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REVIEW ARTICLE

Comorbidities of COPD: Mechanisms and Treatment. Update 2023

Velin Stratev[1]* and Odd-Magne Fjeldstad[1]

[1]Department of pulmonary rehabilitation and lifestyle medicine, Cathinka Guldbergs Hospital, Norway

*velinstratev@gmail.com

Abstract:

Chronic obstructive pulmonary disease (COPD) is chronic disease that affects mostly the lungs but there is growing evidence that it is also a systemic condition associated with a number of accompanying diseases known as comorbidities. Chronic inflammation and oxidative stress are the highlight pathogenic processes that interrelate COPD and comorbidities with additional disease specific risk factors and mechanisms. Through complex interactions COPD increases the risk for certain comorbidities and they in turn have negative impact on health status and contribute to mortality in COPD patients. Treatment of comorbidities in terms of coexistence with COPD may require more specific personalized therapeutic approach. Here we review the pathogenic mechanisms which define COPD as a systemic disease; the most common comorbidities of COPD: cardiovascular disease, diabetes and metabolic syndrome, cachexia, osteoporosis, depression/anxiety and obstructive sleep apnea; the pathways which connect these diseases with COPD and the latest treatment approaches.

1. Introduction:

COPD is a chronic disabling condition which affects the lungs by airflow limitation and is a cause of death of millions of people worldwide, still holding the place of fourth leading cause of mortality[1, 2]. It was considered that COPD is more common in men but increasing evidence show that due to air pollution, indoor exposure and prevalence of smoking, nowadays COPD prevalence is almost equal among men and women[2]. Furthermore, COPD develops usually after the age of 45 years and with the increasing aging of the population the incidence is likely to increase in the future[3].

COPD patients very often have a variety of concomitant chronic conditions that can influence the prognosis or complicate the treatment[3]. Comorbidities contribute to the disease severity and are evenly distributed irrespective of the GOLD stage of obstruction, showed the results of the ECLIPSE study[4]. This was confirmed by recent study among nearly 8000 COPD patients with 5 years observation period, which showed that 9 in 10 patients had at least one, and 51.7% had more than three comorbidities. No gender difference was found in the number of comorbidities[3]. Moreover, the TORCH study[5] demonstrated that the mortality in COPD patients is most often due to the comorbidities than to COPD itself or other respiratory complications. Understanding the underlying mechanisms of comorbidities and their proper treatment may have beneficial impact on COPD natural course and may slow down the disease progression.

2. Pathogenic links between COPD and comorbidities.

The progressive airflow limitation in COPD is a result of two major pathological processes: remodeling and narrowing of the airways and destruction of lung parenchyma with damaging of the alveolar attachments as a result of emphysema. These pathological changes are due to chronic inflammatory process in the lung periphery which is increasing with age and disease progression[6-8]. However, in COPD patients, especially in advanced disease and during exacerbations, there is increased systemic inflammation measured by increased plasma concentrations of inflammatory mediators and acute-phase proteins[9]. In a large population based study the systemic inflammation measured by increased levels of CRP, fibrinogen and leucocyte count was associated with two to four fold increased risk of developing cardiovascular diseases, type 2 diabetes mellitus, lung cancer and pneumonia[10].

Numerous studies[11-13] have shown elevated levels of acute phase proteins in COPD patients: serum levels of CRP are increased during stable state and exacerbation; likewise, levels of serum amyloid A (SAA) are raised during exacerbation and are associated with the severity of the exacerbation. It is still not well established whether these inflammatory markers originate mainly from the lung ('spill-over' theory) or the comorbidities contribute to their raised levels and afterwards they affect the lungs.

Oxidative stress is another key feature in COPD pathogenesis. Oxidative stress occurs when there is increased burden of oxidants

(e.g. cigarette smoke) and/or decreased level of antioxidants in the plasma or in the lungs[14]. The burden of oxidants (reactive oxygen species) can originate from cigarette smoke and environmental/professional exposures or can be produced endogenously by a number of activated inflammatory cells like macrophages, neutrophils and epithelial cells of the airways[15].The excess of oxidants is counteracted by several antioxidant defense enzymes in the respiratory tract, such as catalase, glutathione and superoxide dismutase family. The extracellular antioxidants, especially the glutathione peroxidase family, are activated by cigarette smoke and oxidative stress[15]. A study published by our team[16] among 186 COPD patients and 103 matched controls reported significantly lower levels of superoxide dismutase and glutathione peroxidase in COPD patients with additional decrease during exacerbations. Oxidative stress leads to a number of harmful effects in the human body: protein, DNA and lipid damage[14], increased permeability of the airway epithelium[17], structural cell apoptosis[18], neutrophil sequestration in the lungs, mucus hypersecretion[19], muscle dysfunction[20] and inflammatory cytokines release from different lung cells[21]. The interactions between inflammation and oxidative stress lead to vicious cycle in COPD pathogenesis and have impact on development of comorbidities (figure 1).

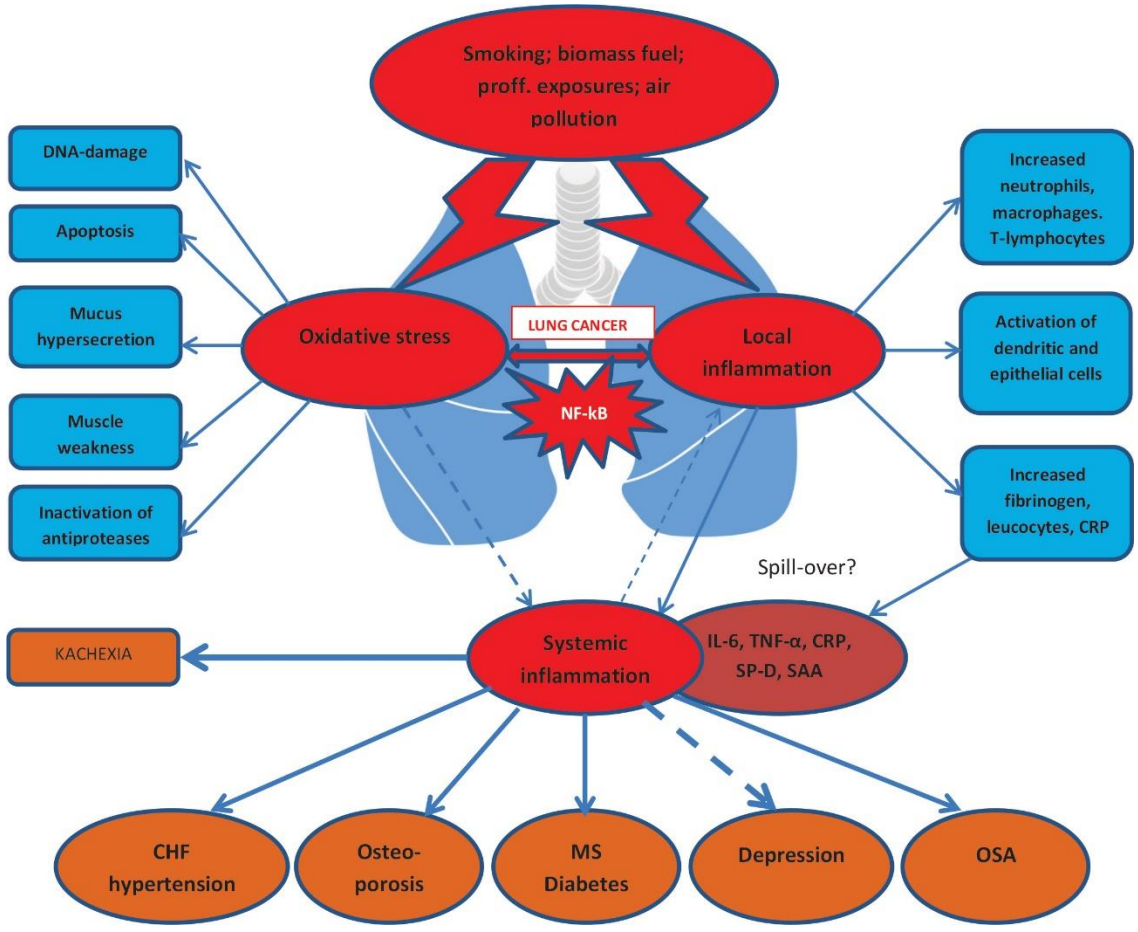

Figure 1. Proposed model of COPD pathogenesis and implication to increased burden of comorbidities[22].

3. COPD and cardiovascular diseases (CVD).

3.1. Interrelating mechanisms

Both COPD and CVD, especially hypertension and ischemic heart disease, are one of the most common diseases in the general population and their prevalence is increasing with age. Chronic systemic inflammation is a corner stone in the pathogenesis of CVD[23,24] and is involved in the occurrence, development and rupture of atherosclerotic plaques[25], leading to coronary heart disease and heart failure[26]. Furthermore, a study on the role of monocytes in the pathogenesis of atherosclerosis shows that inflammation is involved in the entire process, from the onset of injury to the beginning of clinical symptoms[27]. Other studies have shown that inflammation is also involved in the occurrence of arrhythmia. During systemic inflammation, the incidence of atrial fibrillation increases, especially in sepsis, and plasma C-reactive protein (CRP) levels increase before the start of atrial fibrillation[28].

Along with inflammation, oxidative stress is another pathogenic feature of COPD that plays an important role also in the development of CVD[29]. Oxidative stress is almost universal in cardiovascular diseases and is involved in myocardial ischemia-reperfusion injury, heart failure, atherosclerosis, atrial fibrillation and hypertension[28]. Cardiovascular events are one of the leading causes of hospitalization in patients with COPD and contribute significantly to the cost burden of the disease. Chronic inflammation and oxidative stress associated with COPD may be the mechanisms linking COPD with an increased risk of CVD[29].

Another common feature in the pathogenesis of both COPD and CVD is endothelial dysfunction (ED). The endothelium forms a continuous monolayer and thereby is a regulated barrier that separates the intravascular blood compartment from surrounding tissues. ED is classically defined as impaired NO-mediated vascular relaxation[30]. Recent studies have shown that the microvascular barrier is impaired in patients with COPD and that the level of impairment is correlated with the severity of airway obstruction[31,32]. This could be credited to the disruption of endothelial tight junctions observed in patients with COPD, even in the absence of cigarette smoking[33,34]. In an interesting study[35], ED in patients with COPD is shown to be in an intermediate position between healthy patients and patients suffering from coronary artery disease. In a murine model of atherosclerosis, increased oxidative stress was hypothesized to link ED with COPD pathogenesis, especially with regard to the development of emphysema[36]. As stated above, patients with COPD have an increased risk of suffering with CVD. This is of particular relevance, since ED is a common feature in both COPD and the development of atherosclerosis, which in turn can cause CVD such as myocardial infarction and stroke[30].

3.2. Treatment of COPD patients with cardio-vascular diseases.

Primary prevention for reducing the individual risk includes modifiable risk factors such as

smoking, hypertension, obesity, healthy diet and physical activity. Secondary prevention of IHD consists of anti-aggregation therapy (aspirin and clopidogrel) which is provided in the same modality in patient with or without COPD[30].

• Beta-blockers

The use of beta-blockers in COPD patients has been controversial for long time because of their opposing pharmacological effects. The 2016 European Society of Cardiology guidelines recommended the use of beta-blockers in patients with COPD and CVD[37]. Beta blockers are underused in COPD patients with CVD due to concerns about potential side effects, resulting in poor patient outcomes[38]. A recent study on the effect of beta-blockers on the long-term prognosis of Asian COPD patients with heart failure showed that beta-blockers can reduce all-cause mortality in these patients and active use of beta-blockers in COPD patients is advocated[39]. Results of a recent large meta-analysis[40] showed that beta blockers are safe and reduce all-cause and in-hospital mortality in patients with COPD, and selective beta-blockers may even reduce the acute incidence of COPD. They do not counteract the effect of bronchodilators and can be beneficial if there is an increased heart rate caused by bronchodilators. Therefore, the use of beta-blockers should not be restricted in patients with COPD and heart disease.

• Statins

Statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductases, which catalyze the rate-limiting step in cholesterol biosynthesis[41]. Statins were reported to have anti-inflammatory and antioxidant effects in addition to their lipid-lowering properties[42]. Due to these pleiotropic effects, statins have been suggested to have beneficial effects in patients with COPD[43]. Still there are some controversies about the effects of the statins on COPD patients. A recent randomized study stated that one year of treatment with simvastatin at 40 mg per day decreased the risk of exacerbations[44], while the Prospective Randomized Placebo Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE), showed that simvastatin did not have any preventive effect on COPD exacerbations[45]. Possible discrepancy reason can be the differences in studied population.

A recent real case-control study among nearly 27 000 COPD patients and 107 500 matched controls in South Korea[46] showed that statin use was not associated with the occurrence of COPD in the adult population. However, statin use was associated with a reduced probability of exacerbations in participants with COPD, with a greater risk reduction with lipophilic statin use. Statins also reduce the risk of pulmonary hypertension in COPD, with higher daily doses and longer lasting benefits[47]. With all these data available statins can be considered beneficial treatment for COPD patients with concomitant CVD.

• Renin-angiotensin-aldosterone system inhibitors

The renin-angiotensin-aldosterone system (RAAS) is a blood pressure regulating system synthesized by the kidneys in the body,

causing vascular smooth muscle contraction and water and sodium retention, resulting in a blood pressure boosting effect. Renin-angiotensin-aldosterone system inhibitors include angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs). There is relatively few data of the effect of this group of medicines on COPD patients. A Multi-Ethnic Study of Atherosclerosis Lung Study found that the use of ACEI or ARB can delay the development of emphysema, especially in smokers, and the efficacy is dose-related[48]. The most common side effect of ACEIs is cough, usually dry or irritating, occurring in approximately 5–20% of patients [49]. Studies have also shown that the use of ARBS drugs in COPD patients has a lower risk of exacerbation, pneumonia, and mortality compared with ACEI drugs[50]. So angiotensin II antagonists may be a better choice when treatment is needed.

4. Diabetes mellitus (DM) and metabolic syndrome (MS) in COPD patients.

4.1. Diabetes mellitus

Type 2 diabetes (T2D) is a well-established leading comorbidity in COPD[51,52]. A population-based retrospective study from Italy[51] demonstrated a higher prevalence of T2D in COPD patients (18.7%) compared to the general population (10.5%) and women with COPD were significantly more likely to develop T2D compared to women without COPD. Another population based study in Taiwan[52] showed that T2D was present in 16% of patients with COPD, and within a 10-year follow-up period, T2D was newly diagnosed in 19% of COPD patients, showing increased prevalence and incidence of the disease. Furthermore, the association between diabetes and pulmonary disease did not extend to asthma, according to one prospective cohort study[53], suggesting a specific inter-reaction between COPD and diabetes. The common mechanisms linking the two diseases are chronic inflammation and oxidative stress[54].

Chronic inflammation is observed in both T1D and T2D and the majority of the patients with obstructive lung diseases have significantly elevated abdominal adipose tissue[55], and obesity is common in the early stages of COPD[56]. Adipose tissue inflammation is also present in individuals with mild-to-moderate COPD[56]. Furthermore, patients with COPD have higher levels of plasma CRP compared to control subjects, and CRP levels positively correlate with macrophage infiltration of adipose tissue upon biopsy[57]. Various adipokines, including adiponectin, are associated with worse outcomes in COPD[58].

On the other hand, oxidative stress also has been shown to be elevated in COPD patients. Similarly, T2D subjects show increased ROS generation and markers of oxidative stress, as well as decreased antioxidant levels compared to non-diabetics[59]. At the cellular level, oxidative stress negatively regulates insulin signaling via interactions with serine/threonine kinases, contributing to insulin resistance. Systemically, oxidative stress decreases pancreatic β-cell insulin secretion and subsequently impairs insulin signaling in peripheral tissues[60].

4.2. Metabolic syndrome (MS)

Metabolic syndrome is a combination of risk factors which are associated with the

development of atherosclerotic CVD and diabetes. These risk factors include central obesity, hypertension, dyslipidemia and raised blood glucose[61]. Approximately 40%-50% of the general population over the age of 60 years meets the criteria for MS showed NHANES III[62]. According to the International Diabetes Confederation, neither COPD nor cigarette smoking was included as fundamental risk factors of MS. However, an increased prevalence of MS is observed in COPD patients compared to the general population (21–62%)[63–67]. In particular, patients with earlier stages of COPD exhibit the highest prevalence of MS[64,65]. Oxidative stress is shown to play a key role in both COPD and MS. Oxidative stress is present in patients with MS and diabetes mainly at the expense of increased burden of ROS, decreased antioxidant defense and accelerated lipid peroxidation[66]. A study conducted by our team found lower levels of antioxidant enzymes (superoxide-dismutase and glutathione-peroxidase) in COPD patients that present MS, compared to those without the syndrome. The enzyme levels were negatively associated with the indices of overall and abdominal obesity[67].

4.3. Treatment

Excessive use of corticosteroids can cause insulin resistance, MS and diabetes and that is why long-term oral corticosteroid treatment in COPD patients should be avoided. However, inhaled steroids do not affect significantly the insulin resistance[64].

Metformin, a biguanide antidiabetic drug, is recommended as the first-line therapy for T2D due to its efficacy, relative safety, and beneficial effects of reducing HbA1C levels and weight, in addition to its general tolerability[68]. A recent systematic review showed that metformin may improve health status, symptoms, hospitalizations, and mortality in patients with COPD and T2D[69]. In a prospective open-label trial of patients with moderate and severe COPD who also had T2D, the use of metformin showed improvement in symptoms and transitional dyspnea index scores compared to the baseline but lung function tests were unchanged in this study[70]. On the other hand, a recent study in Taiwan suggested that metformin use in patients with T2D and COPD was associated with higher risks of pneumonia, hospitalization for COPD, and invasive mechanical ventilation[71]. However, a recent observational study demonstrated that metformin use was associated with lesser emphysema progression over time in humans, possibly due to metformin protecting against smoke-induced lung, renal, and muscle injury, mitochondrial dysfunction, and ER stress in mice[72]. Hence, the data on the effect of Metformin on COPD alone are still controversial but the use of it in patients with COPD and T2D as comorbidity is a standard treatment.

5. Cachexia in COPD

COPD cachexia is still diagnosed using cross-sectional anthropometric measurements that are highly available in different patient settings. Low body mass index (BMI) and low fat-free mass index (FFMI) have long been recognized as risk factors for increased mortality in patients with COPD[73,74]. Nevertheless, patients with COPD who are

experiencing weight loss, even among those who are overweight or obese, have a higher risk of death compared to those with stable weight[75]. Classically underweight patients are easy to diagnose but it is important to recognize that cachexia can develop in patients with COPD within the whole BMI spectrum[75]. This is why, cross-sectional measurements of BMI and FFMI are often inferior to longitudinal measures of loss of body weight and fat-free mass (FFM) for predicting mortality[76]. Measurement of FFM typically requires techniques such as dual x-ray absorptiometry (DXA) and bioelectrical impedance (BIA), which are often used in research but not generally accessible in pulmonary clinics.

5.1. Pathogenesis of cachexia

Chronic inflammation and oxidative stress are well-known triggers of muscle wasting and dysfunction in cachexia[73] that also stimulate an imbalance in protein and myonuclear turnover, leading to weight and muscle loss in cachectic patients with COPD[77]. The degradation of proteins is increased with a compensatory increase in protein synthesis[78]. In addition, cachectic patients with COPD have a more distinct loss of oxidative muscle capacity than patients without cachexia[77]. Furthermore, an association was observed between reduced serum leptin levels, increased serum adiponectin levels, and increased resting energy consumption in patients with COPD, though this analysis was not limited to patients with cachexia[79]. More recent research[80] has investigated other adipokines, including adiponectin and zinc alpha 2-glycoprotein (ZAG), and reported that serum levels of both adipokines were significantly higher in patients with COPD with cachexia compared to those without cachexia. Adiponectin and ZAG were also associated with weight loss. Other proposed COPD cachexia triggers and mechanisms include altered brain responses to food stimuli, altered gut integrity, and reduced splanchnic extraction[80].

5.2 Treatment approaches

• Nutritional therapy

For treatment of cachexia, oral nutritional supplement could supplement the diet when nutrient requirements cannot be satisfied through habitual dietary intake or when a temporary boost is needed. A recent Cochrane review[81] on supplementation with medical nutrition in patients with COPD showed moderate-quality evidence that nutritional supplementation augments weight gain among patients with COPD, especially if malnourished. With high-quality proteins to stimulate the regenerative response of muscles, these supplements might need to be enriched with additional vitamins, minerals, and trace elements to supply nutrient deficiencies.

Most studies of nutritional interventions for COPD cachexia have focused on short-term efficacy (1–3 months) in clinically stable disease or as an add on to pulmonary rehabilitation, only a few studies have investigated the benefits of nutritional supplementation during the maintenance phase after rehabilitation. The NUTRAIN trial and the INTERCOM trial[82,83] showed that during the 12- to 24-month maintenance

phase after rehabilitation, nutritional interventions did not seem to enhance the long-term outcome of exercise training on physical capacity but did improve plasma levels of the supplemented nutrients, total body weight, physical activity, and generic health status.

• Exercise training

Exercise training is recommended in many diseases associated with skeletal muscle wasting. Exercise should be routinely offered to patients with COPD as part of PR, supported by a significant evidence base in both stable and acute COPD studies. The established benefits of PR in general COPD populations include improved exercise capacity, symptom burden, and health status, and, in the post-acute setting, a lower risk of hospital admission[84]. Individual responses to exercise training in COPD are variable and cannot be readily predicted by any clinical phenotype[85]. Some, but not all, cachectic patients with COPD retain the capacity to improve functional exercise performance with exercise training.

• Pharmacological treatment

✓ **Ghrelin** is a 28-amino acid peptide hormone and has received specific attention as a pharmacologic agent in COPD cachexia. Studies[86-88] show that ghrelin has potential benefits in reversing the breakdown of proteins and weight loss in catabolic states like cancer cachexia and it is thought to affect several vital pathways in the regulation of appetite and body composition. The role in reversing COPD cachexia is still controversial but is a novel potential therapeutic option.

✓ **Megestrol acetate** – Another potentially promising pharmacological agent for COPD cachexia is megestrol acetate, a progestational appetite stimulant with anti-inflammatory effects[89]. In a controlled study, including 145 patients with COPD, megestrol acetate administration improved appetite, body weight, and body image but not exercise tolerance as measured by 6MWD test.

6. Osteoporosis and COPD

Osteoporosis is a systemic bone disease characterized by low bone density and microstructure changes that increase the risk of fractures[90,91]. Because of the reduction of exercise and long-term bed, osteoporosis-related fractures are associated with several adverse health outcomes in COPD, including deteriorated lung function, poor quality of life, increased hospitalization, and mortality rates. A recent review[92] quantitatively analyzed the current evidence on the prevalence and risk factors for osteoporosis in COPD in 58 studies with 8753 participants with COPD and demonstrated a pooled global prevalence of osteoporosis in 38% of COPD patients. The prevalence of osteoporosis in COPD is 2-fold to 5-fold higher than in age-matched healthy control subjects[92].

6.1. Common linking risk factors and mechanisms

The mechanisms of osteoporosis in COPD patients are mostly unknown. However, clinical evidence indicates that osteoporosis and other systemic comorbidities of COPD are associated with general risk factors and disease-specific risk factors.

Smoking is a risk factor for both diseases and nicotine directly or indirectly stimulates the activity of osteoclasts and increases the concentration of blood calcium and urine calcium, leading to osteoporosis[93]. Nicotine also induces apoptosis in human osteoblasts[94]. Furthermore, nicotine reduces estrogen synthesis, promotes estrogen dissociation and metabolism, and makes calcium regulated hormones dysfunctional, thus affecting bone mineral density (BMD)[95]. Another risk factor is reduced physical activity in COPD patients. Exercise plays an important role in regulating bone growth and development as well as bone metabolism[96,97]. Patients with COPD often are not very active due to dyspnea, respiratory failure and shortness of breath after activity in the later stages. Significantly reduced exercise ability is the most important cause of bone loss. Body mass index (BMI) is an important physiological index used to judge the nutritional status and is closely related to BMD. Many studies have confirmed that low BMI and the presence of sarcopenia are associated with osteoporosis and fractures in COPD[98–100]. Low BMI and muscle wasting are frequently observed in severe COPD[100].

The key pathogenic mechanism linking COPD and osteoporosis is chronic systemic inflammation. As stated above, systemic inflammation in COPD may be the direct consequence of a systemic "spill-over" of the ongoing pulmonary inflammation[101]. Neutrophils, macrophages, T lymphocytes, and other inflammatory cells are involved in the pathogenesis of COPD. Many cytokines induced by inflammatory cells are closely related to the occurrence of osteoporosis. They mainly include IL-6[102], IL-17[103], TNF-α[104] and MMP[105]. These cytokines are well known inducers of osteoclasts both in vitro and in vivo and are considered to be involved in the pathogenesis of both primary and secondary osteoporosis[104].

Osteoporosis caused by long-term use of glucocorticoid is the most common secondary osteoporosis. Its incidence is second only to postmenopausal osteoporosis and senile osteoporosis[106]. Glucocorticoids are currently an effective treatment for COPD, but their use is associated with a reduction in BMD and an increased risk of fracture[107]. Inhaled corticosteroids are also associated with moderate to significantly increased risk for fractures showed a meta-analysis which included 16 randomized controlled studies and seven observational studies with more than 86,000 COPD patients[108].

Vitamin D is an essential part of human hormone metabolism. It stabilizes the concentration of serum calcium phosphate. Low blood calcium concentration induces parathyroid hormone secretion, which is released to the kidney and affects the absorption and storage of calcium and phosphorus. According to the Endocrine Society Clinical Practice Guideline, vitamin D deficiency and insufficiency are defined as 25-hydroxy Vitamin D levels below 20 ng/ml and 20–30 ng/ml, respectively[109]. Vitamin D deficiency is consistently reported to be more common in patients with COPD than in healthy controls and increases with disease severity[110–112].

6.2 Treatment of osteoporosis

• Pulmonary rehabilitation

Rehabilitation should be considered a key component of the comprehensive bone health treatment framework for COPD patients. The International Osteoporosis Foundation supports the effects of weight bearing, progressive resistance exercise, strength training and balance training in both the prevention and treatment of osteoporosis[113]. On the other hand, a personalized exercise approach should be considered in COPD patients, which might present several barriers to standard programs usually proposed for the general population[114].

• Vitamin D and calcium supplementation

Vitamin D plays a crucial role in calcium homeostasis, immune regulation and inflammatory response and is a cornerstone of osteoporosis treatment[115]. As stated above, studies has shown that COPD patients had an increased risk of vitamin D deficiency compared to the age-matched population[83]. According to the National Osteoporosis Foundation, the International Osteoporosis Foundation, and the American Geriatric Society, a minimum of 30 ng/mL of vitamin D serum levels is needed to reduce the risk of falls and fragility fractures[116,117]. Therefore, vitamin D might have a key role in a comprehensive rehabilitation approach to COPD-related disability targeting physical performance and pulmonary function[118]. In addition, vitamin D and calcium supplementation are very beneficial pharmacological treatment in COPD patients with osteoporosis and should be considered a milestone of the general therapeutic approach to osteoporosis[119,120].

• Other pharmacological treatment

Pharmacological treatment is a cornerstone in the therapeutic management of osteoporosis for prevention and treatment in patients at higher risk of fragility fracture[121]. However, due to the lack of specific evidence in COPD patients, the main recommendation follows general practice guidelines for the treatment of primary osteoporosis[122]. Approved medications for the treatment of osteoporosis include anti-resorptive drugs such as bisphosphonates, denosumab, and the anabolic agent teriparatide[123].

7. Anxiety and depression in COPD patients

Mental health diseases are leading cause of increased disability and worsened quality of life in elderly patients. Mood disturbances, especially depression, anxiety and dysthymia are common in COPD patients[124]. The frequency of depression varies greatly among patients with stable COPD in a primary care setting ranging, from 10% to 57%, while the prevalence of anxiety varies widely, between 7% and 50% [125]. The variations depend on the studied population and used methodology.

The prevalence of depression was also consistently elevated in patients with COPD and patients with severe COPD were twice as likely to develop depression compared with patients with mild COPD[127].

7.1 Pathogenic linking mechanisms

The mechanism of depression and anxiety in COPD is still not completely understood, as

the relationship is complex[125]. The biological mechanism between COPD and depression is still unknown. One possible suspected mechanism relating depression and COPD is the "overspill" theory, where it is suspected that inflammatory markers spill over into the general circulation causing systemic inflammation. In support of that, markers such as sTNFR-1 (soluble tumor necrosis factor alpha receptor-1) have shown a strong association with depression rates in patients with COPD[128].

Another interrelating mechanism is hypoxia which develops in severe COPD and during exacerbations. A proposed mechanism for the neurological and psychiatric changes is the decreased level of oxygen in the periventricular and subcortical regions of the brain. This leads to damage in the white matter and vascular endothelium - changes similar to those observed on MRI in patients with depression[106]. Risk factors for developing depression are shown on table 1.

Strong associations	*Mixed or weak associations*
Severe dyspnea	FEV1
Quality of life	Low BMI
Long-term oxygen treatment	Significant comorbidity
Exacerbations	Age
Fixed airflow limitation	Gender
Living alone	Social status
Non-supportive family	Smoking

Table 1. Risk factors for depression

7.2 Treatment of anxiety and depression

Managing anxiety and depression should be a multidisciplinary approach to provide the most appropriate form of therapy to COPD patients. Communication and obtaining a clear past medical history are essential in choosing the necessary treatment intervention[129]. Anxiety and depression in COPD patients can be managed pharmacologically and non-pharmacologically in order to attain a holistic approach[125].

• **Cognitive-behavioral therapy (CBT)**

The NICE guidelines recommend the usage of low-intensity psychological interventions (self-support programs) and high-intensity psychological interventions (individual or group cognitive-behavioral therapy) depending on the severity of the mental symptoms[110]. Studies have found that a single two-hour session of CBT can reduce depressive symptoms in mild depressed COPD patient[111]. A recent meta-analysis[112] included 16 randomized controlled trials and

found significant improvements in anxiety, depression, quality of life, and emergency room visits in COPD patients treated with CBT. However, fatigue, exercise capacity, self-efficacy, and sleep quality were not impacted.

• Pharmacological treatment

The pharmacologic options for treating depression and anxiety in COPD patients are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressants, norepinephrine, and dopamine reuptake inhibitors, and melatonergic antidepressants[133]. All antidepressants have similar efficacy and have little effect on lung ventilation, with some precautions for certain classes like tricyclic antidepressants and mirtazapine in COPD patients with hypercapnia[134]. In a few randomized, placebo-controlled studies, sertraline, fluoxetine, citalopram, and paroxetine caused improvements in quality of life, dyspnea, and fatigue[135]. The use of these medications in older patients must be cautious because in some retrospective analysis, the use of SSRI/SNRI in older adults was associated with higher rates of hospitalization for COPD or pneumonia, COPD or pneumonia-related and all-cause mortality [136].

8. COPD and obstructive sleep apnea (OSA)

Obstructive sleep apnea is characterized by a complete cessation (apnea) or significant decrease (hypopnea) in airflow during sleep, caused by recurrent episodes of upper-airway collapse, leading to nocturnal oxyhemoglobin desaturations and arousals from rest[137]. OSA is a highly prevalent disorder in the adult population affecting close to a billion adults between 30 and 69 years old[138]. Both OSA and COPD are common, but epidemiologic research has not convincingly demonstrated co-occurrence beyond what is expected based on their prevalence together[139]. The association of COPD and OSA is known as the COPD–OSA "overlap" syndrome (OS) and is linked with a poor prognosis.

8.1 Linking pathophysiological mechanisms.

COPD can affect directly the sleeping process by reduced sleep quality and oxygen desaturation but there are also some predisposing factors for OSA: rostral fluid shift, smoking, skeletal muscle weakness and some medications (corticosteroids)[140]. It is also widely accepted that COPD and OSA share common pathophysiological mechanisms which include hypoxia and chronic inflammation[140,41]. The levels of a number of pro-inflammatory cytokines and acute-phase proteins are elevated in both conditions, such as TNF-α and CRP, which contributes to increased systemic inflammation and the development of cardiovascular comorbidities[141].

While some of the pathophysiologic changes that occur in COPD are protective against OSA, other physiologic changes increase OSA risk. Considering protective factors, tracheal traction that occurs with hyperinflation, results in an inverse relationship between the amount of emphysema seen on CT of the chest and the AHI among patients referred for sleep testing[142]. On the other hand, the weight loss

from pulmonary cachexia and decreased rapid eye movement (REM) sleep seen in patients with COPD may protect against OSA[143].

The risk of cardiovascular events and death is higher in patients with OS than in patients with OSA or COPD alone[144]. Patients with OS also have a higher burden of risk factors, such as hypertension, diabetes, obesity, atrial fibrillation, peripheral vascular disease, and alcohol use when compared to patients with COPD alone[143,145].

8.2 Treatment of the overlap syndrome

In patients with COPD-OSA overlap syndrome the gold standard of treatment is CPAP treatment. Observational studies have demonstrated that patients with overlap syndrome experience improvements in spirometry, pulmonary artery pressures, blood gas parameters, and sleep architecture within three months of starting CPAP[146]. Additionally, CPAP adherence was independently associated with decreased mortality risk in 227 patients with OS[147].

It is still unknown whether bi-level PAP (BPAP) or CPAP should be used, though one pilot randomized controlled trial of 32 patients with OS and chronic hypercapnia showed more effective normalization of hypercapnia over three months but no difference in lung function, cognitive function, or quality of life[148]. Recognizing concomitant OSA in COPD patients is very important for choosing the best treatment option. Further studies of the effect of different PAP modalities in the treatment of OS are needed.

Conclusion

There is rising amount of evidence that COPD is not just a lung condition but also a systemic disease promoting and enhancing certain comorbidities which occur much more often because of the shared pathogenic mechanisms and risk factors. Still much is unknown about the intimate relationships and of identifying the right treatment targets which can be beneficial for treatment of COPD as a systemic disease. There is an urgent need for new therapies in this area. Some promising results come from immunomodulatory therapies targeting p 38 MAPK (mitogen-activated protein kinase), inhibitors of PI3 (Phosphoinositide 3-kinases) and mTOR (mammalian target of rapamycin) which are highly activated in COPD patients and regulate cell proliferation and apoptosis in the body thus having crucial role in chronic diseases[149]. Effective treatment of COPD as a systemic disease remains a goal for the future.

Corresponding author:
Velin Stratev
Department of pulmonary rehabilitation and lifestyle medicine, Cathinka Guldbergs Hospital, Norway
Email: velinstratev@gmail.com

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