# Comorbidities: Assessment and Treatment

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## Introduction

COPD is an umbrella term that is associated with several systemic manifestation, lung involvement, and comorbidities [1, 2]. Currently, the description of comorbidity is complicated and has three different domains: "(1) the coexistence of one or more diseases with no other causation, (2) coexistence of diseases that share common risk factors and pathogenic pathways, (3) coexistence of diseases that are complicated by the interaction with the lung and systemic manifestation of COPD" [3]. In a very recent study, BODE Investigator Group suggested that COPD is interlinked with several comorbidities larger than non-COPD controls indicating common pathobiological process [4]. The importance of comorbidities is their impact on clinical outcomes of a patient life. COPD is a life-threatening and disabling disease and comorbidities cause additional impact revealing impairment in quality of life and increasing mortality [3].

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COPD patients have higher number of comorbidities (3.7) than controls (1.8). Studies showed that 94% of COPD patients had at least one comorbidity and up to 46% had three or more comorbidities [3]. Comorbidities have significant impact on health status, health care utilization, readmission, and mortality [1, 5, 6]. The National Health and Nutrition Examination Survey (NHANES I) study showed that each increase in comorbidities is associated with 43% higher chance of worse self-rated quality of life [7]. They increase the use of health care resources, the risk of readmission and mortality. Gastroesophageal reflux disease (GERD), depression, anxiety, cardiovascular disease, and pulmonary embolism are associated with exacerbations [6, 8]. Comorbidities have significant impact of clinical outcomes of exacerbations, hospitalization numbers, and the length of stay [6, 9, 10]. Studies showed that the presence of three or more comorbidities was a better predictor of impaired health status than any other demographic or clinical variable [3]. 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 increase economic burden in COPD. The direct costs have escalated from 18 billion dollars in 2002 to 29.5 billons in 2010, the largest part consisting of hospital expenses [3]. Most of the annual direct costs of COPD are associated with comorbidities [3]. According to a recent trial, the chronic kidney disease and the anemia had greater impact on


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health care cost [11]. Comorbidities are not only related with hospitalization. COPD patients use approximately 50% more cardiovascular agents than age-matched and sex-matched controls, and almost twice as many antibiotics, analgesics, and psychotherapeutic medications [3, 12].

Finally, comorbidities are related with higher mortality. In our cohort of severe COPD, Charlson comorbidity index and lung cancer are related with mortality [9]. Toward a Revolution in COPD Health (TORCH) and Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) studies showed that the almost 70% of causes of deaths in COPD were non-respiratory. The major non-respiratory reasons of death were cancer and cardiovascular diseases particularly in mild-to-moderate disease [13–16]. The numbers of comorbidities are related with mortality [9, 16]. The mortality was 2.2-fold increased for patients with 4 and higher points of COPD Specific Comorbidity Test (COTE) index [17].

The most common comorbidities associated with COPD are hyperlipidemia, hypertension, ischemic heart disease, diabetes, skeletal muscle wasting, cachexia, osteoporosis, depression, and lung cancer [1, 2]. Recently, COTE index and COMCOLD (Comorbidities in Chronic Obstructive Lung Disease) are designed to address comorbidities that impacted in morbidity and mortality in COPD [17, 18].

The frequent coexistence of those diseases suggests that they might have common mechanistic pathways or shared risk factors such as smoking, reduced physical activities, and ageing [2]. One of the suggested underlying mechanisms is shared systemic inflammation. The systemic inflammation could arise from smoking, other risk factors, or ageing itself. Ageing is related with comorbidities better than forced expiratory flow rate in one second ($FEV_1$) itself [19].

Some of the causal mechanisms are attributed to systemic effects of COPD [16]. Accordingly, COPD can cause a systemic inflammation so called “spill-over inflammation” and other diseases may develop triggered by that inflammation [1]. Comorbidities are important because they might be the reason of actual mortality, may result in difficulties in controlling COPD and sometimes they might be the actual problem underlying exacerbation. Some comorbidities, i.e., lung cancer, depression, anxiety, and pulmonary embolism, could be easily overlooked under the condition of uncontrolled COPD. The quality of life and the risk of mortality could be increased due to somehow manageable conditions [1] and should be actively searched and aggressively treated according to their own treatment strategies [1].

COPD medication may also contribute to the development and worsening of comorbidities [3]. Bronchodilators could contribute cardiovascular morbidity such as arrhythmias and tremor. Anticholinergics can affect intraocular pressure and bladder functions. Inhaled steroids may increase the risk of cataracts, skin bruising, osteoporosis, and pneumonia. Systemic steroids can contribute to diabetes, hypertension, osteoporosis, muscle dysfunction, and adrenal insufficiency [3].

However, important data are lacking regarding comorbidities. There is no convincing 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. Large-scale prospective studies are needed to address those clinical questions. The best suggested approach in reduction of comorbidities in COPD is reduction of common risk factors. Whether reduction of so-called spill-over inflammation with anti-inflammatory treatment of COPD would also reduce COPD-related comorbidities is still doubtful [5].

Herein we categorized the frequent comorbidities that were described as if the prevalence was greater than 5% in COPD population (Table 19.1) [6].

**Table 19.1** Summary of frequent and important 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.

## COPD and Respiratory System

### Asthma

Asthma COPD Overlap (ACOS) has a prevalence of 20% of patients with obstructive lung diseases (asthma or COPD) and 2% in general population. The coexistence of both diseases causes significant impairment in health status, increased exacerbation, and increased hospitalization. Treatment should cover both inhaled steroids and bronchodilators in ACOS patients. There is limited evidence for treatment recommendation because ACOS patients are excluded from randomized

controlled trials [20]. The detailed information of ACOS has been covered elsewhere in this textbook.

## Lung Cancer

Both COPD and lung cancer have developed in 15–20% of chronic smokers and expected to increase in prevalence and mortality to 2030 [21, 22]. Although ageing, smoking, and family history have been identified as key risk factors, host susceptibility has been indicated in both diseases. The question of whether COPD and lung cancer are linked independent of shared risk factors has been investigated for more than a decade. The first National Health and Nutrition Examination Survey (NHANES I) showed that moderate to severe airway obstruction increased the risk of lung cancer (Hazard Ratio: 2.8) [23]. Later studies showed that both emphysema and airflow obstruction are related with increased lung cancer incidence after adjusting for potential confounders [23–25]. Data have shown that COPD prevalence in a population of lung cancer is 9% up to 50% [17, 26]. COPD prevalence in newly diagnosed lung cancer patients was found to be sixfold greater than in matched smokers [26]. The major impact of lung cancer in COPD is management difficulties and increased mortality [3, 9]. Vice versa COPD has impact on lung cancer in a similar manner with limiting the chance of surgery, increasing postoperative complications and finally increasing the chance of mortality [3, 6, 27].

The underlying mechanisms under COPD and lung cancer are very complex. Genetic factors, ageing, epigenetic mutations, and common inflammatory mechanisms have been identified [5, 22, 28]. Recent advances in genetic epidemiology demonstrate several number of loci are overlapping both in COPD and lung cancer. CHRNA 3/5 (Chr15q25) and FAM13A are among them [22]. Those data have raised two important questions: (1) Do COPD patients or emphysema patients need early screening for lung cancer detection and (2) Is there any place for a genetic-based risk stratification of smokers that might help better targeted therapy, prevention, and early diagnosis? The answer is probably YES for both questions [22, 29]. Supporting that concept, in a posthoc analysis of National Lung Screening Trial, in a subgroup of screened patients who demonstrate airflow limitation, the risk of lung cancer increased twofold, the overdiagnosis was minimal, and they had stage shift favorable for screening [30]. New screening risk models including the information about COPD is under validation [31].

## Pulmonary Fibrosis

The association of combined pulmonary fibrosis and emphysema (CPFE) was first described as a syndrome by Cottin in 2005 as upper lobe emphysema, lower lobe fibrosis, subnormal lung volume and diminished carbon monoxide diffusion capacity (DLCO) and high prevalence of pulmonary hypertension [32]. The combined appearance was first interpreted as a coincidence of two smoking-related diseases; however, in reality, most idiopathic pulmonary fibrosis (IPF) patients do not have emphysema and most COPD patients do not show overt fibrosis either. Therefore the actual pathobiology would be different from what it was historically though and might indicate an individual susceptibility [33].

The prevalence of pulmonary fibrosis has found to be 6.1% in 1664 COPD patients in a recent landmark study performed by BODE group [17]. Pulmonary fibrosis was found to be related with higher mortality (HR: 1.51, CI 95% (1.13–2.03)) [17]. The prevalence of detectable CPFE patients in IPF patients are varied depending on methodology (8–51%) [34].

The patients have heavy smoking history. Telomerase abnormalities can be considered to explain genetic susceptibility [34]. The symptoms of CPFE are more likely to resemble IPF showing progressive dyspnea and dry cough [34]. Paraseptal emphysema is typical for CPFE [32, 34]. Thick walled cystic lesions, lower lobe fibrosis, honeycombing, and traction bronchiectasis are common imaging findings [34]. In respect to associated findings, emphysema is more extended in CPFE patients than IPF patients. The differ-

ence of fibrosis scores between CPFE and IPF is controversial [34].

Those patients have higher risk of pulmonary hypertension. The pulmonary hypertension prevalence was reported as 47–90%. Likewise, lung cancer has been detected with a prevalence of 35.8–46.8% indicating higher prevalence than either COPD or IPF [34]. Both pulmonary hypertension and lung cancer have contributed to worse prognosis of CPFE [34].

### Treatment of CPFE

There is no specific therapy for CPFE. Patients should be treated as either disease alone. Hypoxemia should be corrected by long-term oxygen therapy. Bronchodilation could be an option for CPFE patients with airflow obstruction. It is currently unknown whether pirfenidone or nintedanib is efficacious in CPFE [34]. Lung transplantation is the only therapeutic option [6].

### Chronic Kidney Disease (CKD)

The prevalence of CKD has been shown as 16.7, 22.2, and 39% in different COPD cohorts [17, 35, 36]. The risk of renal diseases is greater in COPD group than non-COPD control groups [37]. Chronic renal failure may exist with the normal serum creatinine level in COPD [3, 35]. The arterial stiffness and endothelial dysfunction could lead to a renal dysfunction [3]. In NHANES III study, all cause of mortality was associated with albumin/creatinine ratio and estimated GFR [38]. CKD has also impact on treatment of COPD and its complications [3, 6].

*Treatment:* CKD in COPD is treated as the same for patients without COPD [1].

### COPD and Endocrinology and Metabolism

Weight loss and muscle wasting are present in 20% of stable COPD patients. This reaches to 40% for patients with respiratory failure and 70% of patients requiring mechanical ventilation [39]. There is a decrease in fat-free mass with decrease in muscle mass (sarcopenia). The muscle mass is influenced by inflammatory cytokines, mechanical load on the muscles, and anabolic axes. There are four anabolic axes: somatotropic, gonadal, adrenal, and insulin [39].

### COPD and Somatotropic Axis

The major component of somatotropic axis is growth hormone (GH) and insulin-like growth factor (IGF-I). IGF-I stimulates muscle protein synthesis and hypertrophy and inhibits protein catabolism [39]. Aging, malnutrition, inactivity, and administration of glucocorticoids are associated with downregulation of the GH/IGF-I system; however, hypoxemia and hypercapnia may result in an increased level of GH/IGF-I levels. Depressed level of IGF-I in COPD may contribute to the decreased muscle mass in COPD; however, resistance to GH or ghrelin action may also be the case in cachexia in COPD.

*Treatment:* The administration of recombinant human GH has produced conflicting results. There are important questions on selection criteria, monitoring and safety of the studies of recombinant GH/IGF-I supplementation in COPD [39].

### COPD and Gonadal Axis

Gonadal axis is a complex network of hormones that includes testosterone and other anabolic hormones. In both men and women, testosterone is responsible for libido, sexual hair, and muscle and bone health. The level of testosterone and its precursor adrenal steroid dehydroepiandrosterone (DHEA) is declined with advanced age. That is called “late-onset hypogonadism” and it accompanies with decreased energy level, libido, bone density, and muscle mass. The research in that field is more focused on men; however, women have similar declined level of androgens [39].

Ageing, chronic comorbidities, hypoxemia, hypercapnia, smoking, administration of

glucocorticoids, systemic inflammation, and obesity are the risk factors of late-onset hypogonadism in COPD. The prevalence of late-onset hypogonadism in normal population is about 3% and in COPD is reported between 22 and 69%. Different results may be due to different sample size and population [39]. Studies did not find a relation between testosterone level and sexual difficulties, health quality surveys, and respiratory muscle performance. In some studies, low level of testosterone has found to be related with a decrease in quadriceps strength and testosterone administration has caused an increase in strength. However, there are also negative studies and the doses and the duration of testosterone administration is not known. Current studies have not shown a difference in exercise performance in hypogonadal and eugonadal COPD patients. Testosterone administration has not made any improvement in exercise performance [39].

*Diagnosis:* The late-onset hypogonadism should be searched when patients concern about erectile dysfunction and other related symptoms. When it happens the repetitive testosterone levels are measured and should be lower than 8 nmol/L or in borderline level (8–11 nmol/L) in order to initiate advance evaluation [41]. ANDROTEST is designed for the purpose of diagnosis showing a sensitivity and specificity close to 70% in detecting low total or free testosterone [40].

*Treatment:* Testosterone therapy should be considered for sexual dysfunction regardless with COPD. However, it is not known that the symptoms are related with normal aging or related with low testesteron [40]. Although hypogonadism is related with obesity, metabolic syndrome and diabetes Type 2, hypertension and cardiovascular disease, testesteron should not be offered for potential additional benefits regarding muscle functions and insulin resistance, if there is no symptoms of sexual dysfunction [41]. We do not know now if there is a causal relationship with low testosterone with those conditions or low testosterone is basically a result of those conditions. For instance, studies showed that losing weight resulted in an increase in serum testosterone levels [42]. There is no clear indication for administration of testosterone in COPD. Testesteron replacement can be related with potential obstacles. The absolute contraindication for testosterone replacement includes prostate and breast carcinoma. The relative contraindications are serum prostate specific antigen >4 ng/mL, a hematocrit >50%, severe lower urinary tract symptoms caused by benign prostatic hypertrophy, untreated or poorly controlled congestive heart failure, and untreated sleep apnea [41]. Late-onset hypogonadism is underdiagnosed, under researched area. Further large randomized studies are needed.

## COPD and Adrenal Axis

The adrenal gland produces a vast array of hormones: cortisol, DHEA and its metabolite, DHEAS. The high levels of cortisol/DHEA or cortisol/DHEAS ratios are thought to create an imbalance between protein synthesis and degradation favoring catabolism. Cortisol mobilizes glucose, free fatty acids, and amino acid; increases appetite; and induces insulin resistance. Studies found that DHEAS levels are lower in COPD patients than in controls. There is no data regarding cortisol levels are altered in COPD [40, 41]. However, it is known that systemic steroids and high dose inhaled steroids increase the risk of adrenal insufficiency. Neither glucocorticoid dose nor duration of treatment can be used to predict adrenal insufficiency [43].

In COPD, the cortisol/DHEAS ratio was greater among patients with reduced muscle mass. On the other hand, administration of DHEA had no effect on body composition, muscle strength or quality of life, and bone mineral density in people without COPD [43].

*Treatment*: There is no evidence that DHEA administration has a significant benefit in COPD [40–42].

## Diabetes Mellitus

Insulin is an anabolic hormone that exerts its action binding to its receptors throughout the body including lung, liver, and skeletal muscle. Insulin improves hypoxia-induced vasoconstriction and causes pulmonary artery vasodilation [39].

Diabetes Mellitus (DM) can result from destruction of pancreatic beta cells. There is insulin deficiency (type 1) and insulin resistance (type 2) in patients with diabetes.

The prevalence of diabetes in patients with COPD is 10–18.7% [39]. The relation between impaired pulmonary function and the risk of diabetes is controversial. In the Framingham Heart Study and NHANES study, there was no association between COPD and the development of diabetes [39]. However, other studies showed contrasting results. In a large nationwide twin cohort in Denmark, patients with chronic bronchitis and COPD had an increased risk of type 2 diabetes after adjusting for age, sex, smoking, and body mass index (BMI) (OR: 1.57 for chronic bronchitis or OR: 2.62 for COPD). The prevalence of type 2 diabetes in COPD group was 6.6% while it was 2.3% in non-COPD control group [44]. In a Women's Health Study, 38,570 women were followed for 12.2 years; during follow-up, 2472 incident type 2 diabetes events were accounted and asthma or COPD was found to be associated with diabetes (RR: 1.37 for asthma and 1.38 for COPD) [45]. In a primary care setting, analyzing the primary care records of 1,204,100 individuals, the physician diagnosed COPD has increased the risk of new onset type 2 DM [46].

Glucose metabolism is more disturbed in COPD patients than non-COPD patients. The etiology behind this phenomenon is not known well. However, shared risk factors and common inflammatory pathophysiology could be reason behind it. Advanced age, hereditary factors, smoking, and low birth weight are the shared risk factors of both diabetes and COPD [47].

### Obesity and Adipose Tissue

Obesity is one of the major risk factors of new onset type 2 diabetes and metabolic syndrome. Obesity could be associated with decreased respiratory volumes. In addition to this, central obesity can enhance systemic inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor $\alpha$ (TNF-$\alpha$). Obesity is also associated with reduced adiponectin which has anti-inflammatory properties [47].

Abdominal obesity is more prevalent in mild-to-moderate COPD (16–24%) than severe disease (6%) and that is associated with airflow obstruction independently from smoking [48, 49]. In a study performed in California, 54% of the COPD patients were obese (BMI > 30 kg/m$^2$) and this rate was higher than the general population. Obesity was more associated with chronic bronchitis than emphysema [50, 51]. On the other hand, low BMI is considered a worse prognostic marker and related with all cause of mortality [52]. However, low BMI seen in advanced COPD is a result of loss of fat-free mass and pathophysiologically similar to cancer cachexia [47]. Supporting these results, another study showed that low BMI was associated with greater mortality compared with normal or high BMI. The loss of three BMI units was associated with increase in all cause of mortality in controls and COPD groups, whereas weight gain was associated with increased mortality only in controls [53]. In a Korean cohort, increased BMI is related with mortality from cardiovascular disease [54]. However in a European cohort, low BMI is related with increased mortality [55]. It seems that in early stages of COPD, obesity is accompanied with cardiovascular disease and insulin resistance leading mortality and in the severe stages the obesity is a protective effect for mortality [56]. It is called obesity paradox and the pathogenesis behind it is not known. Future studies are needed to explain "obesity paradox." Fat-free mass loss could be an explanation behind low BMI seen more in emphysema related with higher mortality [47].

Adipose tissue is an active endocrine organ producing several substances. Leptin and adiponectin are more studied [47, 57, 58]. Resistin may contribute to the dysglycemia and insulin resistance in COPD [59]. More studies are needed if there is a true mechanistic interaction between those markers and COPD [47].

### Systemic Inflammation and Oxidative Stress

Both COPD and type 2 diabetes are related with both enhanced oxidative stress and systemic inflammation. TNF-alpha, IL-6, IL-1B, CRP, and fibrinogen are most studied [47].

Hypoxia could have contribution on COPD. Pancreatic B cells may be damaged by hypoxia. The pathophysiology could be mediated by hypoxia inducible factor 1 family (HIF). Hypoxia-mediated increase in HIF-1alpha can induce adipose tissue fibrosis and resistance to insulin at the level of skeletal muscle [47].

Moreover, COPD is associated with hypogonadism, increased catecholamines, and RAAS (renin–angiotensin–aldosterone systems) and they all related with glucose metabolism [47].

## The Impact of DM Type 2 in COPD

DM has impact on pulmonary vasculature leading to pulmonary microangiopathy showing detrimental effect on alveolar capillary bed. That results in reduced diffusion capacity of carbon monoxide [60]. Studies showed that DM-related nephropathy is significantly associated with the presence of pulmonary capillary dysfunction [47].

DM is associated with the development of muscle dysfunction. Diaphragm could be targeted by DM which could be probably mediated by phrenic neuropathy [47]. In Copenhagen City Study, Framingham Heart Study, and Fremantle studies, subjects with DM had lower values of $FEV_1$ and forced vital capacity (FVC) [61–63]. In Fremantle study, DM is associated with greater lung decline and DM-related airflow limitation was associated with increased mortality [63]. In Normative Aging Study, DM is not associated with accelerated decline of lung function [64].

DM also associated with increased risk of exacerbations. DM-associated inflammation can cause increase risk of pro-inflammatory state that can increase the risk of exacerbation. The systemic glucocorticosteroids are used in exacerbation and that can induce diabetes. Glucocorticosteroids can cause hyperglycemia by increasing gluconeogenesis in the liver and decreasing glucose uptake in the liver and adipose tissue [65]. The estimated DM prevalence among chronic systemic CS user is about 11% within 3 years following treatment [66]. There is evidence that particularly high dose inhaled steroids can increase the risk of type 2 diabetes and can worsen the glycemic control [65, 67].

DM associated the increased risk of infections. Hyperglycemia may particularly increase the risk of methicillin resistant *Staphylococcus aureus* (MRSA). Hyperglycemia is related with increased morbidity and mortality in COPD exacerbation [68]. Comorbid DM prolongs length of stay and increases risk of death in patients with COPD exacerbations (AECOPD) [69, 70].

## The Impact on DM Therapies in COPD

The goal of diabetic care is to achieve glucose levels close to normal levels [39]. Patients should be cared as standard DM patients in achieving this goal [1, 71]. Inhaled steroids in diabetic patients with COPD are conflicting. The studies showed that systemic insulin therapy may be beneficial for DLCO. Oral antidiabetics such as metformin or thiazolidinedione improve FVC that was thought to be due to improved respiratory muscle function [47]. Moreover, metformin has some antitumor effects [47]. Metformin is thought to increase the risk of lactic acidosis, and is considered contraindication for chronic hypoxemic conditions. However, recent studies showed no significant acidosis in metformin users [72].

## COPD and Metabolic Syndrome

Metabolic syndrome is defined as several criteria (Table.19.2) [73]. These criteria are given as an indirect measurement of insulin resistance. The direct measurement of insulin is less established in the routine clinic [73]. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the most widely used. It requires measurement of fasting plasma glucose and insulin levels [73].

The prevalence of metabolic syndrome is reported to be 25, 42.9–57% [74–76]. It seems that metabolic syndrome accompanied milder COPD than severe disease [76]. The impact of metabolic syndrome in COPD is not well studied. However, studies showed that COPD patients with metabolic syndrome have more complaints

**Table 19.2** Metabolic syndrome definition criteria [73]

| | NCEP ATP III | IDF |
|---|---|---|
| | 3 out of 5 | Waist +2 out of 4 |
| Waist circumference | | |
| Males | ≥102 cm | ≥94 |
| Females | ≥88 cm | ≥80 |
| Fasting glucose[a,b] | ≥5.6 mmol/L | ≥5.6 mmol/L |
| High-density lipoproteins[b] | | |
| Males | <1 mmol/L | <1 mmol/L |
| Females | <1.3 mmol/L | <1.3 mmol/L |
| Triglycerides | ≥1.7 mmol/L | ≥1.7 mmol/L |
| Blood pressure | ≥130/85 mmHg | ≥130/85 mmHg |

*NCEP ATP III* national cholesterol education program adult treatment panel III, *IDF* international diabetes federation

[a]Either above cutoff or established diabetes mellitus or specific treatment

[b]Either above cutoff or specific treatment

and more comorbidities [75, 76]. The cardiovascular mortality seen in mild COPD could be related with metabolic syndrome [73].

*Treatment*: Reducing weight, exercise, testesteron, and insulin sensitizers are beneficial in metabolic syndrome. However, there is no specific guideline for the treatment of comorbidities including metabolic syndrome with COPD [73]. It should be treated according to the endocrinological principals [77].

## COPD and Thyroid Disease

The thyroid hormones regulate the metabolism of proteins, lipids, and carbohydrates, and increase the metabolic rate as a result of respiratory drive. Limited data are available on thyroid disease and COPD. The prevalence of thyroidal disease in COPD is not known [39].

## COPD and Hypothyroidism

Impaired thyroid function can present as subclinical hypothyroidism, manifest hypothyroidism, and nonthyroidal illness syndrome. Nonthyroidal illness syndrome is described as low T3, decreased or normal T4, and normal TSH. This was called as euthyroid sick syndrome in the past but that nomenclature is abandoned now. Severe obstruction, hypoxemia, systemic glucocorticosteroid usage, and systemic inflammation can be the etiology behind hypothyroidism. When present hypothyroidism can decrease respiratory drive, respiratory muscle function, exercise capacity and increase the risk for sleep disorder.

*Treatment*: Hypothyroidism in patients with COPD should be treated in the same manner as in patients without COPD [39, 78].

## COPD and Hyperthyroidism

Hyperthyroidism may impair respiratory muscle function, respiratory mechanics, and exercise capacity. As a result, inspiratory and expiratory muscle weakness, decreased lung compliance, and respiratory failure can occur [39].

*Treatment:* Hyperthyroidism in patients with COPD should be treated in the same manner as in patients without COPD [78].

## COPD and Renin–Angiotensin–Aldosterone System

Patients with COPD can develop fluid retention when stable or during exacerbation. Right heart pressure can be normal or increased. Traditionally, volume overload is thought to be caused by right ventricular failure caused by hypoxia-induced pulmonary vasoconstriction. Growing evidence suggests that renal vasoconstriction is central in the fluid retention and that can be triggered by hypercapnia. Development of sodium and water retention in COPD implies poor prognosis [39].

*Treatment:* Although the renin–angiotensin–aldosterone system has been studied for more than 30 years in COPD, few investigations have assessed aiming to reduce fluid retention. Postponing diuretics as long as possible can be one approach because diuretics can aggravate sodium and water retention by several mechanisms. Some authors suggest the use of

angiotensin-converting enzyme inhibitors for increasing sodium excretion. However, the results are inconsistent in different studies [39].

### COPD and Vitamin D

Vitamin D has long been known as essential for musculoskeletal health. However, more recently there has been increased interest in vitamin D regarding its potential noncalcemic effects and its relationship with chronic disease, particularly COPD, since vitamin D hypovitaminosis is a common status throughout the world including socioeconomically underdeveloped and developed countries [79]. There has been interest in a possible link between vitamin D hypovitaminosis and COPD pathogenesis, progression, exacerbations and associated comorbidities.

Vitamin D synthesized in skin under the effect of UV light. It is converted to active form in kidney. Vitamin D regulates calcium and phosphorus metabolism. The desired vitamin D level is above 30 ng/mL. Vitamin D deficiency is described as if the 25(OH) vitamin D level is under 20 ng/mL. Insufficiency is between 20 and 29 ng/mL [80]. The noncalcemic effects are expected with higher levels.

An age-matched controlled study showed that COPD patients had significantly lower vitamin D levels when compared to controls, which might suggest that COPD patients have a higher risk of vitamin D deficiency [81].

COPD itself may comprise additional risks for vitamin D deficiency due to the fact that 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 [81, 82].

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.

*Treatment:* 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 [80].

The guideline suggests that all vitamin D deficient adults should be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1500–2000 IU/day. Higher doses are needed in obese patients and patients with malabsorption syndromes. The serum vitamin D level should not exceed 100 ng/mL. There is no clear evidence to recommend higher dose Vitamin D supplementation for noncalcemic benefits in COPD [80].

## COPD and Musculoskeletal Functions

### COPD and Muscle Dysfunction

Skeletal muscle dysfunction is an important systemic consequence of COPD because of its impact on physical activity, exercise tolerance, quality of life, and survival on the disease [83]. Skeletal muscle function is described by muscle strength (the ability to generate force production), muscle endurance (the ability to sustain a given contraction over time), and muscle fatigue (a physiological sense defined as the failure of force generation resulting from activity under load). Skeletal muscle weakness is characterized by reduced muscle strength, reduced muscle endurance, and the presence of muscle fatigue [84]. Muscle weakness is mainly observed in the lower limb muscle of patients with COPD.

Lower limb muscle weakness is found to be more severe in patients with cachexia and worsens during exacerbations [85–87]. In lower limb muscles, several adaptations develop with COPD; these include muscle fiber type shift from type I towards type IIx muscle fibers resulting in reduced oxidative and increased glycolytic capacity, fiber atrophy, loss of muscle mass, and

decreased capillary density [88]. Importantly, reduced quadriceps strength is found to be a useful predictor for mortality in patients with COPD [89] and the quadriceps muscle weakness is a common feature in patients within all stages of COPD [84, 90].

Reduced quadriceps strength in COPD is associated with reduced exercise capacity [91, 92], compromised health status [93], increased need for health care resources [94], and mortality independent of airflow obstruction [88].

Eighteen to 36% of COPD patients present with net detriment of muscle mass, which is responsible for weight loss in 17–35% of these patients [95]. The estimated overall prevalence of skeletal muscle weakness in patients was shown to be 20–30% [84, 96]. Although skeletal muscle weakness is a feature of cachexia, quadriceps weakness in COPD is not simply an epiphenomenon; indeed, weakness is frequent with a ratio of approximately 2:1 compared with loss of fat-free mass [90].

Seymour et al. have demonstrated that a significant proportion of patients in GOLD stages 1 and 2, or with an MRC dyspnea score of 1 and 2, had quadriceps weakness (28% and 26%, respectively); these values rose to 38% in GOLD stage 4, and 43% in patients with an MRC score of 4 and 5 [97].

The physiopathological interaction between COPD and alterations in limb muscle tissue is still poorly understood. Several factors, such as smoking, corticosteroids, hypoxia, hypercapnia, inflammation, oxidative stress, reduced daily physical activity, vitamin D deficiency, and nutritional deficits, have been proposed to explain the initiation and the progression of muscle dysfunction in COPD [84].

## Etiology

*Smoking:* Smoking was shown to be related to decreased skeletal muscle strength and physical performance in healthy adults [98, 99]. In healthy smokers and patients with COPD, cigarette smoke was shown to induce muscle atrophy, reduce muscle protein synthesis, induce oxidative modifications on muscle proteins [100], and increase the expression of genes involved in muscle catabolism and associated with inhibition of muscle growth [101].

*Corticosteroid use:* Corticosteroids are frequently used in patients with COPD to reduce pulmonary symptoms and to treat exacerbations [102]. Although a short course of systemic corticosteroids may not alter limb muscle function in COPD [103], these anti-inflammatory agents have a trophism for the muscles, and their chronic or repeated use can potentiate muscle atrophy and weakness in patients with COPD [104]. Morphological changes have been reported in the quadriceps in patients with COPD presenting with a corticosteroids-related myopathy [105].

*Hypoxia:* Hypoxia may contribute to muscle wasting in COPD by a variety of mechanisms, including reduced anabolic hormone levels [106], increased levels of pro-inflammatory cytokines [107] and by the generation of ROS (reactive oxygen species) that contribute to oxidative stress [108].

*Hypercapnia:* The phosphocreatine (PCr)/phosphate (Pi) ratio is significantly lower [109] during exercise in COPD patients, with faster PCr depletion [110], and postexercise recovery is slower in patients compared with healthy controls. The ratio of PCr to Pi is closely related to that of adenosine-tri-phosphate (ATP) to adenosine-di-phosphate (ADP) and, hence, is a useful marker of muscle energy status. Acute hypercapnia leads to intracellular acidosis that has marked effects upon muscle cell metabolism, including decreases in ATP, PCr, and adenosine nucleotides [111, 112]. Furthermore, acute hypercapnia in healthy humans reduces limb muscle and diaphragm contractility [113, 114].

*Inflammation:* Systemic inflammation has been postulated as a major etiological factor in the skeletal muscle dysfunction commonly seen in COPD. TNF-$\alpha$ levels are elevated in patients who fail to gain weight during a rehabilitation and re-feeding program, whereas increased blood levels of IL-6 (interleukin-6), interleukin-8 (IL-8), TNF-$\alpha$, and CRP (C-reactive protein) in COPD patients have been associated

with increased resting energy expenditure, giving support to the concept that pro-inflammatory cytokines play a role in COPD-associated cachexia [90].

*Oxidative Stress:* The most important triggers for the development of oxidative stress in patients with COPD are cigarette smoke and systemic inflammation [84]. Oxidative stress was found to be associated with decreased quadriceps muscle strength and was shown to cause increased bone resorption during severe COPD exacerbations [115].

*Vitamin D deficiency:* Vitamin D was shown to play an important role in the growth of skeletal muscles, muscle contractility, and myogenesis [116] as well as in the development of the growth plate, mineralized bone, and osteoclastogenesis [117]. Therefore vitamin D deficiency may contribute to limb muscle dysfunction [84].

*Inactivity:* Physical inactivity was found to be crucial in the development of skeletal muscle weakness in patients with COPD. It is believed to result in quadriceps weakness due to mechanical unloading of the muscle and due to muscle wasting [118, 119].

Also, nutritional depletion is associated with reduced upper and lower limb muscle force, a loss of force at higher stimulation frequencies, slowing of muscle relaxation rate, and a reduction in muscle endurance [90].

## Treatment

Several interventions have been used in an attempt to improve muscle function in patients with COPD. These and their respective effects on limb muscles are summarized in Table 19.3 [83].

Pharmacological (testosterone replacement therapy, vitamin D and calcium supplementation) and non-pharmacological treatments (exercise training, prevention of falls and balance training and nutritional counseling) are applied in the management of musculoskeletal problems in patients with COPD [83, 84].

Aerobic exercise training, resistance/strength training, and inspiratory muscle training are done in exercise training taking into account overload, specialization, individual differences, and reversibility principles [83, 120]. Supplemental oxygen given during exercise reduces ventilatory requirements for a given workload and increases oxygen supply to muscles exercising at high exercise levels and maximal exercise tolerance [83]. Transcutaneous neuromuscular electrical stimulation (NMES) is suitable for severe deconditioned patients with COPD, during exacerbation periods, transferred to intensive care or bedridden patients with COPD [83, 84]. Water exercises are useful for severe dyspneic patients with COPD with advanced age and physical comorbidities. Muscle strength, functional capacity,

**Table 19.3** Effects of treatments for limb muscle dysfunction in chronic obstructive pulmonary disease [83]

| Treatment | Mass | Strength | Exercise tolerance | Survival |
|---|---|---|---|---|
| Exercise | + | + | + | ? |
| Oxygen | ? | ? | + | + |
| Nutrition alone | – | – | – | ? |
| Nutrition + exercise | + | + | + | ? |
| Nutrition + exercise + anabolic hormones | + | + | + | ? |
| Testosterone | + | + | – | ? |
| Growth hormones | + | – | – | ? |
| Ghrelin | ? | ? | ? | ? |
| Megestrol | – | ? | – | ? |
| Creatinine | ? | ? | – | ? |
| 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

and quality of life have been improved with whole body vibration therapy in patients with COPD and it increased benefits obtained by pulmonary rehabilitation program [84].

Effects of nutritional supplementation are controversial in stable COPD patients. Improvements were observed in body composition, muscle function, exercise capacity, and health status with pulmonary rehabilitation programs with additional nutritional supplementation in COPD patients with nutritional deficiency. Response to nutritional supplementation is very variable and is associated with patient characteristics, type of treatment, and treatment compliance [83, 120]. Testosterone and its analogs are anabolic agents that increase muscle protein synthesis and muscle mass and reduce muscle protein degradation and fat mass. Their benefits increase when combined with resistance training. They are not routinely recommended because of possible side effects. Growth hormone and secretagogues provide significant weight and lean body mass gain in patients with COPD and malnutrition but their results on respiratory and limb muscle strength and exercise capacity are still controversial. They are not recommended due to possibility of carcinogenic effects, side effects, and high costs in COPD patients with muscle dysfunction [83]. Positive effects in terms of disease prognosis are achieved in patients with COPD with early intervention for comorbidities. Future studies should focus on mechanisms of muscle dysfunction and mechanisms-based treatment.

## COPD and Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by low bone mineral density (BMD) and microarchitectural changes, leading to impaired bone strength and increased risk of fracture [121]. Osteoporosis is a well-recognized comorbidity of COPD patients and is an important area of consideration for therapeutic interventions. The most commonly used tool to measure BMD is dual-energy x-ray absorptiometry (DEXA), which is used to define osteoporosis and provides a useful estimate of fracture risk [122]. According to the World Health Organization (WHO), a T-score greater than −1 is accepted as normal, T-scores between −1 and −2.5 are classified as osteopenia, and T-scores of less than −2.5 are defined as osteoporosis [122].

The prevalence of osteoporosis in COPD varies between 4 and 59%, depending on the diagnostic methods used and the severity of the COPD population [123]. More than half of the patients with COPD recruited for the large TORCH trial (6000 patients) had osteoporosis or osteopenia as determined by DEXA scan [124]. COPD could be a risk factor for osteoporosis. In NHANES study including 14,828 subjects over 45 years, osteoporosis prevalence was found 16.9% in subjects with COPD and 8.5% in subjects without COPD [125, 126]. In another cross-sectional study, the prevalence of osteoporosis was 75% in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV disease, and strongly correlated with reduced fat-free mass (FFM). Another important finding in this study was that the prevalence rate was high even for males, with an even higher incidence in postmenopausal women [127, 128].

Recently, in COPD Gene cohort with 3321 current or ex-smoker COPD patients, male smokers had significantly greater risk for osteoporosis and fracture. The osteoporosis prevalence was greater in severe COPD reaching 84%. Emphysema was found to be associated with osteoporosis [129].

### Etiology

*Corticosteroids use:* Oral glucocorticosteroids (OGCs) have both direct adverse effects on bone and indirect effects attributable to muscle weakening and atrophy [130]. These effects are both dose-dependent and duration-dependent. At supraphysiologic concentration GCs profoundly inhibit osteoblast function and bone formation. Prolonged GC use leads to reduction in bone turnover impaired bone renewal and bone loss [66]. Bone mineral loss can be as high as 15.8% among inhaled corticosteroids (ICS) users. The fracture risk is 75% higher among OGCs users [131]. However, the ICS studies have not shown consistent findings regarding bone mineral loss. Some studies showed no aggragation in bone

loss; however, others showed excess bone loss with high doses [65, 132–134].

*Chronic inflammation:* Studies suggest that COPD and associated systemic inflammation is a risk factor for osteoporosis independent of other potentiators [135, 136]. In Liang et al. study, the presence of systemic inflammation was associated with a greater likelihood of low BMD, and multivariate logistic regression analysis showed that TNF-a and IL-6 were independent predictors of low BMD [136].

*Vitamin D deficiency:* Vitamin D along with PTHs plays a key role in regulating calcium and bone homeostasis [125]. Vitamin D deficiency increases the susceptibility to osteoporotic fractures because of low BMD. It also increases the fracture risk by causing swaying of the body and falls because of muscle weakness [125]. Various factors that have been implicated for the deficiency of vitamin D in COPD patients include poor diet, less exposure to sunlight because of decreased physical activity, accelerated skin ageing, renal dysfunction, depression, and treatment with corticosteroids [137].

*Anemia:* Anemia is a common entity in COPD patients, and its prevalence varies from 7.5 to 34%, depending upon the selected populations and the diagnostic tools to determine the hemoglobin level [138]. Korkmaz et al. demonstrated significantly higher prevalence of anemia in patients with low BMD of the femur and spine [139]. Rutten et al. reported 20% prevalence of anemia among 321 COPD patients admitted for pulmonary rehabilitation, and anemia was also found to be an independent predictor of low BMD [140]. The pathophysiological nexus between anemia and osteoporosis is not clear; however, human and animal experiments suggest the role of anemia-associated hypoxia as the potential mechanisms for the development of osteoporosis [141].

*Smoking:* Smoking induces osteoporosis by several potential mechanisms: altered metabolism of calciotropic hormone; dysregulation in the production, metabolism, and binding of estradiol; altered metabolism of adrenal cortical hormone; and effects on collagen metabolism and bone angiogenesis [142].

*Hypogonadism:* Sex steroids play a crucial role in maintaining skeletal integrity via stimulating bone formation and inhibiting bone resorption [143]. The reported prevalence of hypogonadism in men with COPD varies from 22% to 69% and has been associated with osteoporosis, depression, and muscle weakness [144].

## The Impact of Osteoporosis

Osteoporosis is related with vertebral compression fractures. Lumbal and thoracal regions are most affected. Every single compression causes 9% reduction in vital capacity. Osteoporosis could be progressive over the years in COPD. In a study with 3-years follow-up, the prevalence of osteoporosis increased from 47 to 61% [145]. Vertebral compression fractures increase the risk of hip fractures [125]. The prevalence of hip fractures is not exactly known in COPD. However in a Danish cohort hip fracture in COPD patients showed poor prognosis with 60–70% higher risk of death [125, 146].

## The Diagnosis of Osteoporosis

The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual-energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site [147]. An individual's BMD is presented as the standard deviation above or below the mean BMD of the reference population, as outlined in Table 19.4 [148].

**Table. 19.4** WHO Definition of Osteoporosis Based on BMD [148]

| Classification | BMD | T-score |
|---|---|---|
| Normal | Within 1 SD of the mean level for a young-adult reference population | T-score at –1.0 and above |
| Low bone mass (osteopenia) | Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population | T-score between –1.0 and –2.5 |
| Osteoporosis | 2.5 SD or more below that of the mean level for a young-adult reference population | T-score at or below –2.5 |
| Severe or established osteoporosis | 2.5 SD or more below that of the mean level for a young-adult reference population | T-score at or below –2.5 with one or more fractures |

## Prevention and Treatment of Osteoporosis

### Non-pharmacological Management

Active smoking cessation should be instituted at the earliest. Weight-bearing and strengthening exercise should be encouraged. Overuse of ICS in COPD must be avoided. ICS use should be restricted to COPD patients with forced expiratory volume (FEV1), 50% of predicted. Unnecessary prolonged use of oral steroids during COPD exacerbations should be avoided [125].

### Pharmacological Management

Pharmacological interventions consist of calcium and vitamin D supplementation and antiresorptive therapy. Vitamin D and calcium supplementation is an integral part in the prevention and treatment of osteoporosis [125], but there is no worldwide consensus on optimal dietary intakes and optimal levels of serum vitamin D level.

All symptomatic COPD patients should be evaluated for the presence of following minor criteria:

- BMI <21 kg/m$^2$
- Current smoking
- Use of ethanol >3 units/day
- Age > 65 years
- Parent hip fracture
- Rib fracture
- Menopause
- Inactivity
- FEV1, 50% predicted

and major criteria:

- Systemic corticosteroids (3 months/year)
- Major fragility fracture (spine/hip) [125]

BMD of the hip and lumbar spine should be measured by DEXA scan along with serum 25-OH D if at least three minor or one major criterion is present. Pharmacologic therapy is indicated in the following conditions [149]:

1. COPD with documented fragility hip or vertebral fractures,
2. *T*-score below −2.5SD, and
3. −2, 5 < *T*-score < −1 and one major criterion.

Also the FRAX tool uses updated, evidence-based estimates of absolute fracture risk and was created for the purpose of quantitatively integrating numerous clinical factors into a clinically useful risk prediction model [150].

Readers are referred to American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis Guidelines for the treatment of glucocorticoid-induced osteoporosis [150].

## COPD and Cardiovascular Diseases

COPD and cardiovascular diseases (CVD) are leading causes of mortality globally. In 2005, COPD and CVD caused an estimated 120,000 and 830,000 deaths, respectively, in the United States. Clinicians have long recognized that there is a very high prevalence of CVD among patients with COPD, and, indeed, CVD is the major contributor to morbidity and mortality in patients with COPD [151]. COPD and coronary artery disease (CAD) are both highly prevalent and share common risk factors, such as exposure to cigarette smoke, older age, sex, and inactivity [152]. However, it is also thought that systemic inflammatory changes related to COPD may increase the risk of CVD independently [153]. Additionally, pathophysiologic changes associated with COPD can directly impact heart function; for instance, emphysema and lung hyperinflation may impair left ventricular filling and lower cardiac output or cause pulmonary hypertension and right-sided heart failure [151].

## Ischemic Heart Disease

Cardiovascular diseases are the leading causes of death in patients with mild-to-moderate COPD, chief among which is ischemic heart disease (IHD). The prevalence of IHD in COPD patients ranges between 16.1 and 53% and includes various descriptions (coronary artery disease, angina, and myocardial infarction (MI)) [6].

There are multiple sources of evidence demonstrating a high prevalence of IHD in COPD

patients. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, "heart trouble" as opposed to IHD was reported in 26% of 2164 COPD patients compared with 11% of 337 smoking controls ($p < 0.001$), with a MI reported in 9% versus 3% ($p < 0.001$) [154].

A combination of increased risk factors in patients with COPD, chronic systemic inflammation accelerating atherosclerosis, vascular endothelial dysfunction, physiological stress from comorbidities, and acute inflammation following exacerbation are likely to be involved [155].

Though the exact mechanisms are yet to be elucidated, the temporal relationship of ischemic events with acute exacerbations and correlation of systematic inflammatory markers such as C-reactive protein and fibrinogen with increased IHD implicate inflammation as a significant contributor [155].

Arterial stiffness (measured by aortic pulse wave velocity), an independent predictor of cardiovascular events and mortality, is increased in patients with COPD and was correlated with computed tomography-quantified emphysema and airflow obstruction [6].

Sex-related differences have been investigated in most chronic diseases, including COPD and IHD. Disparity between men and women is mostly a result of behavioral and environmental factors, coupled with biological and gender-based genetic factors [156].

Imbalance of thrombotic/antithrombotic mechanisms, with increased procoagulant activity, has been postulated in COPD [157]. Accordingly, comorbidities related to altered thrombotic status, such as cardiovascular disorders, myocardial infarction and pulmonary embolism, are fairly common in patients with COPD [158].

## Heart Failure

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) frequently coexist in clinical practice [159]. The diagnosis of heart failure in COPD patients requires careful clinical history taking including symptoms of orthopnea and paroxysmal nocturnal dyspnea, in addition to cardiovascular examination. Biomarkers such as N-terminal precursor of Brain Natriuretic Peptide (NT-proBNP) have proved useful in differentiating COPD from heart failure both in the stable state and in the acute setting [160]. Both conditions share some risk factors including cigarette smoking, advanced age, and systemic inflammation [161].

The prevalence of COPD among individuals with HF ranges from 20 to 32% of cases, and 10% of hospitalized HF patients also suffer COPD. The hospital HF adjusted prevalence is three times greater among patients discharged with COPD when compared with patients without this disease [160]. COPD is a predictor of mortality in heart failure; indeed, 5-year survival in heart failure patients with COPD is 31% compared with 71% in its absence [162].

Shared etiological factors such as increased age and smoking, together with the high prevalence of hypertension and IHD in patients with COPD, confer much of the increased risk of heart failure in COPD patients. Systemic inflammation is thought to accelerate atherosclerosis and thereby increase the risk of heart failure [6].

## Hypertension

Hypertension is generally asymptomatic and thus would not be expected to particularly impact on COPD patients [160]. Overall the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing [163]. However, hypertension is consistently one of the most prevalent comorbid diagnoses in COPD patients reported in 40–60% [160]. The pathophysiological links of COPD and hypertension are not yet well described. However, 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.

## Venous Thromboembolism (VTE)

Acute pulmonary embolism (PE) and deep venous thrombosis (DVT) are manifestations of the overall disease known as venous thromboembolism (VTE) [158]. Chronic obstructive pulmonary disease (COPD) is a moderate predisposing factor for VTE, principally when associated with hospitalization [164]. The presentation of pulmonary embolism is similarly subtle with nonspecific clinical features such as acute dyspnea, tachycardia, and pleuritic chest pain. While COPD remains a clinical diagnosis, PE requires objective confirmation of clot by an imaging study to warrant appropriate anticoagulation therapy [165].

In the absence of typical symptoms such as productive cough, fever, or decreased breath sounds diffusely, obtaining laboratory and diagnostic studies such as D-dimer, B-type natriuretic peptide, troponin, and arterial blood gas may be helpful in defining other underlying pathologies. Similarly, a nonresponse to aggressive COPD treatment with beta-agonists, antibiotics, and steroids in patients with typical presentations supports evaluation for other causes of dyspnea [165].

During COPD exacerbations, VTE is found in 3–29% of cases [166, 167]. The former consideration may particularly apply during COPD exacerbation, a situation in which undiagnosed PE was found in an autopsy study in up to 30% of COPD patients who died [168]. The prevalence of PE in patients with COPD is important because of combined morbidity and mortality. In a follow-up of 1487 patients from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, Carson et al. found an adjusted estimated relative risk of death at 1 year with COPD and PE of 1.94, compared with 1.1 for patients with PE alone. The 1-year mortality of those with COPD and PE was 53.3%, in contrast to 15% of those with PE alone [169].

The three factors of Virchow's triad are observed in COPD (systemic venous endothelial dysfunction, coagulopathy, and venous stasis due to a physical inactivity), which explains their predisposition to venous thromboembolism (VTE) [170]. Also platelet activation has been shown to be increased in stable COPD as detected by platelet-monocyte aggregates and further increased during exacerbations. Fibrinogen levels are directly as well as related to the incidence of cardiovascular events, and are higher in stable COPD patients than in healthy controls [160].

## Treatment of Heart Disease

Despite having similar disease mechanisms, there are substantial differences between IHD and COPD in their current treatment strategies.

The most striking difference in these treatment strategies is the use of beta-agonists in COPD and beta-blockers in heart disease. This has led to contrasting indications and subsequent underuse, particularly of beta-blockers, of some classes of drug [156]. Recent data, such as the TORCH trial, suggest that drugs used to treat COPD, such as long-acting beta2-agonists, are tolerated and have an acceptable safety cardiovascular profile [171, 172]. Beta-blockers, on the other hand, are most important of coronary artery disease (CAD) treatment, but their use in patients with COPD remains uncertain. The main concern is that these drugs might induce bronchospasm and worsen lung function. However, data have shown that beta-blockers, especially if cardioselective, may also be beneficial and related with lower mortality in patients with COPD, with the only exception in the most severe requiring long-term oxygen treatment [171–174].

Recent studies have suggested that the use of beta-blockers in inpatients with exacerbations of COPD is well tolerated and may be associated with reduced mortality [175, 176]. Also, the findings of a meta-analysis confirmed that beta-blocker use in patients with COPD may not only decrease the risk of overall mortality but also reduced the risk of exacerbation of COPD [177].

Angiotensin-converting enzyme (ACE) inhibitors have been associated with reduced exacerbations and mortality in COPD. Furthermore, lowering of ACE levels has been postulated to decrease lung inflammation and improve respiratory muscle function. At present, this data is mainly limited to observational studies. Therefore, guidelines suggest their use in COPD and cardiovascular disease but not yet for COPD alone [93].

## COPD and Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is one of the most common causes of chronic cough and a potential risk factor for exacerbation of COPD [178–180]. Use of PPI/H2RA and self-reported history of GERD were associated with an increased risk of moderate-to-severe exacerbations and hospitalized exacerbations [181]. The ECLIPSE study identified a history of heartburn or reflux as an independent predictor of frequent exacerbator status. Old age, female gender, medical aid insurance type, and many COPD medications except inhaled muscarinic antagonists were associated with GERD [160]. The prevalence of GERD in COPD patients ranged between 7.7 and 30%. However, Casanova et al. used 24-h pH monitoring to assess acid GERD prevalence and demonstrated that 62% of patients with severe COPD ($FEV_1$ range 20–49%) versus 19% of controls had acid GERD [182]. Importantly, 58% of the COPD patients with GERD were asymptomatic [6].

The key underlying mechanism of GERD is transient relaxations of the lower esophageal sphincter allowing stomach contents to move into the esophagus and often as high as the larynx and mouth, particularly when intra-abdominal pressure is raised [160]. Also laryngopharyngeal sensitivity is important in preventing pulmonary aspiration. Patients with cough and GERD have significantly reduced laryngopharyngeal sensitivity to air stimuli compared with healthy subjects [183]. In addition, medications such as theophylline and inhaled beta2-agonists may decrease the lower esophageal sphincter pressure, could facilitate GER [184, 185].

### Treatment of Gastroesophageal Reflux Disease

Treatment of the GERD is not altered by the presence of COPD, that it should be treated more aggressively [6]. Regarding treatment of the peptic ulcer disease in the context of COPD, no alteration to standard acid suppression therapy is required. The severity of COPD may, however, complicate the ability to perform endoscopic or surgical procedures in terms of anesthetic safety. With regard to the treatment of COPD, steroids can delay the healing of ulcers, and thus minimization of oral steroids in the context of recent ulcer is prudent [6].

## COPD and Malnutrition

Changes in body composition are frequently seen in COPD. Decreased weight and muscle mass effect COPD patients undesirably and malnutrition is related with increased mortality and morbidity [186, 187]. BMI below 20 $kg/m^2$ is defined as malnutrition for COPD patients. Weight loss has been reported in about 50% of patients with severe COPD and, although less common, it is observed in about 10–15% of mild-to-moderate COPD [188].

Malnutrition in COPD is the consequence of an imbalance between energy intake and consumption. Inadequate intake is caused by dyspnea resulting from the effort of eating and by impaired leptin regulation, a hormone that reduces food intake [189]. 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 [186, 190].

### Treatment of Malnutrition

Nutritional supplementation especially for undernourished COPD patients provides weight gain, improves respiratory muscle strength, exercise capacity, quality of life, and anthropometric measurements [191]. Energy consumptions of COPD patients are 20–25 kkal/kg/day for females and 25–30 kkal/kg/day for males. 7–8% of daily energy from saturated fatty acids, 12–15% of daily energy from monounsaturated fatty acids, and 7–8% of daily energy from polyunsaturated

fatty acids should be met. There has been no strict criteria about protein content of diet in COPD patients. Amount of protein should be 1.2–1.5 g/kg/day (15–20% of total energy) to have positive nitrogen balance and support immune system.

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 [186]. Enteral (nasogastric, naso-jejunal, gastrostomy) or parenteral nutrition can be used for COPD patients without oral intake. Early enteral nutrition protects tissue damage and gastrointestinal system, improves immune system and decreases bacterial translocation. Therefore early enteral nutrition accelerates recovery and improves survival in critically ill patients [192].

## COPD and Sleep Disorders

Recent International Classification of Sleep Disorders, 3rd edition (ICSD-3) was published by The American Academy of Sleep Medicine Board in 2014. This guide identifies seven major categories of sleep disorders that include insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and other sleep disorders. COPD is associated with the heading of sleep-related breathing disorders and more closely the subheading of sleep hypoventilation syndromes [193].

Patients with COPD have a higher prevalence of insomnia, nightmares, and daytime sleepiness than the general population, with close to 50% of patients are reporting significant disturbance in sleep quality [194].

Sleep has negative effects on breathing such as changes in central respiratory control (chemosensitivity decreases even in 20–25%), airway resistance (Raw increases and respiratory secretions accumulate), and muscle contractility (decreases especially in REM sleep). During sleep, partial carbon dioxide ($PaCO_2$) increases 2–8 mmHg while partial oxygen pressure ($PaO_2$) decreases 3–10 mmHg and oxyhemoglobin saturation (SpO2) decreases ~2%. All those changes do not have an adverse effect in healthy individuals but may cause trouble in patients with COPD.

Sleep is typically fragmented with diminished slow wave and rapid-eye-movement (REM), 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 profound in COPD, which can result in clinically important nocturnal oxygen desaturation (NOD). The coexistence of OSA and COPD is common; however, there is little convincing evidence that one disorder predisposes to the other [195].

In the literature, nocturnal COPD symptoms such as nocturnal cough and wheezing were reported up to 53%, and also difficulty initiating or maintaining sleep and excessive daytime sleepiness as 23% [196]. In addition, those have been reported in a significant number of patients and may affect sleep quality in those patients. Several studies have shown that sleep quality is worse in people with COPD compared to healthy individuals. Beyond symptoms, there are nocturnal alterations in ventilation and gas control in patients with COPD [197].

Sleep-induced hypoxemia-nocturnal oxygen desaturation (NOD) is defined as "an $SpO_2$ (oxyhemoglobin saturation) during sleep of <90% for more than 5 min with a nadir of at least 85%" or "> 30% of total sleep time with an $SpO_2$ of <90%" in subject with a baseline awake $SpO_2$ of ≥90%. [198, 199]. 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 [195]. Hypoxic pulmonary vasoconstriction is considered a major driver of the development of pulmonary hypertension and cor pulmonale in COPD, NOD also could cause nocturnal cardiac arrhythmias and nocturnal sudden cardiac death [200, 201]. In another study, daytime hypoxemia, hypercapnia, and reduced $FEV_1$ were found to be predictors of right-heart failure

[202]. McNicholas et al. described nocturnal death was highest among "blue-bloater" type of COPD patients with type 2 respiratory failure, which is more associated with sleep-disordered breathing [203].

Hypoventilation causes the most important gas-exchange alteration during sleep in COPD patients, leading to hypercapnia and hypoxemia, especially during REM sleep. Blood gases alterations lead to increased arousals, sleep disruption, pulmonary hypertension, and higher mortality [198]. Sleep-induced hypoventilation is characterized by elevated levels of $PaCO_2$ while asleep, defined in the ICSD-3 as a level≥45 mmHg or "disproportionately increased relative to levels during wakefulness" [199].

Overlap syndrome first described by Flenley almost 30 years ago, as a coexistence of two diseases: obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) [204]. While OSA and COPD carry its own comorbidities and complications, it has been surmised that patients with overlap syndrome may have a worse prognosis than patients with only one of either disease [204]. Taking into account the individual prevalences of COPD and OSA, it has also been suggested that the prevalence of overlap syndrome in adults aged 40 years and over is 0.5%–1% [205]. The combination of obstructive sleep apnea and COPD does have implications with respect to outcome. The "overlap syndrome" is associated with lower and longer nocturnal oxyhemoglobin desaturations, and produces more severe pulmonary hemodynamic complications. Patients with the overlap syndrome have been reported to exhibit diurnal hypercapnia more frequently, and concomitant COPD patients at risk for overlap syndrome (those with polycythemia, cor pulmonale, or neuropsychological impairment) should be appropriately screened. Oximetry will show sawtoothing oxygen desaturation during NREM periods, with persistently low SpO2 during REM.

There are some indirect data about the prevalence of overlap syndrome. In the Sleep Heart Health Study, a large community-based cohort study which included polysomnography and spirometry, 0.5% of the participants had airflow obstruction [206]. In a European study with predominantly mild COPD patients, OSA occurred in 3% [207].

## Diagnosis

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 [208]. Additionally, it has been suggested that patients with COPD who develop morning headaches following nocturnal oxygen supplementation should undergo a diagnostic polysomnogram. Nocturnal oxymetry is recommended to evaluate gas exchange during sleep in COPD patients. However, the utility of overnight oxygen saturation measurements in suggesting OSA in COPD is quite limited. Nocturnal oximetry may be more useful for evaluating the effectiveness of nocturnal oxygen therapy. Sleep studies are usually indicated when there is a possibility of sleep apnea or obesity-hypoventilation syndrome. Unattended overnight polysomnograms performed in an ambulatory setting (also known as "portable" or "home" sleep studies) have been a common modality for screening for OSA in high-risk patient populations. These studies utilize a limited number of channels, and exact sleep time and arousals from sleep as determined by electroencephalography are often not available [209]. The American Academy of Sleep Medicine (AASM) defines OSA by at least five events per hour of sleep with associated symptoms such as daytime sleepiness, respiratory pauses during sleep, or gasping arousals [199].

## Treatment

The first management principle of sleep-related breathing disturbances in COPD should be to optimize oxygenation. But the concentration of added oxygen should be carefully titrated to bring the arterial oxygen tension ($PaO_2$) up into

the mildly hypoxemic range in order to minimize the tendency towards carbon dioxide retention, particularly during sleep [209].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that supplemental oxygen therapy be provided to patients whose oxygen saturations fall below 88% or who have a $PO_2$ less than 55 mmHg during wakefulness or $PO_2$ between 55 and 60 mmHg with evidence of pulmonary hypertension, congestive heart failure, or polycythemia [208].

In particular, there appears to be a low risk of serious carbon dioxide retention with carefully controlled oxygen therapy during exacerbations of COPD even when relatively high flow oxygen supplementation is required to bring the $SaO_2$ into the region of 90–92% [210]. Thus, the priority in oxygen supplementation should be to provide sufficient oxygen to bring the $SaO_2$ level above 90%, but doing so in a controlled fashion to avoid excessive supplementation. Oxygen supplementation during sleep is best delivered via nasal cannulae, since face masks are more likely to become dislodged during sleep [211]. In the chronic setting, indications for supplemental oxygen are best determined by measures that indicate the overall magnitude of hypoxemia during sleep, such as the cumulative time spent with $SaO_2 < 90\%$.

In addition to correction of hypoxemia is particularly important and in recent years considerable interest has focused 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 ($PaCO_2 > 55$ or 50–54 mmHg with NOD), or (c) $PaCO_2$ 50–54 mmHg with recurrent hospitalization related to episodes of hypercapnic respiratory failure [212]. NPPV appears to decrease the inspiratory work of breathing, reduce diaphragmatic electromyogram activity, improve $PaO_2$, decrease $PaCO_2$, and increase minute ventilation [213]. Either volume or pressure modes are equally effective, but pressure support appears to be better tolerated and more comfortable. Sleep quality and diurnal $PaO_2$ and $PaCO_2$ levels are better with NIV plus supplemental oxygen than with oxygen alone [214]. Patients with the overlap syndrome should also be treated by nocturnal pressure support and the choice between continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) can be determined based on the pattern of sleep-disordered breathing. In cases where OSA predominates, CPAP may be most appropriate, whereas in cases where there is evidence of significant nocturnal hypoventilation with associated periods of sustained hypoxemia, BIPAP may be more appropriate. Newer modalities of pressure support, such as adaptive servo ventilation, may be particularly suited to patients with the overlap syndrome [215].

## Anxiety and Depression in COPD

Patients with COPD who have perceptions of poor health are likely to experience anxiety, depression, sleep disturbance, and problems with daily functioning like patients with any chronic disease. Depending on the methodology and the definition, the prevalence of anxiety and depression are varied between 8 and 80% of COPD patients who report depression and/or anxiety [216–218]. Depression and anxiety are more prevalent in COPD than other diseases and than general population. There is a bidirectional relation between anxiety (RR:1.83), depression (RR:1.27), and COPD. While anxiety and depression increase the worse prognosis in COPD, COPD increases the risk of depression (RR: 1.69) [219]. Hence, $FEV_1$% predicted has been correlated with increased risk of depression [218]. The known risk factors of anxiety and depression include physical disability, oxygen dependence, respiratory symptoms, increased number of comorbidities, female sex, current smoking, low socioeconomic class, marital status, living alone, and poor quality of life [216, 218].

Comorbid depressive symptoms in patients with COPD are associated with poorer survival,

longer hospitalization stay, persistent smoking, increased symptom burden, and poorer physical and social functioning. Interventions that reduce depressive symptoms may potentially affect COPD outcomes [220]. In its final stages, COPD is a severely disabling condition that is characterized by dyspnea, which causes substantial anxiety. Anxiety is associated with an impaired quality of life and increased hospital admissions. Untreated comorbid anxiety can have devastating consequences for both patients and their relatives [221].

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. Quality of life is strongly impaired in COPD patients and patients' quality of life emerges to be more correlated with the presence of depressive symptoms than with the severity of COPD [222]. Whether patients with a history or family history of psychiatric disorders might be predisposed to developing anxious or depressed responses, and whether these responses are especially difficult to treat among those with premorbid conditions, remains to be evaluated. However, it is likely that an improved understanding of the psychiatric history in patients and their families, as well as the role of anxiety or depressive reactions to illness, will influence the management of psychological impairments and ultimately improve health-related quality of life (QoL).

## Treatment

Management of comorbid depression and/or insomnia complaints in COPD patients requires careful consideration of the effects of medications. In addition to medications, alternative non-pharmacologic treatments should also be considered, such as cognitive behavioral therapy [223, 224].

Pulmonary rehabilitation programs have gained increased acceptance in the treatment of COPD, mainly due to their capacity to stabilize and, in some instances, to reverse many physiopathogenic factors involved in airway obstruction [225, 226]. However, studies exploring the role of psychotherapy in the pulmonary rehabilitation program as a way to alter subject anxiety and depression levels have yielded ambiguous results [227–229].

Pulmonary rehabilitation programs have also been described for COPD patients for comorbid 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 [230].

In a study it was shown that in patients with severe COPD, pulmonary rehabilitation induces important changes on depression and anxiety independent of changes in dyspnea and health-related quality of life [231].

In another study comparing cognitive behavioral group treatment and COPD education for anxiety and depression symptoms in COPD patients, it was found that both therapies achieved sustainable improvements in QoL for COPD patients experiencing moderate-to-severe symptoms of depression or anxiety [232].

## COPD and Anemia

World Health Organization (WHO) defines anemia as an hematocrit level, 39% in males and 36% in females [233]. Iron deficiency is common in patients with congestive heart failure, where it has been identified as an independent predictor of mortality [234]. In COPD, iron deficiency could be particularly deleterious since hypoxemia is common, is a marker of disease severity and is important in the pathophysiology and extrapulmonary manifestations of the condition [235]. Hypoxemia and pulmonary hypertension in COPD are both predictors of mortality [235, 236].

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 [237]. Systemic inflammation seems to be an important factor for its establishment and

repeated bursts of inflammatory mediators during COPD exacerbations could further inhibit erythropoiesis. However, renal impairment, malnutrition, low testosterone levels, growth hormone level abnormalities, oxygen supplementation, theophylline treatment, inhibition of angiotensin-converting enzyme, and aging itself are additional factors that could be associated with the development of anemia [238].

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. Anemia in COPD is associated with greater health care resource utilization, impaired quality of life, decreased survival, and a greater likelihood of hospitalization [239].

In a study, a linear relationship was found between hemoglobin levels, exercise capacity, and quality of life [240]. In a database cohort of 2524 COPD patients being prescribed long-term oxygen therapy for the first time, authors reported a prevalence of anemia of 12.6% in males and 8.2% in females, higher than that of polycythemia (8.4% of the patients) defined by an hematocrit level 54% [241]. The ANTADIR hematocrit study suggests that low hematocrit values are associated with an increased morbidity [241].

Schönhofer et al. demonstrated that correction of anemia with blood transfusions among 20 patients with severe COPD significantly reduced disease-related elevations in minute ventilation and work of breathing, suggesting that anemia correction may be beneficial in alleviating dyspnea and improving exercise capacity [242]. They also demonstrated that among five patients with severe anemia, successful treatment of anemia resulted in an increased ability to wean patients from mechanical ventilation [243].

In a recent study, it has been demonstrated that a high prevalence of non-anemic iron deficiency in COPD may be driven by inflammation. Inflammation elevates hepcidin, which reduces serum iron and dietary iron absorption. Hepcidin is therefore important in the pathogenesis of the anemia of chronic disease [244].

## Treatment

As in other chronic conditions, anemia predicts a worse outcome in COPD, both in the setting of admission with an acute exacerbation and in the long term so it is very important to manage anemia in management of COPD. Therapeutic possibilities include both the manipulation of iron status through intravenous iron therapy and hepcidin antagonists becoming available in recent years [244].

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