Key Points
1. COPD is a disorder that affects multiple systems beyond the lungs; these nonpulmonary manifestations include cardio- and cerebrovascular, oncologic, musculoskeletal, hematologic, psychological, and endocrine effects.
2. Much of the early mortality related to COPD is caused by cardiac and oncologic effects of COPD; late mortality is caused by respiratory failure.
3. Significant COPD-related morbidity is due to nonpulmonary manifestations.
4. In general, management of the extra-pulmonary manifestations of COPD is the same as treatment of these processes when they are not associated with COPD.
5. It remains to be determined if treatment of COPD ameliorates its nonpulmonary manifestations and whether management of COPD’s extrapulmonary processes improves the health and wellbeing of individuals with COPD.

10.1 Introduction

Although COPD is usually defined and managed as a disorder confined to the lungs, numerous investigations over the past decade have demonstrated that COPD is associated with multiple nonpulmonary manifestations that contribute significantly to its morbidity and mortality. These associated processes include cardiac and cerebrovascular, oncologic, musculoskeletal, hematologic, psychological, and endocrine effects (Cavailles, 2013; Albu, 2012; Huertas, 2011; Nussbaumer-Ochsner, 2011; Barnes, 2009; Decramer, 2008; Augusti 2007; Augusti, 2008; Fabbri, 2008).

10.2 Inflammation in COPD

The pathophysiologic process linking pulmonary and nonpulmonary manifestations of COPD has been postulated to be inflammation. For a detailed review of the pathogenesis of pulmonary and systemic inflammation in COPD, please see chapter 6, Pathogenesis of COPD.

10.3 COPD Mortality

As discussed in Chapter 9, Natural History of COPD, Phenotypes, and Gender Differences in COPD, the major causes of death in individuals with early COPD (measured
by severity of airflow limitation (AFL)) are lung cancer and cardiac disease (Sin, 2006; Mannino, 2006). During acute exacerbations of COPD, the leading causes of death are heart failure (37.2%), pneumonia (27.9%), pulmonary (20.9%), and respiratory failure (14%) (Zvezdin, 2009). Even when adjusted for sex and smoking history, individuals with AFL have an increased risk for acute myocardial infarction, hazard ratio (HR) 3.53 [95% confidence interval, 3.02–4.13] and for stroke, HR 2.79 [2.56–3.04] (Feary, 2010). For individuals aged 35–44 years old, the risk is even greater, acute myocardial infarction, HR 10.34 [3.28–32.60] and stroke, HR 3.44 [0.85–13.84] (Feary, 2010).

A 17 year longitudinal study of mortality among patients with COPD from 1987 to 2004 who were started on long term oxygen in Sweden showed that 71% of patients died of respiratory causes, 16% circulatory processes, and 7.6% from cancer (Ekstrom, 2011). However, the adjusted annual change in mortality due to COPD declined by 3.0% annually whereas nonrespiratory causes of death rose by 6.3% annually. Another Swedish longitudinal study of 21,361 patients diagnosed with COPD from 1999 to 2009 showed that the number of COPD exacerbations declined from 3.0 to 1.3 exacerbations/patient/year and the number of hospitalizations decreased from 1.02 to 0.2 per patient per year (Stallberg, 2014). Long acting anti-cholinergic and inhaled corticosteroid/long acting beta agonist prescriptions increased from 0% to 36% and 37% of patients, respectively (Stallberg, 2014). Thus, respiratory morbidity and mortality among those with COPD are declining but nonrespiratory morbidity and mortality are increasing. These improvements in respiratory mortality may be due to better pharmacologic and nonpharmacologic management of COPD. The increase in nonrespiratory related mortality suggests that greater identification and management of nonpulmonary processes associated with COPD may be warranted to improve the longevity and health of individuals with COPD.

10.4 Cardio- and Cerebral-vascular Disease

The prevalence of cardiovascular (CV) disease in individuals with COPD, 20–22%, is over two-fold greater than in the general population who do not have COPD, 9% (Mannino, 2008). Among patients with AFL, the prevalence of cardiovascular disease is increased over 2 fold (odds ratio (OR) = 2.7, 95% CI 2.3–3.2) (Finkelstein, 2009). Reduced FEV\textsubscript{1} is associated with increased CV mortality independent of age, gender, and smoking history (Sin, 2005A). Adjusted CV mortality rises by 28% for every 10% decrease in FEV\textsubscript{1} (Sin, 2005B). Coronary artery calcifications detected by CT scanning were increased in individuals with COPD compared with smokers with normal spirometry or nonsmokers and correlated with dyspnea, exercise capacity, all cause mortality, and inflammatory markers (IL6, IL8, CCP 16, SP D, and neutrophils) but not FEV\textsubscript{1} or acute exacerbations of COPD (Williams, 2014).

Acute COPD exacerbations are associated with an increased rate of myocardial infarction. Elevated cardiac enzymes occur in 17–27% of patients hospitalized for
COPD exacerbations and MI occurs in 1:12 patients (McAllister, 2012). There is a 2.27 fold increase in MI during the 5 days after onset of a COPD exacerbation (Donaldson, 2010). Acute COPD exacerbations may increase the risk of cardiac ischemia and infarction through demand ischemia, acute coronary syndrome with plaque rupture, peripheral arterial stiffness, interactions between the heart and lungs including increased right and left ventricular afterload due to increased intrathoracic pressures, medication effects, and cardiac muscle mass depletion (Harvey, 2014; Visca, 2013).

β blockers significantly decrease mortality after myocardial infarction in patients with COPD (Quint, 2013). Of 1063 patients with COPD presenting with an initial MI from 2003–2008, the mortality HR was 0.59 [95% confidence interval (CI), 0.44–0.79] for those who were taking β blockers at presentation and 0.50 [95% CI, 0.36–0.69] for those who started β blockers during that admission (Quint, 2013). β blockers are tolerated well by patients with all stages of COPD including individuals who demonstrated bronchodilator responsivity during spirometry testing (Salpeter 2002, 2003, 2004, 2005).

10.4.1 Heart Failure

Approximately 19–48% of patients with heart failure have COPD and 9–52% of patients with COPD have heart failure (Hawkins, 2009). The relative risk of developing heart failure among patients with COPD is 4.5 controlling for age and cardiovascular risk factors. Coexistent COPD and heart failure is associated with greater mortality and healthcare utilization than either disorder alone (Hawkins, 2013).

It may be difficult to distinguish COPD and heart failure because the symptoms frequently overlap and include nonspecific features such as exertional dyspnea, fatigue, and reduced activity. The presence of lower extremity edema may be due to cor pulmonale or left ventricular failure. Emphysematous changes may mask the presentation of pulmonary edema on chest radiographs and it may be difficult to determine heart size. Echocardiography may be technically difficult in patients with COPD due to hyperinflation and attenuation of the ultrasound signal. Minor elevations in B-type natriuretic peptide (BNP) may be nonspecific and due to cor pulmonale, pulmonary hypertension, left, right, or biventricular failure. A BNP greater than 400 pg/ml suggests left ventricular failure and warrants evaluation of LV function with an ECHO. Finally, use of inhaled bronchodilators in patients who have heart failure but do not have COPD is associated with a 69% increase in mechanical ventilation and a 40% increase in intravenous vasodilator use (Singer, 2008).

Most pharmacologic treatment trials of respiratory medications for COPD have excluded concomitant heart failure. Chronic β blocker use in individuals with COPD and CHF is considered to be safe and β blockers can be continued during hospitalizations for COPD exacerbations (Stefan, 2012). Statins, ACE inhibitors, and angiotensin receptor blockers reduce respiratory related hospitalizations among individuals with
COPD (Mancini, 2006) and statin and ACE inhibitor use at the time of admission is associated with a reduction in mortality (Mortenson, 2009). In contrast, patients with left ventricular heart failure who are treated with β agonists have increased mortality and hospitalization (Au, 2003). The use of systemic steroids (more than 20 mg/d of prednisone) increases the risk of heart failure decompensation (Souverein, 2004) and phosphodiesterase inhibitors are associated with an increased risk of dysrhythmias (Barnes, 2013). There is an increasing need to assess and determine the optimal management of COPD in individuals who also have heart failure (Hawkins, 2009, 2011, 2013; Mentz, 2012).

**10.5 Lung Cancer**

Of 100 smokers, approximately 20 will develop COPD, and, of those 20 individuals, 5 will develop lung cancer whereas of the 80 smokers who do not develop COPD, only 5 will develop lung cancer (Young, 2009). Thus, the risk of lung cancer is significantly greater in smokers with COPD, 1:4, compared with smokers who do not have COPD, 1:16. (Figure 10.1) The relative risk of lung cancer in individuals with a diagnosis of COPD is 2.22 [1.66–2.97], chronic bronchitis 1.52 [1.25–1.84], and emphysema 2.04 [1.72–2.41] (Brenner, 2011). The visual detection of emphysema on CT scans increases the odds ratio for lung cancer, 3.5 [2.71–4.51] (Smith, 2012).

Between 50% and 90% of all lung cancer patients have COPD (deTorres, 2007; Turner, 2007; Wilson, 2008; Young, 2009). COPD is associated with a 2 to 6-fold increase in lung cancer risk compared with smokers who do not develop COPD (deTorres, 2007, 2011; Mannino, 2003; Turner, 2007; Wilson, 2008; Young, 2009). AFL increases the risk of lung cancer independent of the smoking history (Wilson, 2008). Several studies have found that the risk of lung cancer is greater in individuals with mild to moderate AFL compared to those with more severe COPD (Young, 2009;
Anthonisen, 2005; deTorres, 2011); whereas others have found that the lung cancer risk increases with the decline in lung function (Mannino, 2003). The presence of COPD portends a worse prognosis for individuals with lung cancer (Kiri, 2010). Thus, not only is the risk for lung cancer greater for smokers who develop AFL, they generally do worse.

10.5.1 Pathogenetic Links Between COPD and Lung Cancer

The strong association between lung cancer and COPD has spurred studies to discover common cellular and molecular pathways for these two processes (Houghton, 2013; Adcock, 2011; Yang, 2011; Young, 2011). Inhalation of tobacco smoke in genetically susceptible individuals may generate inflammation and reactive oxygen species within the lungs and systemically (El-Zein, 2012). These inflammatory cytokines and reactive biochemical compounds may induce or repress gene expression and cause alterations in genetic and epigenetic complexes leading to deranged cellular proliferation and altered lung airway and parenchymal anatomy and function (Lee, 2009). Other recently discovered biologic pathways are also common to the development of COPD and lung cancer. MicroRNA's modulate post-translational gene regulation and are critical for lung development, pulmonary inflammation, and the development of bronchogenic carcinoma (Sittka, 2013). The biologic processes maintaining telomeres, the DNA-protein caps on the ends of chromosomes, have also been implicated in the pathogenesis of several pulmonary processes including idiopathic pulmonary fibrosis, COPD, and lung cancer and may be another common pathway that is deranged in these disorders (Ganser, 2013). Unifying pathogenetic processes for COPD and lung cancer are being intensely investigated to identify common pathways and means to interdict the development of both of these disorders.

10.5.2 Lung Cancer Screening

Based upon the American National Lung Screening Trial that demonstrated a 20% reduction in lung cancer mortality in the group that underwent low dose CT scan screening examinations, current recommendations advise lung cancer screening for smokers or former smokers with at least 30 pack years smoking history and age between 55 and 74 years (The National Lung Screening Trial Research Team, 2011; Wender, 2013). Although lung cancer screening has not been recommended for individuals with COPD, based upon the results of the NLST, low dose chest CT scanning screening may be beneficial for individuals with COPD, even with moderate AFL. Earlier detection of AFL and diagnosis of COPD may identify individuals with even greater potential benefit from lung cancer screening (Sekine, 2012).
10.5.3 Management of Lung Cancer

Multiple clinical practice guidelines for lung cancer have been published (von Dincklage, 2013). Evaluation and management of suspected lung cancer in a patient with COPD begins with radiographic and cardiopulmonary physiologic assessments (Backhus, 2013). In general, once the histopathological diagnosis is confirmed or the clinical suspicion for lung cancer is sufficiently high, the critical decision is to determine whether the patient is a candidate for surgical excision of the cancer. Only 15–25% of lung cancers are operable at the time of diagnosis (Von Groote-Bidlingmaier, 2011). Essential components for the determination of a patient’s candidacy for surgical resection of bronchogenic carcinoma include radiographic staging of the cancer and assessment of cardiovascular and pulmonary physiologic function. Because of the high prevalence of coronary artery disease among individuals with COPD, ascertainment of the cardiovascular risk for anesthesia and thoracic surgery should be pursued. If either the FEV1 or DLCO are less than 80% of predicted, the postoperative lung function should be calculated by either quantitative perfusion scans or the anatomic method based upon the number of lung segments to be resected. If either the FEV1 or DLCO % predicted is less than 40%, the patient is at increased risk for perioperative respiratory complications including death, infections, respiratory compromise or failure, and requirement for supplemental oxygen. In patients with marginal pulmonary physiologic function, cardiopulmonary exercise testing demonstrating a maximal oxygen consumption (VO2 max) less than 15 ml/kg/min precludes surgery (Colice, 2007). Combined lung volume reduction surgery and lung cancer surgical resection in a selective population of patients with emphysema in a upper zone predominant distribution and cancer stage amenable to resection may improve postoperative lung function and respiratory symptoms as well as permit resection in patients who might otherwise not be considered for surgery (Choong, 2009; Colice, 2007).

Historically, the most common lung cancer subtype among male smokers was squamous cell carcinoma but more recent studies show that by the mid 1990’s adenocarcinoma was the most frequent histopathologic subtype regardless of gender or smoking history (Devesa, 2005).

Surgery is the first line treatment for lung cancer depending upon stage and surgical and operative risk factors. For patients with nonresectable lung cancer, chemotherapy, radiation therapy, or combination therapy may be pursued after referral to oncologists and radiation specialists.

Pulmonary rehabilitation may benefit patients with lung cancer and COPD by improving quality of life, performance status, oxygen consumption, exercise tolerance, chemotherapy-associated fatigue, and perioperative morbidity and mortality (Pasqua, 2013; Shannon, 2010; Nici, 2009). Palliative care improves the quantity and quality of life in individuals with lung cancer (Davis, 2012; see chapter 19, End of Life Issues/Palliative Care).
The clinical syndrome of combined pulmonary fibrosis and emphysema (CPFE) has recently been defined by the presence of breathlessness, upper lobe emphysema, lower lobe fibrosis, and deranged pulmonary gas exchange (Jankowich, 2012). Nearly all patients with this syndrome have been smokers and 90% are male (Jankowich, 2012).

**Figure 10.2:** Flow volume loop from a patient with combined pulmonary fibrosis and emphysema. The flow volume loop demonstrates reduced peak expiratory flow rates and scooping of the expiratory loop.

### 10.6 Pulmonary Fibrosis

The clinical syndrome of combined pulmonary fibrosis and emphysema (CPFE) has recently been defined by the presence of breathlessness, upper lobe emphysema, lower lobe fibrosis, and deranged pulmonary gas exchange (Jankowich, 2012). Nearly all patients with this syndrome have been smokers and 90% are male (Jankowich, 2012).
Patients typically present with breathlessness and pulmonary physiologic testing reveals profoundly reduced DLCO but relatively preserved lung volumes due to pseudonormalization. This effect is due to the opposite effects of the fibrosis which reduces lung volumes and emphysema which causes hyperinflation; these two opposing forces result in relatively normal lung volumes whereas both adversely affect DLCO, causing it to be disproportionately reduced. (Figure 10.2 and 10.3). The reduction in DLCO is associated with significant hypoxemia and requirement for supplemental oxygen (Cottin, 2005). The chest radiograph often shows basilar reticulo-linear opacifications with reduced upper zone lung markings (Figure 10.4 and
Chest CT scans demonstrate emphysematous changes in the upper lung zones and reticular opacifications with honeycombing in the lung bases. (Figure 10.6) The median survival is only 2.1–8.8 years and is adversely affected by the development of pulmonary hypertension and lung cancer which occur frequently in association with CPFE.

Treatment of CPFE depends upon early recognition and smoking cessation, institution of supplemental oxygen to prevent desaturation, and management of COPD. It is not yet known whether the recently discovered effective treatments for idiopathic pulmonary fibrosis, pirfenidone or nintedanib, are beneficial in patients with CPFE. It is also not known whether PH treatment modulates the disease course. Lung cancer screening has not been assessed in patients with CPFE but the increased incidence of lung cancer would suggest potential benefit to earlier detection if the patients are candidates for surgical resection.

Figure 10.4: Posterior-apical chest radiograph demonstrating increased bi-basilar reticulo-linear opacifications with preservation and areas of reduced apical lung markings.
Although polycythemia associated with hypoxemia is often considered the principle hematologic manifestation of COPD, anemia occurs in 7.5–32.7% of patients with COPD (Yohannes, 2011; Cote, 2007; Chambellan, 2005; Shorr, 2008; Nowinski, 2011; Portillo, 2013). Only 6% of 683 patients with COPD had polycythemia whereas 17% had anemia (Cote, 2007). COPD–related anemia is characterized by a normal to low MCV, low serum iron, and normal to increased ferritin and is associated with higher systemic inflammation (including IL6 and CRP), greater healthcare costs, and mortality (Kollert, 2013). The anemia of COPD is believed to be due to chronic inflammation (anemia of chronic disease). Inflammatory cytokines such as TNF α and IL6 suppress hepcidin synthesis and inhibit erythropoietin which decreases iron availability and decreases erythropoiesis.

Figure 10.5: Lateral chest radiograph from a patient with combined pulmonary fibrosis and emphysema.

10.7 Hematologic Manifestations

Although polycythemia associated with hypoxemia is often considered the principle hematologic manifestation of COPD, anemia occurs in 7.5–32.7% of patients with COPD (Yohannes, 2011; Cote, 2007; Chambellan, 2005; Shorr, 2008; Nowinski, 2011; Portillo, 2013). Only 6% of 683 patients with COPD had polycythemia whereas 17% had anemia (Cote, 2007). COPD–related anemia is characterized by a normal to low MCV, low serum iron, and normal to increased ferritin and is associated with higher systemic inflammation (including IL6 and CRP), greater healthcare costs, and mortality (Kollert, 2013). The anemia of COPD is believed to be due to chronic inflammation (anemia of chronic disease). Inflammatory cytokines such as TNF α and IL6 suppress hepcidin synthesis and inhibit erythropoietin which decreases iron availability and decreases erythropoiesis.
Anemia in patients with COPD is associated with higher levels of dyspnea and diminished 6 minute walk distances (Cote, 2007) and anemic individuals with COPD have reduced exercise capability during cardiopulmonary exercise testing with greater breathlessness (Bouton, 2011). Patients with COPD and anemia have worse quality of life measured by the physical functioning and physical component scores on the Short Form-36 survey compared with those with normal hemoglobin levels (Krishnan, 2006). Anemia is associated with increased healthcare utilization, prolonged...
length of hospital stay, more frequent readmissions, greater healthcare costs, and mortality among individuals with COPD (Chambellan, 2005; Shorr, 2008; Nowinski, 2011; Halpern, 2006; Barba, 2012; Martinez-Rivera, 2012; Martinez-Rivera, 2012; Celli, 2004). The one year mortality after hospitalization for a COPD exacerbation was approximately 40% in anemic individuals but only 10% in those with normal hematocrits (Martinez-Rivera, 2012).

It is not known whether treatment of anemia associated with COPD improves survival, alters respiratory symptoms, reduces healthcare utilization, or COPD related health care costs. Red blood cell transfusions may assist in ventilator liberation and reduce minute ventilation and work of breathing in critically ill patients with COPD who require mechanical ventilator support (Schonhofer, 1998A, 1998B).

The number of circulating bone marrow-derived progenitor cells is reduced in patients with COPD (Huertas 2011, 2010; Palange, 2006; Fadini, 2006).

10.8 Musculoskeletal

The prevalence of osteoporosis is greatly increased in individuals with COPD and ranges from 24–69% depending upon the population studied and the severity of AFL (Graat-Verbom, 2009). Vertebral fractures occur in 24%-63% of patients with COPD and predominantly involve T7, T8, and T12 (Jorgensen, 2007; Nuti, 2009; Papioannou, 2003; McEvoy 1998). Approximately 10% of patients admitted with COPD exacerbations have chest radiographs documenting vertebral compression fractures (Majumdar, 2010). These compression fractures may decrease patients’ heights affecting the normative equations for predictive values used in the interpretation of pulmonary function testing. Therefore, it may be beneficial to consider using arm span in determining the predicted normal values in patients with COPD who have severe vertebral fracture associated kyphosis. Further, the vertebral fractures may lead to a reduction in lung volumes. Each vertebral fracture is associated with a 9% reduction in the FVC (Leech, 1990).

Osteoporosis is more prevalent in patients with COPD who have emphysema and an increase in the RV to TLC ratio, a lower BMI, are older, have used systemic steroids or chronic supplemental oxygen, and have worse AFL (Graat-Verboom, 2012; Ogura-Tomomatsu, 2012). Systemic inflammation measured by CRP, TNFα and IL 6 is greater in patients with COPD with osteopenia or osteoporosis than in those individuals with normal bone density (Liang, 2011).

Of 12,646 Veterans undergoing hip fracture surgery in the VHA from 1998 to 2005, 5,944 (47%) had COPD and a diagnosis of osteoporosis was known before the hip fracture in only 3% of cases (Regan, 2013). Using the FRAX® tool to estimate the risk of hip fracture in Spanish patients admitted with an acute exacerbation of COPD, 1.8% (95%CI: 0.9–3.6) had a 10 year probability of > 20% for a major osteoporotic fracture and 49.7% (95% CI: 44.8–54.7) had a probability of hip fracture >3% (Diez-Mangiano,
Thus, nearly half of individuals with hip fractures have COPD and the presence of COPD portends a very high likelihood of future hip fracture.

The 3 year fracture rate HR ranged from 5.1–6.3 across the various treatment and placebo groups in the TORCH trial (Ferguson, 2009). Hip fractures occurred most commonly, followed by wrist, spine, and rib fractures.

10.8.1 Risk Factors for Fractures in Individuals with COPD

Osteoporosis and falls are major risk factors for fractures and occur commonly in individuals with COPD. In an analysis of 14,828 subjects participating in the National Health and Nutrition Examination Survey (NHANES) from 1999–2008, individuals with physician-diagnosed COPD were more likely than those without physician-diagnosed COPD to have osteoporosis (16.9% vs 8.5%) and more likely to report mobility difficulty (55.6% vs 32.5%) and dizziness/balance problems (41.1% vs. 23.8%) (Schnell, 2012)

10.8.2 Osteoporosis

In individuals with COPD, the prevalence of osteoporosis and osteopenia range from 9–69% and 27–67%, respectively (Graat-Verboom, 2009; Lehouck, 2011; Graat-Verboom, 2011; Jorgensen, 2007; Rittayamai, 2012). In a longitudinal cohort study of 102 patients with COPD, 16 of 48 (33%) patients with normal initial bone density developed osteoporosis over 3 years (Graat-Verboom, 2012). In the TORCH trial, 18% of men and 30% of women had osteoporosis and 42% of men and 41% of women had osteopenia at baseline based on bone mineral density measurements (Ferguson, 2009).

Evaluation of bone mineral density in patients with COPD should include a comprehensive history and physical examination to identify risk factors associated with reduced bone mineral density, fractures, and bone loss, determination of vitamin D levels, DEXA, and spine radiographs, especially in individuals with back pain, height loss, or kyphosis (Mazokopakis, 2011). Treatment of osteoporosis in individuals with COPD includes pharmacologic and nonpharmacologic interventions (Table 10.1).

10.8.3 Falls

Despite the presence of multiple predisposing factors to falls, the prevalence and incidence of falls in individuals with COPD has not been studied extensively. In a study comparing 36 patients with COPD with 20 normal individuals, hypoxemia, dyspnea, and fatigue were associated with balance impairment and falls (Ozalevli, 2011). In a retrospective study, 46% of 39 participants with COPD (mean FEV1% predicted
42%) reported at least one fall in the preceding year. Those with self-reported falls scored lower on the Activity-Specific Balance Confidence (ABC) Scale (66 v 82) and the Berg Balance Scale (BBS) (45 v 49), and had prolonged times on the Time Up and Go Test (TUG) 17 v 14 s. Falls correlated with the use of supplemental oxygen and dyspnea severity (Beauchamp, 2009). Another retrospective study found that 25% of 80 patients with COPD (mean FEV1% predicted 47.5%) reported a fall in the prior year and 29% expressed a fear of falling (Hellstroem, 2009). In a prospective study of 101 patients with COPD (mean FEV1% predicted 46%) for 6 months, 31.7% reported at least one fall and the fall incidence rate was 0.1 (95% CI: 0.06–0.14) falls per person/month. Risk factors for falls included age, sex, oxygen requirement, history of prior falls, co-morbidities, number of medications (Roig, 2011A).

Factors contributing to the increased risk of falling in patients with COPD include alterations in proprioception (Janssens, 2013), impaired postural and balance control mechanisms (Roig, 2011B; Beaucham, 2009; Butcher, 2004; Eisner, 2008; Smith, 2010), slower reaction times, reduced physical activity levels, and skeletal muscle weakness (Beauchamp, 2012).

### 10.8.4 Muscle Weakness

Skeletal muscle dysfunction in patients with COPD is characterized by muscle atrophy (decreased mass and cross-sectional area), deranged distribution of fiber types (fewer oxidative fibers and more glycolytic fibers), altered metabolic capacity (diminished mitochondrial enzyme activities and expression), and reduced vascular supply (loss of capillary density) that cause diminished muscle strength and endurance (Kim, 2008; Gea, 2013). Factors that contribute to skeletal muscle dysfunction include disuse and inactivity, systemic inflammation, malnutrition, corticosteroid use, hypoxemia, senescence, and myocyte biochemical derangements including reactive oxygen and nitrogen species production, and muscle fiber degradation due to increased calpain and caspase activities (Kim, 2008). Quadriceps muscle strength is

### Table 10.1: Management of Osteoporosis Associated with COPD

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<tr>
<th>Pharmacologic</th>
<th>Nonpharmacologic</th>
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<td>Calcium and vitamin D</td>
<td>Balanced nutrition</td>
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<td>Bisphosphonates</td>
<td>Smoking cessation</td>
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<tr>
<td>Teriparatide</td>
<td>Exercise, including pulmonary rehabilitation</td>
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<td>Strontium ranelate</td>
<td>Fall prevention</td>
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<td>Denosumab</td>
<td>Lung volume reduction surgery (Mineo 2005)</td>
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20–30% less in individuals with moderate to severe COPD compared with those who do not have COPD (Gosselink, 1996; Bernard, 1998; Franssen, 2005).

10.9 Diabetes

Approximately 12.6–14.5% of individuals with COPD have diabetes mellitus (DM) (Mannino, 2008, Laghi, 2009). Patients with COPD have an odds ratio of developing diabetes of 2.04 [1.97–2.12] compared with those who do not have a physician diagnosis of COPD (Feary, 2010). The relative risk of diabetes is 1.8 [1.1–2.8] in patients with COPD compared with those with asthma (Rana, 2004). The presence of both DM and COPD increases the risk of death and the length of hospitalizations for patients with AECOPD and diabetes is 10.3% longer than those who do not have DM (Burt, 2013; Parrapil, 2010; Emerging Risk Factors Collaborative, 2011). In one study, the length of stay increased by 10% for each mmol/L increase in mean glucose level (Burt, 2013).

Treatment with prednisone is associated with afternoon and evening hyperglycemia rather than elevated morning glucose levels (Burt, 2011). Therefore, it may be beneficial to monitor glucose levels later in the day and adjust insulin type and dosing for individuals with COPD and DM who require insulin and are being treated with long term corticosteroids.

Individuals with COPD and metabolic syndrome have more frequent and longer exacerbations than those who do not have metabolic syndrome (Kupeli, 2010).

10.10 Conclusion

Over the past decade, COPD has been recognized as a systemic process that extends beyond the lungs to involve nearly all other organs and systems. This widespread involvement is believed to be mediated through systemic inflammation. Respiratory failure is the major cause of mortality in individuals with more severe respiratory impairment whereas cancer and cardiovascular processes predominant in those individuals with more mild airflow limitation. Death due to respiratory causes has been decreasing with improvements in COPD management but mortality due to nonrespiratory causes is increasing. The systemic manifestations of COPD are increasingly being recognized as contributing to the mortality and morbidity caused by COPD. The increase in nonrespiratory related mortality and morbidity suggests that earlier identification and management of nonpulmonary processes associated with COPD may be warranted to improve the longevity and health of individuals with COPD.
10.11 Summary Points

1. Comorbidities associated with COPD contribute significantly to COPD mortality and morbidity.
2. In individuals with similar smoking histories, the presence of airflow limitation increases the risk of lung cancer by approximately 3–4 fold.
3. Ischemic heart disease and heart failure contribute significantly to COPD morbidity especially in those with less severe disease (more mild to moderate AFL).
4. Individuals with COPD can be treated safely with β blockers and, with concurrent myocardial ischemia, have lower mortality than those who do not receive β blockers; in contrast, β agonists are associated with increased morbidity and mortality especially in patients with COPD and heart failure.
5. Fractures occur more often in individuals with COPD due to increased prevalence of osteoporosis/penia, muscle weakness, and gait and balance instability.
6. Increased awareness, detection, and treatment of nonpulmonary manifestations of COPD will be critical in improving quality of life and wellbeing of individuals with COPD.

References


COPD Is a Multi-Organ Disorder: Systemic Manifestations


References


References


