

# Chronic Obstructive Pulmonary Disease and Comorbidities

## *KOPB i komorbiditeti*

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**SUMMARY** \_\_\_\_\_ COPD very often coexist with comorbidities, usually sharing the same risk factors and negatively influencing other diseases. COPD and comorbidities are caused and worsened by inflammatory and oxidative mechanisms with prevalence ranging from 20% to 81%. Cardiovascular diseases (CD) have the highest incidence and potentially the highest risk of death, taking into account other comorbidities. Common pathophysiological mechanisms are endothelial dysfunction, pro-coagulant and pro-inflammatory conditions and obesity. The most common cardiovascular comorbidities are coronary heart disease, heart failure, arterial hypertension and peripheral vascular disease. Reduction in FEV1 increases the rate of coronary events and mortality. Timely diagnosis of CD in COPD patients is necessary, as well as making diagnosis of COPD in patients with CD. Invasive and noninvasive assessment of CHD is often difficult in COPD patients because they exhibit respiratory limitations during exercise and stress. Arterial hypertension and peripheral vascular disease occur frequently in COPD patients due to endothelial dysfunction. Pulmonary function is negatively correlated with blood pressure in a healthy population and COPD patients. The prevalence of heart rhythm disorders is 12%–14% in COPD patients and atrial fibrillation is the most common among them. Inhaled long-acting beta-2-agonists have an acceptable safety profile in cardiovascular patients. Osteoporosis is the major COPD comorbidity, which is often under-diagnosed and correlated with poor overall health status and COPD prognosis. Vitamin D deficiency relates to COPD and its comorbidities reducing innate and acquired immunity. Lung cancer, metabolic syndrome, obesity, malnutrition, depression, obstructive sleep apnea, muscle dysfunction and anemia are COPD comorbidities as well.

**KEY WORDS:** COPD, comorbidity, cardiovascular diseases, osteoporosis, vitamin D deficiency, obesity, lung cancer, depression

**SAŽETAK** \_\_\_\_\_ KOPB je često udružen s komorbiditetima s kojima dijeli iste rizične faktore i ima negativan utjecaj na druge bolesti. KOPB i njegove komorbiditete uzrokuje i pogoršava upala i mehanizam oksidacije u rasponu od 20 do 81 %. Najveću incidenciju i najveći smrtni rizik nose kardiovaskularne bolesti. Uobičajeni patofiziološki mehanizam je endotelna disfunkcija, prokoagulantno i proinflamatorno stanje te pretilost. Najčešći kardiovaskularni komorbiditeti su koronarna bolest srca, srčano zatajivanje, arterijska hipertenzija i periferna vaskularna bolest. Smanjenje FEV1 povećava učestalost koronarnih događaja i mortalitet. U bolesnika s KOPB-om neophodna je pravovremena dijagnoza kardiovaskularne bolesti kao i dijagnoza KOPB-a u kardiovaskularnih bolesnika. Invazivna i neinvazivna procjena kroničkoga srčanog zatajivanja je otežana u bolesnika s KOPB-om jer bolesnik može imati ograničenja respiracije za vrijeme vježbanja i stresa. Arterijska hipertenzija i periferna vaskularna bolest su česte u bolesnika s KOPB-om zbog endotelne disfunkcije. Funkcija pluća je negativno povezana s krvnim tlakom i u zdravoj populaciji i kod bolesnika s KOPB-om. U bolesnika s KOPB-om prevalencija poremećaja srčanog ritma iznosi 12 do 14 %, a među njima je najčešća fibrilacija atrijske. Inhalacija dugodjelujućeg beta 2 agonista ima prihvatljivu podnošljivost kod kardiovaskularnih bolesnika. Osteoporoza je glavni komorbiditet kod bolesnika s KOPB-om, ali je često nedovoljno dijagnosticirana i povezana s cjelokupno lošim zdravstvenim statusom i prognozom KOPB-a. Nedostatak vitamina D povezan je s KOPB-om i komorbiditetima koji smanjuju urođeni i stečeni imunitet. Karcinom pluća, metabolički sindrom, pretilost, malnutricija, depresija, opstruktivna apneja za vrijeme spavanja, disfunkcija mišića i anemija također su komorbiditeti KOPB-a.

**KLJUČNE RIJEČI:** KOPB, komorbiditeti, kardiovaskularne bolesti, osteoporoza, manjak vitamina D, debljina, rak pluća, depresija



COPD very often coexist with other diseases, and comorbidities in COPD are the rule, rather than exception. These conditions usually share the same risk factors (smoking cigarettes, indoor and outdoor air pollution, etc.) and may have a negative influence to other disease. The prevalence of COPD comorbidities in COPD patients ranges from 20% to 81% (1, 2). The importance of the relationship between COPD and comorbidities is well recognized nowadays and reported in Chapter 6 in the Global Initiative for COPD (2).

Comorbid diseases are present in all GOLD stages, influenced and worsened not only by the inflammatory and oxidative mechanism in COPD, but also by COPD sequelae (impaired physical activity, active smoking, anxiety and depression, etc.). Some comorbid diseases with symptoms suggesting COPD may be overlooked (e.g. heart failure, lung cancer, infection, depression). Therefore, the treatment approach to a COPD patient must include not only the treatment of comorbid disease but the disease identification as well.

## Pathogenic mechanisms in COPD comorbidities

COPD and comorbidities are caused and worsened by the inflammatory mechanism and imbalance in oxidative/anti-oxidative mechanisms. The chronic inflammation in lungs is caused by pro-inflammatory mediators and oxidative stress. The pro-inflammatory mediators are produced and secreted not only by inflammatory cells recruited from the circulation (alveolar macrophages, neutrophils, T-lymphocytes), but also by structural cells (epithelial cells, endothelial cells, fibroblasts) (3). Oxidative stress is increased in these patients and may activate the nuclear factor- $\kappa$ B, impair anti-proteases' roles, autoantibodies production, resistance to corticosteroids and DNA damage. Systemic inflammation contributes and worsens comorbidities (cardiovascular diseases, osteoporosis, diabetes, etc.). Therefore, the treatment of lung inflammation by inhaled or systemic anti-inflammatory therapies also has favorable effects on COPD and its comorbidities.

## Cardiovascular diseases

Cardiovascular associated diseases have the highest incidence and potentially the highest risk of death, taking into account other comorbidities. The reason is common pathophysiological mechanisms caused by endothelial dysfunction (4), pro-coagulant (5) and pro-inflammatory conditions, and obesity with high Body Mass Index (BMI) (6), but also common risk factors such as smoking. The most common cardiovascular comorbidities in COPD patients: coronary heart disease, heart failure, arterial hypertension and peripheral vascular disease. Mortality in COPD due to cardiovascular cause occurs in 12% to 37% in various studies (7).

### Coronary heart disease

Reduction in FEV<sub>1</sub> by 10% increases the rate of non-fatal coronary events by 20% and mortality by 28% (8). The presence of three-vessel disease and lower FEV<sub>1</sub> were independently associated with survival rates from COPD (9). Symptoms related to myocardial ischemia (pressure and chest pain, dyspnea on exertion) may also be present in COPD patients. In addition, the triggers for the manifestation and symptoms exacerbation are the same (physical effort, stress, exposure to cold). McAlister studied the history of chest pain in patients hospitalized for COPD exacerbation and noted that 51% had chest pain and 40% had pain whose characteristics were highly suspicious for myocardial ischemia (10).

Therefore, timely diagnosis of CD in patients with COPD is necessary, as well as diagnosing COPD in patients with CD. However, noninvasive assessment of coronary heart disease is difficult in COPD patients because they often

exhibit respiratory limitations during exercise. Therefore, stress tests often cannot be performed or cannot show beneficial results, and a pharmacological stress test can lead to pronounced bronchospasm. Echocardiography often cannot validly assess the condition in patients with COPD due to hyperinflation and technical limitations (11). More recently, scanning (MSCT) coronary angiography has been used to assess stable CD, and coronary angiography has a medical justification for performing it more frequently in these patients. Some studies have shown that arterial stiffness and rigidity associated with COPD may be due in part to increased arterial calcification that also correlates with emphysema severity.

### Heart failure

COPD and heart failure (HF) are conditions that often coexist in the same patient, with a prevalence of COPD in 20% to 30% of patients with HF (12). COPD is one of three major comorbidities that have an effect on quality of life and outcome of patients with heart failure with reduced ejection fraction (13). Unrecognized HF was diagnosed in 20.5% of COPD patients treated in primary practice (14). In the ECLIPSE study, the prevalence of HF in patients with moderate to severe COPD was 7% (15).

In addition, COPD is a significant predictor of poor prognosis in patients with HF. Physical inactivity and metabolic syndrome are conditions that cause HF in the general population, and therefore contribute to HF in COPD patients. COPD is a predictor of mortality in HF, and FEV<sub>1</sub> is an independent predictor of all-cause death in patients hospitalized for HF (16, 17). Markers of myocardial injury are used not only to diagnose myocardial injury but also to indicate left ventricular dysfunction in finding the etiology differentiate dyspnea. NT pro-BNP is a biomarker associated with increased mortality in stable and acute heart disease, but also a predictor of mortality 30 days after hospitalization due to COPD exacerbation.

### Arterial hypertension

Arterial hypertension (AT) and peripheral vascular disease (PVD) occur frequently in COPD patients due to endothelial dysfunction caused by inflammatory mediators and oxidative stress. Pulmonary function is negatively correlated with blood pressure in a healthy population and in patients with COPD. The prevalence of heart rhythm disorders is 12% to 14% in patients with COPD, and atrial fibrillation (AF) is the most common among them. AF is more common in patients with a more severe form of the disease and more pronounced bronchial obstruction.

The management of patients with COPD and cardiovascular comorbidities is complex. Drug treatment strategy for patients with COPD and cardiovascular comorbidities is

based on COPD therapy consistent with disease severity, but also on cardio selective beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or antiplatelet agents. Long-acting beta-2-agonists have an acceptable safety profile in cardiovascular patients.

## COPD and osteoporosis

Osteoporosis is the major COPD comorbidity which is often under-diagnosed and correlated with poor overall health status and COPD prognosis. Several studies have examined the status of vitamin D in COPD patients. Forli et al. have reported the presence of severe deficiency (vitamin D concentrations were lower than 20 µg/L) in patients with the terminal stage of chronic lung disease who were awaiting transplantation (18).

Belgian authors clearly showed the positive correlation between vitamin D concentration and FEV<sub>1</sub>. Significantly higher vitamin D concentration was also observed in healthy smokers compared to COPD patients who are smokers (19). Vitamin D concentration decreases with COPD progression and this difference becomes higher. After classification of patients according to GOLD stage, a significant difference is noticeable already in GOLD 2 stage. Patients in stage IV had the lowest concentration of vitamin D. The results of an American study performed on more than 14,000 American citizens older than 20 years suggest that people with oxygen saturation over 88% have significantly higher blood vitamin D concentrations (20).

The causes of vitamin D deficiency in the general population and COPD patients have been studied in various studies. Some of the most important findings so far could be: insufficient sun exposure, decreased synthesis of vitamin D precursors in the skin, vitamin malabsorption in the gastrointestinal tract, obesity and type II diabetes, obesity, older age, deficient food intake, inadequate activation in the liver and sequestration in adipose tissue. These underlined causes dominate in COPD patients.

It is well known that bone formation and resorption are related to the close interaction of osteoblasts and osteoclasts. Osteoblasts constitutively express on their surface a ligand for a nuclear factor receptor activator κB (RANK-L). They differentiate into mature active osteoclasts when this ligand binds to its receptor on pre-osteoclast cells. Osteoblasts secrete osteoprotegerin that blocks the RANK/RANK-L interaction and regulates bone turnover. The imbalance between OPG and RANK-L increases osteoclast activity and it is thought to be one of the major mechanisms in the pathogenesis of osteoporosis. Systemic inflammation, corticosteroid use and lower vitamin D levels contribute to this imbalance. Therefore, the vitamin D supplementation with 700-800 IU/day is recommended for COPD patients

while ensuring adequate calcium intake (1000 mg/day). This supplementation should not start before determining the patient's vitamin D status (21).

How does vitamin D deficiency relate to COPD comorbidities? Vitamin D activates innate immunity and suppresses acquired immunity, stimulates the synthesis of antimicrobial peptides cathelicidin and beta-defensins. It thus limits the inflammation and infection, which are the first steps in COPD pathogenesis. Therefore, the vitamin also controls the systemic comorbidities of COPD: cardiovascular diseases, lung cancer, myopathy, diabetes and osteoporosis.

Vitamin D also has a positive effect on COPD comorbidities such as skeletal muscle weakness, cardiovascular disease and cancer. Conventional therapy cannot stop the COPD progression, so it is necessary to investigate the wider potential of the vitamin's pleiotropic effects and to define the optimal blood concentrations of 25 (OH) D.

## Lung cancer

COPD and lung cancer are strongly associated and coexist in a large number of patients. Smoking remains the main risk factor for both COPD and lung cancer.

Van Den Eeden and Friedman are the first authors who studied the relationship between FEV<sub>1</sub> and lung cancer among smokers and never-smokers (22). Proportional hazards models revealed a decreasing trend in risk of lung cancer incidence with increasing FEV<sub>1</sub> in current and former smokers. This negative relationship between FEV<sub>1</sub> and lung cancer was analyzed in meta-analysis published by Zhang X. et al. (23). De Torres et al. reported the incidence of 8.5 % in patients with lung cancer in COPD, with higher incidence (83.8%) in patients older than 64 years (24). Over half (51%) had at least one comorbid condition and 43% had chronic lung disease. Distinct comorbidity profiles are independent predictors of treatment and survival. Lung emphysema is an important independent risk factor for lung cancer (25).

Lung cancer should be treated as usual, regardless of the existence of COPD, and COPD should be treated according to actual guidelines. A multidisciplinary approach is the best way to choose the optimal management for patients with lung cancer and impaired lung function due to COPD.

## COPD and other comorbidities

Depression, metabolic syndrome and diabetes, obesity, malnutrition, depression, obstructive sleep apnea, skeletal muscle dysfunction and anemia are also COPD comorbidities. These diseases are caused by inflammatory mechanisms, and associated with poorer quality of life, worse prognosis and high risk for multi-morbidity.

They should be carefully examined and treated as usual, regardless of the existence of COPD, and COPD should be treated according to COPD guidelines with a multimodality care plan.

## Conclusion

COPD very often coexist with comorbidities, usually sharing the same risk factors and negative influencing to other

disease. The prevalence of COPD comorbidities ranges from 20% to 81% and most often they are cardiovascular diseases, osteoporosis, lung cancer, depression, metabolic syndrome, obesity, malnutrition, obstructive sleep apnea and anemia. They should be carefully examined and treated as usual, regardless of the existence of COPD, and COPD should be treated according to COPD guidelines.

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