreover, low intake and steroid therapy increase muscle wasting. Impaired muscle strength worsens respiratory failure, treatment response during exacerbations and prolongs weaning time from mechanical ventilation. Therefore, decreased fat free mass is more important than weight loss in COPD patients. And also electrolyte imbalance contributes muscle weakness (57). Undernourished COPD patients have longer hospital stays and more readmissions than nourished COPD patients.

Oral nutritional supplements (as powders, puddings or liquids) can be used to supplement the diet when nutrient requirements cannot be satisfied through normal food and drink. Enteral (nasogastric, naso-jejunal, gastrostomy) or parenteral nutrition can be used for COPD patients without oral intake (58).

COPD and CARDIOVASCULAR DISEASE

Cardiovascular disease is the most significant nonrespiratory contributor to both morbidity and mortality in COPD. Ischemic heart disease, heart failure, systemic hypertension and atrial fibrillation are the most common cardiovascular comorbidities in COPD.

COPD and ischemic heart disease (IHD) are both highly prevalent and share common risk factors, such as exposure to cigarette smoke, older age and sedentarism (59). The prevalence of IHD in COPD patients ranges between 16%-53%.

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) frequently coexist in clinical practice (60). COPD and heart failure share some risk factors including cigarette smoking, advanced age, and systemic inflammation. The prevalence of COPD among individuals with HF ranges from 20% to 32% of cases, and 10% of hospitalized HF patients also suffer COPD (61). Heart failure has been demonstrated to worsen the prognosis of COPD (62).

Hypertension is very common in COPD patients, but is not associated with increased mortality (63). Although the pathophysiological relationship between COPD and hypertension are not yet clear described. It seems feasible that accelerated aging, loss of connective tissue and increased arterial stiffness may predispose patients to systemic hypertension and an increased risk of cardiovascular disease in COPD patients (63).

Atrial fibrillation and COPD are often coexisted (64). The pathogenesis of atrial fibrillation in COPD is multifactorial and includes risk factors such as hypoxemia, acidosis and reduced FEV₁ (64). The prevalence of atrial fibrillation in COPD patients has been reported to 23.3% (65).

Although having similar disease mechanisms, there are differences between IHD and COPD in their current treatment strategies, and the most significant difference is use of beta-agonists in COPD and beta

blockers in heart disease (66). The researchs have shown that cardioselective beta blockers may be beneficial in COPD patients with IHD (67). Angiotensin-converting enzyme (ACE) inhibitors have been associated with reduced exacerbations and mortality in COPD (68).

COPD and SLEEP DISORDERS

Patients with COPD have higher prevalences of sleep problems such as insomnia, significant disturbance in sleep quality, nightmares and daytime sleepiness than the general population (69). Moreover, co-existence of obstructive sleep apnea (OSA) and COPD is also common and all negative effects of sleep do not have an adverse effect in healthy individuals but may cause problems in patients with COPD (70). Sleep is typically fragmented with diminished slow wave and rapid-eye-movement (REM) sleep, which likely represents an important contributing factor to daytime symptoms such as fatigue and lethargy. Furthermore, normal physiological adaptations during sleep, which result in mild hypoventilation in normal subjects, are more pronounced in COPD, which can result in clinically important nocturnal oxygen desaturation (NOD). The co-existence of OSA and COPD is also common, principally because of the high prevalence of each disorder, and there is little convincing evidence that one disorder predisposes to the other (70).

Proposed mechanisms for NOD are ventilation/perfusion mismatch, hypoventilation, increased upper airway resistance, reduced chemoresponsiveness, REM related muscle atonia and greater reduction in functional residual capacity during sleep. Hypoxic pulmonary vasoconstriction is considered a major driver of the development of pulmonary hypertension and cor pulmonale in COPD, and NOD also could cause nocturnal cardiac arrhythmias, nocturnal sudden cardiac death (71).

General consensus statements suggest screening for sleep disordered breathing in COPD patients who complain of symptoms typically associated with sleep-disordered breathing such as excessive daytime somnolence and frequent nocturnal arousals from sleep (1).

The first management principle of sleep-related breathing disturbances in COPD should be to optimise oxygenation. But the concentration of

Table 2. Effects of treatments for limb muscle dysfunction in chronic obstructive pulmonary disease (40)

Treatment	Mass	Strength	Exercise tolerance	Survival
Exercise	+	+	+	?
Oxygen	?	?	+	+
Nutrition alone	-	-	-	?
Nutrition + exercise	+	+	+	?
Nutrition + exercise + anabolic hormones	+	+	+	?
Testosterone	+	+	-	?
Growth hormones	+	-	-	?
Ghrelin	?	?	?	?
Megestrol	-	?	-	?
Creatin	?	?	-	?
Antioxidants	?	?	?	?
Vitamin D alone	?	?	?	?
Vitamin D + exercise	?	?	?	?

(+): Studies support that the treatment has a favorable effect on the outcome, (-): Studies support that the treatment has no favorable effect on the outcome, (?): There are no supporting data for a treatment effect on the outcome.

added oxygen should be carefully titrated to bring the arterial oxygen tension (PaO₂) up into the mildly hypoxaemic range in order to minimise the tendency towards carbon dioxide retention, particularly during sleep (72). In addition to correction of hypoxaemia is particularly important and in recent years, considerable interest has focussed on the potential benefits of noninvasive ventilation (NIV). Nocturnal positive pressure ventilation (NPPV) is the delivery of mechanically assisted breaths without placement of an artificial airway, usually with the use of a fitted nasal mask. According to consensus report, indications for usage of NPPV include: (a) symptoms (e.g. fatigue, dyspnea, or morning headache); (b) physiologic criteria (PaCO₂ > 55 mmHg or 50-54 mmHg with NOD), or (c) PaCO₂ = 50-54 mmHg with recurrent hospitalization related to episodes of hypercapnic respiratory failure. Sleep quality and diurnal PaO₂ and PaCO₂ levels are better with NIV plus supplemental oxygen than with oxygen alone (73).

ANXIETY and DEPRESSION IN COPD

Depression and anxiety are more prevalent in COPD than other diseases and than general population, while anxiety and depression increase the worse prognosis in COPD, COPD increases the risk of depression (RR= 1.69). There is a bidirectional relation between anxiety (RR= 1,83) depression (RR= 1.27) and COPD (74). It is not easy to diagnose depression in COPD patients because of the overlapping symptoms between COPD and depression. However, the six-item Hamilton

Depression Subscale (HAM-D-6) appears to be a useful screening tool (75). Pulmonary rehabilitation programs have also been described for COPD patients for co-morbid anxiety and depression. By means of progressive exercise, training of respiratory function, and psycho-education, patients obtained better exercise tolerance, less dyspnea, and better quality of life (76).

COPD and ANEMIA

Fatigue and dyspnea are the major symptoms of anemia, and these can be related to reduced oxygen carrying capacity of blood. Furthermore, this symptom complex in patients with COPD will inevitably contribute the morbidity and mortality associated with impaired quality of life and reduced exercise capacity. The prevalence of anemia in patients with COPD varies from 7.5% to 33%. Anemia of chronic disease (ACD) is probably the most common type of anemia associated with COPD. ACD is driven by COPD-mediated systemic inflammation anemia in COPD is associated with greater healthcare resource utilization, impaired quality of life, decreased survival, and a greater likelihood of hospitalization (77).

CONCLUSION

Nightly three % of the COPD patients have at least one comorbidity. It is well known that the number of the comorbidities has an inverse relation with the outcome of COPD. Some of the comorbidities are related with mortality in COPD. Lung Cancer and

cardiovascular diseases are the best known prognostic ones. Some of the comorbidities are known as an impactor of disease management and exacerbations. Diabetes mellitus is a best example of it. Osteoporosis and the imbalance of body composition have great impact on quality of life. Depression and anxiety are often overlooked and are well related with the rate of exacerbation and symptom management. Therefore, even though the evidence is not well established, the current guidelines recommend the active search of the common comorbidities in COPD.

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