Osteoporosis in Chronic Obstructive Pulmonary Disease

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a lifestyle-related chronic inflammatory pulmonary disease associated with significant morbidity and mortality worldwide. COPD is associated with various comorbidities found in all stages of COPD. The comorbidities have significant impact in terms of morbidity, mortality, and economic burden in COPD. Management of comorbidities should be incorporated into the comprehensive management of COPD as this will also have an effect on the outcome in COPD patients. Various comorbidities reported in COPD include cardiovascular disease, skeletal muscle dysfunction, anemia, metabolic syndrome, and osteoporosis. Osteoporosis is a significant comorbidity in COPD patients. Various risk factors, such as tobacco smoking, systemic inflammation, vitamin D deficiency, and the use of oral or inhaled corticosteroids (ICSs) are responsible for its occurrence in patients with COPD. This review will focus on the prevalence, pathogenesis, risk factors, diagnosis, and treatment of osteoporosis in COPD patients.

KEYWORDS: COPD, osteoporosis, RANK, osteoprotegerin

Introduction

Chronic obstructive pulmonary disease (COPD) is a lifestyle-related chronic inflammatory pulmonary disease and a major cause of morbidity and mortality globally. The projection is that by the year 2020, COPD would become the third leading cause of death globally.¹ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 update defined COPD as a “common preventable and treatable disease, characterized by persistent airflow limitation that is progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”² The importance of comorbidities has been reflected in the recent GOLD guideline. Comprehensive management of COPD should include routinely the assessment for comorbidities as comorbidities are associated with an increase risk of hospitalization, mortality, and worsening health status.³⁻⁴ Various comorbidities reported in COPD patients include cardiovascular disease, lung cancer, osteoporosis, diabetes, anxiety/depression, and obstructive sleep apnea.⁵ Osteoporosis is the most common metabolic bone disorder worldwide and is a significant comorbidity in COPD patients.⁶⁻⁷ The World Health Organization (WHO) defined osteoporosis as “a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰ The strength of the bone depends on bone mineral density (BMD) and bone quality. The BMD is measured by the dual-energy X-ray absorptiometry (DEXA) scan, whereas the bone quality is measured by the microarchitecture analysis, markers of bone turnover, accuracy of bone health assessment, and low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰ The strength of the bone depends on bone mineral density (BMD) and bone quality. The BMD is measured by the dual-energy X-ray absorptiometry (DEXA) scan, whereas the bone quality is measured by the microarchitecture analysis, markers of bone turnover, accuracy of bone health assessment, and low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰ The strength of the bone depends on bone mineral density (BMD) and bone quality. The BMD is measured by the dual-energy X-ray absorptiometry (DEXA) scan, whereas the bone quality is measured by the microarchitecture analysis, markers of bone turnover, accuracy of bone health assessment, and low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰ The strength of the bone depends on bone mineral density (BMD) and bone quality. The BMD is measured by the dual-energy X-ray absorptiometry (DEXA) scan, whereas the bone quality is measured by the microarchitecture analysis, markers of bone turnover, accuracy of bone health assessment, and low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰ The strength of the bone depends on bone mineral density (BMD) and bone quality. The BMD is measured by the dual-energy X-ray absorptiometry (DEXA) scan, whereas the bone quality is measured by the microarchitecture analysis, markers of bone turnover, accuracy of bone health assessment, and low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”¹⁰

Impact of Osteoporosis on COPD Patients

Osteoporosis is a silent disease unless it is complicated by fractures. Patients with osteoporosis are at an increased risk of fracture, particularly fragility fractures. Frailty fractures are caused by injury that would be insufficient to break a normal
bone. The impact of osteoporosis- and osteoporosis-induced fractures in COPD patients is enormous.

The most common type of osteoporosis-induced fracture is the vertebral compression fractures (VCFs). VCFs are associated with back pain and kyphosis. Kyphosis can cause loss of height, resulting in impaired lung function. Every single VCF decreases the vital capacity by 9%, and the lung function impairment is most notable when kyphotic angle is more than 55°. The impact of reduced lung function would be more pronounced in COPD patients with already poor lung reserve. Patients with rib fractures may develop exacerbations of COPD because of chest pain-induced hypoventilation and decreased ability to expectorate. Moreover, osteoporotic fractures in COPD may further decrease the mobility of the patients, thereby, predisposing them to the risk of deep venous thrombosis (DVT) and pulmonary embolism. Therefore, diagnosis and prevention of osteoporosis should be an important goal in the management of patients with COPD. This review will focus on epidemiology, pathogenesis, diagnosis, and management of osteoporosis in patients with COPD.

**Low BMD in COPD Patients**

The National Health and Nutrition Examination Survey (NHANES), which included 14,828 subjects aged 45 years or older, noted a 16.9% prevalence of osteoporosis in COPD patients compared with 8.5% in subjects without coexisting COPD. Graat-Verboom et al. in a systematic review of 13 studies involving 775 COPD patients reported an overall prevalence of osteoporosis of 35.1% (range 9–69%) and osteopenia of 38.4% (range 27–67%). There were more male patients (67% vs. 33%). Predictors of osteoporosis or a low BMD in COPD patients include low BMI, low fat-free mass index (FFMI), severity of COPD, and treatment with corticosteroids. In a cross-sectional study, Silva et al. evaluated the BMD of clinically stable COPD patients by DEXA scan and reported osteoporosis and osteopenia each in 42% of patients. There was a significant correlation between BMD and BMI, level of physical activity, and BODE index (Body-mass index, airflow Obstruction, Dyspnea, and Exercise). They also reported significantly impaired pulmonary function tests in patients with low BMD than in patients with normal BMD. However, no correlation was found between BMD and sun exposure, corticosteroid treatment, or smoking. There are very few studies related to the prevalence of osteoporosis in COPD patients in India. Hattiholi and Gaude measured the BMI in COPD patients by DEXA scan. They reported osteoporosis in 68 patients (66.6%) and osteopenia in 20 patients (19.6%). Independent predictors of low BMD in COPD patients are severity of COPD, number of exacerbations, and steroid cumulative dose of >1,000 mg. Bhattacharyya et al. studied BMD by ultrasound bone densitometer in a small number of advanced COPD patients and reported osteopenia/osteoporosis in 27 (73%) patients. There was male predominance in both the studies. There were certain limitations of Bhattacharyya et al study. First, they included only advanced COPD patients. Second, BMD was measured by ultrasound bone densitometer and not by DEXA scan. Lastly; a single heel measurement was used in their study. The multicentric TORCH (TOwards a Revolution in COPD Health) study, which included 658 COPD patients, had reported osteoporosis in 23% and osteopenia in 43% patients at the hip or the lumbar spine on DEXA scan.

Osteoporosis tends to progress in COPD patients also. In a three-year follow-up study, osteoporosis prevalence increased from 47% to 61% in stable COPD patients. Clinically, stable patients of COPD, defined as not treated for an acute COPD exacerbation in the previous six months, were included in the study. The increased prevalence is mainly because of vertebral fractures. The predictors of progression of osteoporosis are lower baseline T-score at the trochanter level and vitamin D deficiency. Osteoporosis is an undertreated entity in COPD patients as 82% of osteoporotic COPD patients were not prescribed any specific treatment in a study.

**Vertebral Fractures in COPD**

The most common locations of VCFs are the thoracic-lumbar junction (T12–L1) and mid-thoracic area (T7–T8). Presence of VCFs is a strong risk for the development of future vertebral fractures. About 60–70% of VCFs are asymptomatic and are not diagnosed, allowing the relentless progression of underlying osteoporosis. Furthermore, the kyphotic deformity causes paraspinal muscle contraction to maintain posture that increases the load across the vertebral bodies and explains the subsequent VCFs development. Patients with osteoporosis-related VCFs are associated with a 2.8-fold increased risk of hip fracture and a 5-fold increased risk of subsequent vertebral fracture within three years. VCFs, in general, increase the rate and duration of hospitalization and worsen the health-related quality of life.

Since most cases of VCFs remain asymptomatic, underdiagnosis of VCFs is a common occurrence, and the IMPACT study reported the phenomenon of underdiagnosis as a global problem with the frequency being 34%. This leads to the undertreatment of osteoporosis, resulting in its progression. VCFs are common in patients with COPD, with a prevalence ranging from 49% to 63% depending on systemic glucocorticoid therapy.

Chest radiographs are an important tool in the diagnosis of VCFs, as they can visualize the mid-thoracic (T7–T8) spine and the thoracic-lumbar junction (T12–L1) adequately and can potentially identify about 80–90% of VCFs. A common aspect in the management of acute exacerbation of COPD (AE-COPD) is to recommend a chest radiograph, so it can be a valuable tool in the diagnosis of vertebral fractures also.

Majumdar et al. prospectively studied the prevalence of VCFs in COPD patients with acute exacerbation, and reported a prevalence of 9% of VCFs diagnosed by posteroanterior and lateral chest radiographs. Patients with VCFs were generally

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older, sicker, had more severe and longer duration of COPD, and had a low BMI. However, after adjustment for age, sex, and duration of COPD, the only independent correlation was BMI. Nuti et al. detected vertebral fractures by lateral chest radiograph in 40% of 2,981 COPD patients. The risk of vertebral fractures is related to COPD severity and glucocorticoid treatment, both inhaled and oral. Additional risk factor is low values of quantitative ultrasound (QUS) at calcaneus. Long-term corticosteroid administration is, therefore, a major risk factor for osteoporosis.

**Hip Fractures**

Hip fractures are the most serious among osteoporosis-induced fractures because of their high morbidity and mortality. Mortality related to surgery itself is 4%, and the one-year mortality rate varies from 14% to 36%. Other consequences of hip fractures are loss of independence, increased health care utilization, depression, cognitive impairment, high cost, and increased risk of future fracture. The exact prevalence of hip fractures in patients with COPD is not known, but the presence of COPD in patients with hip fractures carries a poor prognosis. de Luise et al. in the Danish cohort study reported a 60–70% higher risk of death following hip fracture in patients with COPD than those without COPD. The risk of death attributable to COPD remained elevated even at the end of one year, and it was 14%. Also Regan et al. showed poor outcome in COPD patients who had hip fractures. COPD was diagnosed in 47% of the 12,646 patients with hip fracture. The mortality rate increased in severe COPD. Severe COPD patients had one-year mortality of 40.2% compared to 31.0% in mild COPD and 28.8% in non-COPD patients. Modifiable risk factors identified in adjusted models are current smokers, use of general anesthesia, and delays to surgery. In a retrospective cohort study, risk of hip fractures was evaluated in patients receiving oral corticosteroids in the United Kingdom general practice. The most common reason for oral corticosteroid use was respiratory disease (40%). The relative risk of hip fracture and vertebral fracture was 1.61 and 2.60, respectively. A dose-dependence relationship was reported. The relative risk of hip fracture was 1.77 in patients receiving a relatively low daily dose of prednisone (2.5–7.5 mg/day), and it was increased to 2.27-fold for those patients receiving prednisone dose of ≥7.5 mg/day.

**Skeletal Microstructural Abnormalities**

Microarchitectural distortion also occurs in osteoporosis, but very few studies had focused on demonstration of the microarchitectural abnormalities of bone tissue. It is important to know the bone architecture first for better understanding of microarchitectural changes. There are two major kinds of bone, trabecular (spongy) and cortical. Trabecular bone gives supporting strength to the ends of the weight-bearing bone and is the major site of bone remodeling, whereas the cortical bone forms the shafts of the long bone. Osteoporosis affects both the trabecular and cortical bones. Osteoporosis decreases the number and size of trabecular bone. The trabeculae also become thinner and rodlike, replacing the stronger platelike shape. It also causes loss of the cortical bone. Kulak et al. evaluated the bone microstructure and remodeling in postmenopausal women with COPD. Kulak et al. performed microcomputed tomography (μCT) and bone histomorphometry analysis of the transiliac bone biopsy sample in postmenopausal women with COPD. They demonstrated significant lower mean cancellous bone volume, trabecular number, and trabecular thickness in patients with COPD compared to controls. Trabecular separation and cortical porosity were significantly higher in COPD patients compared to control. Patients with GOLD stages III and IV showed a lower bone formation rate than those with GOLD stages I and II. These microarchitectural changes are responsible for reduced bone strength and increased risk of fractures. The evaluation of bone microstructure is important as COPD patients with a normal BMD can have vertebral fractures.

**Pathogenesis of Osteoporosis in COPD**

Bone is a dynamic tissue and in a continuous process of wear and tear. Modeling and remodeling has an important role to play in maintaining a healthy skeleton. Remodeling is the physiological process of new bone formation by the osteoclasts preceded by the osteoclasts-mediated bone resorption. Bone modeling, on the other hand, is characterized by the process of bone formation but not preceded by prior bone resorption. It is estimated that about 25% of trabecular bone and about 3% of cortical bone are replaced in adults every year. Parathyroid hormone (PTH), vitamin D, and gonadal hormones are the key regulators of bone formation and resorption. Osteoporosis develops because of an imbalance between bone formation and bone resorption, either excessive resorption or decreased formation. Osteoblasts, osteoclasts, and osteocytes interactions are important for the process of bone remodeling. Osteoclasts are multinucleate giant cells derived from blood monocytes/macrophage lineage. Osteoclastogenesis is stimulated by the monocytes/macrophage colony-stimulating factor (M-CSF) and the receptor activator of nuclear factor-κB (RANK)-ligand (RANKL). Osteoclasts function as bone eaters by secreting a mixture of hydrogen and chloride ions and proteolytic enzymes. By secreting hydrogen ions, they make an acidic microenvironment, which is necessary for the activation of proteolytic enzymes that subsequently dissolve the bone collagen. Bone resorption helps in the clearance of microdamaged bone tissue and makes the foundation for the laying of new bones (Fig. 1).

Osteoblasts are derived from the mesenchymal stem cells (MSCs) and form new bones. Osteocytes are the cells that initiate bone remodeling as these cells detect microdamages within the bone. Osteocytes after detecting the microdamages communicate with the osteoblasts and osteoclasts, which in turn initiate bone remodeling.
Osteoprotegerin (OPG)/RANK/RANKL Axis

OPG, RANK, and RANKL systems, also known as the OPG/RANK/RANKL axis, play a critical role in the pathogenesis of osteoporosis. RANKL expressed on the surface of osteoblasts, bone stromal cells, and activated T cells plays a key role in the process of bone resorption. RANKL binds specifically to the receptor, RANK, is expressed in osteoclast progenitors/mature osteoclasts. The RANKL–RANK interaction results in the activation of osteoclastogenesis by promoting maturation of osteoclast progenitors into mature osteoclasts. It also inhibits apoptosis of osteoclasts. RANKL is therefore linked to the resorption of bones. OPG, an anti-inflammation protein, derived from the osteoblasts and bone stromal cells inhibits osteoclastogenesis. It acts as a soluble decoy receptor specific for RANKL. Binding of OPG with RANKL inhibits the RANKL–RANK interaction on the osteoclast cell membranes, thereby inhibiting osteoclastogenesis and subsequent bone loss. Impairment of the fine balance between RANK and OPG is responsible for the development of osteoporosis – either through an increase in RANKL or a decrease in OPG (Fig. 2).

Bucay et al. studied the role of OPG deficiency in OPG-knockout mice generated by the targeted deletion of the OPG gene. They demonstrated development of an osteoporotic skeletal phenotype, including high bone-remodeling rate, decreased BMD, and increased incidence of fragility fractures and bone deformities in OPG-knockout mice. These effects stem from the unopposed RANKL activity because of the absence of a decoy receptor. OPG-knockout mice are the first animal model for studying osteoporosis. Therefore, OPG is an important negative regulator of osteoclastogenesis. Another molecule that stimulates osteoclastogenesis is M-CSF. M-CSF increases the number of osteoclast progenitors, and RANKL then binds to its receptor RANK expressed on the surface of osteoclast progenitors. Various hormones, growth factors, and cytokines regulate the OPG/RANK/RANKL axis. Proresorptive cytokines are IL-1, IL-7, IL-17, and tumor necrosis factor-alpha (TNF-α) as they upregulate RANKL, whereas IL-4, IL-13, and interferon-γ are antiresorptive cytokines as they suppress osteoclastogenesis.

COPD and OPG/RANK/RANKL Axis

Bai et al. studied the level of inflammatory cytokines and OPG/RANK/RANKL protein levels in 80 stable male COPD patients. They found a significant correlation between radiographic emphysema measured by low-attenuation area (LAA%) and low BMD in COPD patients who are current or former smokers. Compared to COPD patients with normal BMD, patients with low BMD had significantly higher levels of RANKL and a higher RANKL/OPG ratio. The serum levels of IL-6 and TNF-α were also found to be significantly higher in the COPD patients with low BMD, but the level of IL-1β, although higher in the low BMD group than in the normal BMD group, did not reach statistical significance. Cytokines such as IL-6, TNF-α, and IL-1β are secreted by bone stromal cells and monocytes and increase the production of both RANKL and OPG, but their dominant effect is on the RANKL. Eagan et al. also noted significantly lower levels of OPG in COPD patients compared to the control. The characteristics of COPD is the development of systemic inflammation with resulting rise in the serum levels of inflammatory cytokines eg, IL-6, TNF-α, and IL-1β. These cytokines tilt the balance of the OPG/RANK/RANKL axis toward RANKL, which results in the development of osteoporosis in COPD patients. Interestingly, the elevated RANKL can also upregulate the expression of IL-6 and TNF-α, which may augment inflammatory milieu of COPD patients.

Wnt/β-catenin Signaling System

Another signaling pathway of importance in osteoporosis is Wnt/β-catenin signaling system. Wnt/β-catenin signaling

Figure 1. Pathogenesis of osteoporosis in COPD.

Figure 2. Relationship between RANK, RANKL, and OPG.
system is one of the main mechanisms controlling osteoblastogenesis. First, Wnt/β-catenin pathway promotes osteoblastogenesis by stimulating differentiation of pluripotent MSCs toward the osteoblast lineage and decreasing differentiation of MSCs toward adipogenic lineage. Second, Wnt signaling promotes osteoblast survival by inhibiting its apoptosis. Wnt/β-catenin signaling system also inhibits the osteoclastogenesis process by stimulating production and secretion of OPG. Therefore, activation of Wnt/β-catenin signaling promotes bone formation, whereas inhibition of Wnt signaling promotes bone resorption and contributes to osteoporosis.

Kneidinger et al analyzed the Wnt/β-catenin signals in the lung tissues obtained from COPD patients undergoing lung transplantation and reported decreased activity of Wnt/β-catenin signals in COPD patients. The impaired activity of Wnt/β-catenin signals may explain the occurrence of both emphysema and osteoporosis.

**Role of Matrix Metalloproteinases (MMPs)**

MMPs are a large family of calcium-activated endopeptidases responsible for the degradation of extracellular connective tissue matrix. Regulation of MMP activity is important to prevent untoward consequences, and tissue inhibitors of metalloproteinases (TIMPs) play an important role in regulating the local activities of MMPs in tissues. Balance between MMPs and TIMPs is essential in order to maintain homeostasis in the body, and tilting the balance in favor of MMPs results in the development of various disease processes.

MMPs are produced by osteoclasts and osteoclast progenitors, as well as by monocytes/macrophages. MMPs stimulate osteoclastic bone resorption and promote osteoporosis. In contrast, TIMPs prevent bone loss. Bolton et al measured MMP level in 70 clinically stable COPD patients and reported increased circulating levels of MMP-9 in patients with COPD compared with the healthy controls. The rise in MMPs was not associated with a similar change in circulating TIMP-1 and -2 levels. Among COPD patients with reduced BMD, the MMP-9 rise was greater in those with osteoporosis than in those with osteopenia, COPD patients with no bone disease, and control subjects. An increase in MMP level is therefore a marker of osteoporosis. Zhang et al studied MMP-9, TNF-α, and OPG/RANK/RANKL systems in 90 male patients with clinically stable COPD and reported higher MMP-9 level in patients with osteoporosis than in patients with normal BMD. As in the work of Bolton et al., no difference in TIMP-1 serum level was detected among the three groups. An increase in MMP level may therefore explain the occurrence of osteoporosis in patients with COPD and may also explain the correlation between radiological emphysema and osteoporosis.

**Risk Factors for Osteoporosis in COPD**

- **Vitamin D deficiency.** Vitamin D along with PTHs plays a key role in regulating calcium and bone homeostasis. First, the 25(OH)D$_3$ is the form measured in the blood as the half-life of 25(OH)D$_3$ is 10.4 days, whereas the 1,25(OH)$_2$D$_3$ is not measured as the circulating half-life is only 4 hours. Second, serum 1,25(OH)$_2$D$_3$ level can be normal or even elevated despite the presence of vitamin D deficiency. Low 25(OH)D$_3$ level increases PTH secretion, which augments the conversion of 25(OH)D$_3$ to 1,25(OH)$_2$D$_3$. The Endocrine Society’s clinical guidelines defined vitamin D deficiency as a 25(OH)D$_3$ level below 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a 25(OH)D$_3$ level between 21 and 29 ng/mL (52.5–72.5 nmol/L).

**Studies of vitamin D deficiency in COPD.** Vitamin D deficiency is common in COPD patients. Forlì et al. quantified vitamin D level in 71 patients with advanced respiratory diseases waiting for lung transplantation, and 46 of them had COPD. The majority of this cohort (both normal weight and underweight patients) suffered from vitamin D deficiency (25(OH)D$_3$ <20 ng/mL). Vitamin D deficiency was associated with reduced femoral neck T-scores in underweight patients. Romsen et al. similarly reported vitamin D deficiency in 58% of 151 patients with moderate–to–very severe COPD entering the pulmonary rehabilitation program. They reported positive correlation between plasma vitamin D level and BMD. The prevalence of vitamin D deficiency was also related to severity of COPD as deficiency increased significantly from GOLD stage II to stage IV. Vitamin D deficiency was 43% in GOLD stage II patients, 50% in GOLD stage III patients, and 76% in GOLD stage IV patients. However, both of the aforementioned studies did not have control. Janssens et al. analyzed the 25(OH)D$_3$ levels and the variants of vitamin D binding gene in patients with COPD. The prevalence of vitamin D deficiency was 31% in healthy smokers, 39% in GOLD grade I patients, 47% in GOLD grade II patients, 60% in GOLD grade III patients, and 77% in GOLD grade IV patients. Therefore, a high prevalence of vitamin D deficiency was demonstrated in patients with COPD compared to age-, sex-, and smoking-matched controls. They also reported higher risk of COPD in homozygous carriers of the rs7041 T allele of vitamin D-binding gene. This study suggests a strong relationship between GOLD stages of COPD and vitamin D deficiency.

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 aging, renal dysfunction, depression, and treatment with corticosteroids. Depression may be associated with lower levels of vitamin D because of several reasons. Depressed patients perform less physical activity and spend more time indoors than outdoors. Smoking decreases vitamin D level by accelerating skin aging, thereby, decreases the skin production of vitamin D. Smoking can also decrease circulating levels of 25(OH)D$_3$ and 1,25(OH)$_2$D$_3$ by 10% and PTH level by 20%. It decreases serum PTH levels either by decrease in secretion or an increased smoking-augmented hepatic metabolism.
Mechanisms of osteoporosis development in Vitamin D deficiency. Vitamin D deficiency is characterized by low serum 25(OH)D level that results in reduced serum calcium level and compensatory increase in serum PTH level. PTH enhances the production of calcitriol by stimulating 1-α-hydroxylase enzyme in the proximal convoluted tubules. Calcitriol increases intestinal calcium and phosphate absorption. Calcitriol increases the expression of RANKL on the surface of osteoblasts leading to augmented RANK/RANKL interaction. RANK/RANKL interaction causes bone resorption and subsequent decrease in BMD. Bone resorption leads to increase in serum calcium level. However, there is a check on this system. Increased serum calcium level decreases PTH secretion. Calcitriol also checks bone resorption by increasing the expression of mature osteoblasts. However, this inhibition of bone resorption is less active in cancellous bone, effectively making this region susceptible for resorption. Vitamin D deficiency, therefore, 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.

Corticosteroids use. Oral and inhaled corticosteroids (ICSs) are frequently prescribed in COPD patients. ICSs are used in moderate-to-severe COPD, reducing the frequency of exacerbation and improving quality of life. Oral steroids are used on hospitalized patients with exacerbation of COPD, and they cause shortening of the hospitalization period and early improvement of lung functions. Glucocorticoid use is the most common cause of iatrogenic and secondary osteoporosis. In a meta-analysis of seven cohort studies of 42,000 subjects, current and prior use of glucocorticosteroids (GCSs) was found to be a predictor of the increased risk of fractures, independent of previous history of fractures and BMD. The greatest risk of fractures is noted during the first three to six months after beginning of steroids therapy, and the risk persists for one year after the cessation of corticosteroid use, indicating reversibility of the process. A meta-analysis of randomized controlled trials (16 trials) and observational studies (7 trials) revealed that in patients with COPD, ICS use was associated with a modest but statistically significant increase (>20%) in the risk of fractures. Similarly, in a nested case–control study, including 1708 COPD patients with non-vertebral fractures and 6817 matched control subjects, current use of high-dose ICS (more than 700 µg/day) was associated with an increased risk of non-vertebral fractures compared with patients with no ICS exposure (adjusted odds ratio = 1.68; 95% confidence interval, 1.10–2.57). The impact of ICS on BMD is dose dependent. In a randomized controlled trial, Mathioudakis et al. had shown that long-term use of low-dose ICS protects the COPD patients from developing osteoporosis. This is secondary to the decrease in lungs inflammation, which further decreases the systemic spillover. However, at higher doses, ICS may gain access to the systemic circulation and can produce systemic side effects. The impact of other drugs, for example, antileukotrienes and phosphodiesterase-4 inhibitors, on the systemic inflammation and BMD requires investigation in future.

Mechanisms of corticosteroids-induced osteoporosis. There are some unique characteristics of GCSs-induced fractures. First, fractures because of GCSs occur even with normal BMD, unlike fractures occurring in patients with postmenopausal osteoporosis. Second, with long-term GCSs therapy, the number of osteoclasts is usually maintained in the normal range, whereas the number of osteoblasts falls and bone formation is substantially reduced. This is in contrast to postmenopausal osteoporosis or hyperparathyroidism; both of them are characterized by increased bone formation and resorption. Third, loss of bone strength occurs even before the loss of BMD. GCSs-induced osteoporosis occurs in two phases; a rapid phase of bone loss via osteoclasts mediated bone resorption, followed by the later phase of bone loss caused by decreased bone formation. GCSs exert their effects on both osteoblasts and osteoclasts in osteoporosis, but the most important effect is inhibition of osteoblasts functions. GCSs impair osteoblast recruitment and activity, and promote apoptosis of osteoblasts and osteocytes. They affect both the trabecular and cortical bone formation, but the trabecular bone is initially more affected than the cortical bone.

GCSs inhibit osteoblast differentiation and function at pharmacological doses by inhibiting Wnt/β-catenin and bone morphogenetic protein 2 (BMP-2) signaling system necessary for osteoblastogenesis. Decreased osteoblastogenesis diverts the MSCs toward the adipocyte lineages. In cultured cell lines, steroids increased the expression of Dickkopf-1 (Dkk-1), an antagonist of Wnt signaling system. Increased level of Dkk-1 inhibits the Wnt signal in osteoblasts, which may explain the mechanisms of glucocorticoid-induced osteoporosis.

Apoptosis of osteocytes is also a significant event as it is responsible for the hardening of bones and consequently increased fracture risk compared with soft bones. Osteocytes also perform an important function of repairing microdamage that is also jeopardized by GCSs. Osteocytes via hypoxia-inducible factor-α (HIF-α) enhance VEGF level, and therefore, promote angiogenesis within the skeleton. GCSs decrease angiogenesis by promoting apoptosis of osteocytes, therefore decreasing the level of VEGF. Decreased level of VEGF reduces bone hydration, resulting in reduced strength of the bone. GCSs are also osteostrogenic as they increase the expression of M-CSF, IL-6, and RANKL and decrease the expression of OPG in stromal and osteoblastic cells. They also inhibit apoptosis of osteoclasts.

In addition, there are some indirect effects also. GCSs reduce intestinal calcium absorption and enhance renal calcium loss. High-dose GCSs can cause hypogonadism in men and premenopausal women by suppressing testosterone and/or estrogen levels, which can result in further bone loss. Steroid-induced proximal myopathy results in muscle weakness and higher frequency of falls and fractures.
Risk factors for GCS-induced osteoporosis include advanced age, glucocorticoid receptor genotype, female sex, increased expression of 11β-hydroxysteroid dehydrogenase (11β-HSD1), low bodyweight (body-mass index <24 kg/m²), low BMD, and cumulative steroid dose. Cumulative dose depends on both high dose and duration of treatment of greater than three months. Even alternate day therapy is not safe.\textsuperscript{109}

Different steroids have variable effects on the bone. Deflazacort causes less bone loss compared to other steroids. Prednisone and deflazacort produced a rate of bone loss of \(-3.0\%\)/year and \(-1.1\%\)/year, respectively.\textsuperscript{110} This variable effect can be explained by the variable effects of steroids on the OPG/RANK/RANKL axis. Deflazacort was a poor stimulator of RANKL gene expression, unlike prednisolone. Deflazacort stimulates the RANKL gene by one-to-three-fold compared to seven-fold by prednisolone. Therefore, deflazacort has less potential to cause bone loss than prednisolone.\textsuperscript{111}

**Low body-mass index/low fat-free mass (FFM)/sarcopenia.** Low BMI has been recognized as a key risk factor for low BMD and future risk of fragility fracture, whereas a high BMI is protective against osteoporosis.\textsuperscript{112,113} De Laet et al.\textsuperscript{114} in a large meta-analysis of 12 prospective population-based cohorts of 60,000 men and women, described an inverse and non-linear relationship between BMI and total fractures, osteoporotic fractures, and hip fractures. There was an increasing fracture risk with BMI \(<25\text{ kg/m}^2\). For every standard deviation (SD) decrease in BMI, the age-adjusted risk for fractures increased by approximately 18%.\textsuperscript{115} Low BMI is not uncommon in COPD patients as a large population-based study from China detected BMI of less than 18.5 kg/m² in 21% patients.\textsuperscript{116} The risk of low BMI is even higher in advanced COPD.\textsuperscript{117}

Changes in the body composition are important physiological derangements in COPD patients. Our body composition broadly consists of two components: fat mass and FFM. FFM contains the metabolically active organs, and skeletal muscle is the largest of these organs.\textsuperscript{118} BMI is less sensitive to changes in the body composition as BMI can be normal or even high despite the presence of low FFM.\textsuperscript{119} Normal FMMI is \(\geq 16\) (men) or \(\geq 15\) (women).\textsuperscript{120} Based on BMI and FMMI, Schols et al.\textsuperscript{120} proposed the following definitions: cachexia (low BMI and depleted FMMI), muscle atrophy (normal BMI and depleted FMMI), semi-starvation (low BMI and normal FMMI), normal (normal BMI and normal FMMI), overweight (overweight BMI and normal FMMI), and obese (obese BMI and normal FMMI). Among outpatients with moderate-to-severe COPD, FMM was depleted in 26% of patients,\textsuperscript{121} and in patients eligible for pulmonary rehabilitation, the loss was 35%.\textsuperscript{122} Apart from low FMM, COPD patients are also associated with reduced muscle strength and sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP)\textsuperscript{122} defined sarcopenia by the reduced muscle mass and at least one of either low muscle strength or physical performance. The Korea National Health and Nutrition Examination Survey (KNHANES) detected sarcopenia in 32.8% of male patients and 12.2% of female patients with COPD.\textsuperscript{123} Several studies have reported significant correlation between sarcopenia and osteoporosis and/or BMD. Coin et al.\textsuperscript{124} detected a significant higher prevalence of osteoporosis in sarcopenic groups compared with non-sarcopenic groups (46% vs. 0%; \(P < 0.05\)). Bolton et al similarly reported a very high prevalence of osteoporosis (50%) and osteopenia (50%) in cachectic COPD patients.\textsuperscript{125} Various factors linking low FMM with osteoporosis include reduced physical activity, vitamin D deficiency, inflammatory mediators, genetic factors, and the use of corticosteroids.\textsuperscript{126} Systemic inflammation causes loss of both FMM and BMD as inflammation can cause skeletal muscle atrophy and protein breakdown.\textsuperscript{127} Low mechanical loads on the bones because of low BMI and FMM loss can reduce the bone formation.

The relationship between fat and bone has become an important topic nowadays. Adipose tissue might affect the bone by various mechanisms. Adipose tissue produces several bone-active substances, together called adipokines, which include TNF-\(\alpha\), leptin, adiponectin, and resistin.\textsuperscript{127} Leptin modulates bone cells either directly or indirectly via the central nervous system. Leptin promotes proliferation and differentiation of osteoblasts via its receptors present on the osteoblasts.\textsuperscript{128,129} Leptin inhibits the osteoclast function by reducing the production of RANK and RANKL and increasing OPG production.\textsuperscript{130} Leptin promotes skeletal mass formation via these mechanisms. Leptin deficiency results in reduced bone formation and increased bone resorption. Vondracek et al.\textsuperscript{131} reported significantly lower body-mass and serum leptin concentrations in men with COPD and osteoporosis compared with men with COPD but without osteoporosis. However, the central action of leptin is opposite to peripheral action. Experimental infusion of leptin into the third ventricle results in bone loss and weight loss.\textsuperscript{132,133} It causes bone loss via inhibition of bone formation and stimulation of bone resorption. Peripheral effect of leptin normally predominates.\textsuperscript{134} Pobeha et al.\textsuperscript{135} specifically studied the relation between expressions of leptin and OPG in the adipose tissue, and development of osteoporosis in patients with COPD. COPD patients with osteoporosis had significantly lower serum levels and adipose tissue expressions of leptin, OPG, in association with increased serum \(\beta\)-crossoptin (marker of bone turnover).

Anemia and osteoporosis. 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.\textsuperscript{136} Several studies reported a connection between anemia and BMD. Cesari et al.\textsuperscript{137} in the InCHIANTI study conducted among the elderly Italian population documented anemia and low hemoglobin levels negatively and independently associated with bone mass and density. Low hemoglobin levels are associated with higher bone loss in the cortical bone in women, independent
of systemic inflammation. Similarly, Korkmaz et al. demonstrated significantly higher prevalence of anemia in patients with low BMD of the femur and spine. They also documented that the presence of anemia among Turkish postmenopausal women was an independent predictor of low BMD of the spine, after adjusting for BMI and other confounders. Anemia is also associated with higher fracture risk among healthy multiethnic elderly women. 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. 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.

**Reduced physical activity.** Physical inactivity is an important modifiable risk factor for osteoporosis, and several studies have suggested that exercise can prevent bone loss. Gustavsson et al. in a six-year longitudinal study found that their subject, a young ice hockey player, lost BMD of the femoral neck rapidly after decreased physical activity. A systematic review had suggested that exercise can reduce falls, fall-related fractures, and several risk factors for falls in individuals with low BMD. Physical activity does this by increasing the BMD. Exercise reduces the age-related decrease in BMD by approximately 1% per year in postmenopausal women. The Cochrane database demonstrated that aerobicics, weight-bearing, and resistance exercises are effective for improving the BMD of the spine in postmenopausal women, and walking improves the BMD of the hip.

Polidoulis et al. further analyzed the impact of exercise on bone structure and strength by peripheral quantitative CT (pQCT) scan analysis and showed that by maintaining cortical and trabecular volumetric BMD, exercise may decrease the bone loss in postmenopausal women. Physical inactivity decreases BMD by reducing osteoblast recruitment and differentiation and inducing its apoptosis. It also causes osteoprogenitor cell differentiation toward adipocyte lineages. Osteoblastogenesis is influenced by insulin-like growth factor (IGF), BMPs, PTH, and sclerostin. Lin et al demonstrated via animal experimentation that mechanical unloading increased sclerostin level in wild mice and sclerostin inhibits bone formation by inhibiting the Wnt signaling pathway. Physical inactivity, therefore, reduces the Wnt signaling pathway. Patients with COPD have significantly reduced levels of physical activity compared with healthy control subjects. In transgenic mice experiments, Robinson et al. showed that mechanical loading activates the Wnt/β-catenin pathway and enhances the sensitivity of osteoblasts/osteocytes to mechanical loading. This may explain another aspect of development of osteoporosis in COPD patients because of physical inactivity. Therefore, regular physical activity can be an important goal in the prevention of osteoporosis. Improved physical activity also resulted in improved BMD: COPD patients who underwent lung volume reduction surgery showed an improvement in BMD because of an increase in physical activity.

**COPD exacerbations.** Exacerbation of COPD can also be a risk factor for reduced BMD. Kiyokawa et al. in a longitudinal study measured BMD of thoracic vertebra by CT scan. They noted that COPD exacerbation was independently associated with progression of osteoporosis. Stanujkovic et al. provided the mechanistic link between COPD exacerbations and osteoporosis. Exacerbations of COPD are associated with augmentation of inflammation, hypoxia, protease/antiprotease imbalance, and oxidative stress, all of these may contribute to increased bone resorption as evidenced by the elevated type I collagen fragments level, which is a predictor of bone loss. Other factors are use of steroids during exacerbations and physical inactivity. The systemic inflammation is augmented in patients with reduced lung function, and systemic inflammation is a recognized risk factor for osteoporosis, cachexia, and weight loss. Osteoporosis progression should be evaluated in COPD patients, especially in those with a history of frequent exacerbations.

**Smoking.** Smoking is an important risk factor for COPD. Smoking may also cause osteoporosis. A meta-analysis by Ward and Klesges demonstrated that tobacco smoking had a cumulative, dose-dependent independent effect on bone mass. Smokers had significantly reduced bone mass compared with nonsmokers at several major sites of osteoporosis-related fractures, including the hip, lumbar spine, and forearm, but the effect is most pronounced at the hip. Overall, the greatest effect was seen in men and elderly. Smoking induces osteoporosis by several potential mechanisms: altered metabolism of calcitropic hormone; dysregulation in the production, metabolism, and binding of estradiol; altered metabolism of adrenal cortical hormone; effects on the RANK–RANKL–OPG system; and effects on collagen metabolism and bone angiogenesis.

**Hypoxia and hypercapnia.** Dimai et al. evaluated the impact of hypercapnia on the BMD and noted a lower BMD, arterial pH, and a higher serum cross-linked telopeptide of type I collagen (ICTP), a bone resorption marker in COPD patients with hypercapnia than COPD patients with eucapnia. The BMD and serum ICTP level were not different between compensatory respiratory acidosis and uncompensated respiratory acidosis, clearly indicating the role of hypercapnia rather than uncompensated respiratory acidosis as the cause of bone resorption. Carbon dioxide directly stimulates the osteoclasts as, first, they have receptor for CO₂ and second, CO₂ stimulates the carbonic anhydrase II within the osteoclasts, leading to activation of osteoclastic-mediated bone resorption. Hypoxia has also got a role in the development of osteoporosis. Hypoxia blocks the growth and differentiation of osteoblasts, whereas it strongly stimulates osteoclast–mediated bone resorption. Hypoxia inhibits osteoblast formation by reducing the expression of RUNX2, a key transcription factor required for stem cell selection toward osteoblastic lineage and osteoblast differentiation.
Hypogonadism. Sex steroids play a crucial role in maintaining skeletal integrity via stimulating bone formation and inhibiting bone resorption. The reported prevalence of hypogonadism in men with COPD varies from 22% to 69% and has been associated with osteoporosis, depression, and muscle weakness. Although, hypogonadism is an independent risk factor for the development of osteoporosis both in men and women, the role of testosterone deficiency in osteoporosis development is modest in nature. On the other hand, levels of estradiol are more closely linked to skeletal health than the levels of testosterone even in men.

Diagnostic Imaging of Osteoporosis

Osteoporosis is a disease that affects the bone mass and bone microarchitecture. Bone mass can be assessed by measuring the BMD, whereas bone microarchitecture can be assessed only by bone biopsy, which is not routinely done in developing countries. Measurement of BMD by DEXA scan is the gold standard for the diagnosis of osteoporosis. It is also used to monitor the response to treatment and to measure the body composition. BMD is reported as the SD of means, the T- and Z-scores. The T-score is the difference in the number of SDs between the mean BMD value of the patient and the mean BMD of a young sex-matched adult control population. The Z-score is the difference in the number of SDs between the mean BMD value of the patient and the mean BMD of a race-, sex-, and age-matched reference population. Reduction of 1 SD in the BMD value increases fracture risk by 1.5- to 3-fold. In postmenopausal women and in men aged 50 years and above, T-score is used to stratify patients into one of the following categories: normal, osteopenia (low bone mass), and osteoporosis. Normal DEXA-scan report is shown in Figure 3. The WHO definition is shown in Table 1.

The Z-score is used in premenopausal women, younger men (<50 years), and children. Based on the BMD, patients can be classified as those with normal BMD for age defined as Z-score higher than –2.0 and low BMD for age defined as Z-score of –2.0 or lower. Hip and spine are the common sites of osteoporotic fracture, so these are the preferred sites for scan. The International Society for Clinical Densitometry advocates BMD measurement of the lumbar spine and the hip and to diagnose osteoporosis based on the lowest T-score of the measured locations. Lumbar spine is preferred as it is enriched with high proportion of trabecular bone, allowing for early detection; however, in patients with degenerative changes in the spine, spine BMD measurement has limited use. The BMD of the forearm should be measured in very obese patients or in patients where BMD of spine or hip is either not measurable or not interpretable because of severe degenerative disease or extensive surgical instrumentation. Although, DEXA scan is an easy-to-use technique coupled with high precision and low-radiation dose (1–6 μSv), it has some disadvantages also. DEXA scan is a two-dimensional (2D) measurement, and it only measures density/area (in grams per square centimeter), not the volumetric density; therefore, the measured BMD is called the areal BMD. Areal BMD is susceptible to bone size and will overestimate the fracture risk in individuals with a small body frame, who will have lower areal BMD than normal-sized individuals. Another pitfall of areal BMD is that it is sensitive to degenerative changes of the spine and may report increased BMD and falsely low fracture risk. Suitability of DEXA for follow-up study is questionable as it requires ≥2 years to detect statistically significant changes in areal BMD. DEXA scan does not detect bone microarchitecture changes. The BMD measurement alone does not reliably predict osteoporotic fractures. WHO had developed a web-based fracture risk algorithm (FRAX), based on use of up to 10 variables, including the current age, gender, low body-mass index (kg/m²), a prior osteoporotic fracture (including morphometric vertebral fracture), parental history of hip fracture, oral glucocorticoids ≥5 mg/day of prednisone for ≥3 months (ever), current smoking, alcohol intake (three or more drinks per day), rheumatoid arthritis, secondary osteoporosis, and femoral neck BMD. FRAX estimates an individual’s 10-year probability of fracture. COPD patients are at high risk of developing VCFs, and early recognition of VCFs is important since their presence is an important risk of future fractures. Both the DEXA scan and the vertebral fracture assessment using X-ray should be used together to diagnose osteoporosis in patients with COPD as vertebral fractures can occur in COPD patients with a normal BMD on DEXA-scan result.

The diagnostic modality of choice for vertebral fractures is the visual semiquantitative assessment method described.
The reduction in vertebral height and morphologic changes are noted visually. Vertebral deformities are classified morphologically into wedge, biconcave, or crush and are graded as normal (grade 0), grade 1 (reduction of 20–25% of height and 10–20% of projected vertebral area), grade 2 (reduction of 26–40% of height and 21–40% of projected vertebral area), and grade 3 (reduction of >40% of height and projected vertebral area). The FRAX algorithm does not reliably predict the development of osteoporotic vertebral fractures in patients presenting with more than moderately severe COPD. Two additional risk factors identified in advanced COPD are low FEV\textsubscript{1} and the presence of chronic respiratory failure, indicating the requirement for the development of a COPD-specific FRAX algorithm.

Measurement of Bone Quality

Recently, various techniques have been developed to assess the bone quality, though most are in use for research purposes. These are quantitative ultrasonography (US), magnetic resonance (MR) imaging and MR spectroscopy, multidetector CT, quantitative CT (QCT) and high-resolution peripheral quantitative CT (HR-pQCT).

Quantitative CT. Unlike DEXA, which is a 2D method, QCT is a 3D imaging modality. It is useful in young children because it measures a volumetric BMD and is not affected by bone size. It measures BMD of both cortical and trabecular area separately. Trabecular bones being more active metabolically are more sensitive to changes.

QCT is generally applied to the lumbar spine on whole-body CT scanners. The standard QCT scans the lumbar vertebrae with a mineral reference phantom in the same field. It measures the attenuation of the lumbar vertebrae in Hounsfield unit (HU) and transforms it into a bone mineral equivalent (mg/cm\textsuperscript{3}) using standardized software. High-resolution peripheral QCT (HR-pQCT) is a low-radiation method for assessing bone microarchitecture and volumetric BMD in cortical and trabecular compartments of the distal radius, tibia, and metacarpals. The radiation dose to the patient from a HR-pQCT single-scan is estimated to be 3 μSv. HR-pQCT measures structural parameters such as total, cortical, and cancellous BMD; trabecular thickness; trabecular separation; and trabecular number and mechanical parameters such as bone stiffness and failure load. Disadvantages of HR-pQCT include its limitation to peripheral skeletal sites and providing no direct insight into bone quality in the lumbar spine or proximal femur, common sites for osteoporotic fragility fractures.

The T-score thresholds defined by the WHO for diagnosis of osteoporosis are not applicable to either peripheral or central QCT scan. In the lumbar spine, a trabecular BMD of 80–120 mg/cm\textsuperscript{2} is defined as osteopenic and a BMD <80 mg/cm\textsuperscript{2} as osteoporotic on QCT. Romme et al. studied the role of routine chest CT in osteoporosis assessment. The authors measured the average attenuation of thoracic vertebrae 4, 7, and 10 on chest CT and compared these measurements with the lowest BMD of the hip and lumbar spine (L1–L4) on DEXA scan in COPD patients. A strong correlation was found between the average attenuation of the three thoracic vertebrae and the lowest BMD of the hip and lumbar spine with an attenuation threshold value of 147 HU. However, more studies are required to establish its role in osteoporosis detection.

Detection of Microstructural Changes

The bone microarchitectural changes can be assessed either by the histomorphometric analysis or the μCT analysis of bone biopsy samples. Detection of microarchitectural changes is difficult in routine clinical practice because of its invasiveness. The 3D micro-CT images and morphometric calculations on human trabecular bone (lumbar vertebra) are shown in Figure 4 A and B.

![Figure 4. (A) 3D micro-CT image (17 μm/pixel) of human trabecular bone (lumbar vertebra), size of the volume of interest: 10 × 10 × 19 mm. (B) 3D micro-CT image (17 μm/pixel) of human trabecular bone (lumbar vertebra). This bone has very low bone volume fraction, with a mainly rod-like appearance. Image courtesy: Dr Egon Perilli, Flinders University, Adelaide, SA, Australia.]
Relationship between CT Quantification of Emphysema and BMD

Few studies evaluated the relationship between radiological extents of emphysema with BMD. Bon et al demonstrated that radiographic emphysema is a strong predictor of low BMD, and it was independent of airflow obstruction and other osteoporotic risk factors. The most plausible mechanistic link between the two could be systemic inflammation as the authors revealed a positive correlation between the osteoclastogenic cytokine IL-6 and the percentage of low-attenuation lung units measured by QCT. Ohara et al found a significant correlation between CT extent of emphysema and CT measured BMD of the thoracic and lumbar vertebrae (T4, T7, T10, and L1) in 65 male patients with COPD. Multiple regression analysis showed that only LAA% and BMI were predictive of BMD among age, BMI, smoking index, FEV₁, arterial blood gas, and LAA%, indicating COPD as an independent risk factor for low BMD.

Prevention and Treatment of Osteoporosis in COPD Patients

The general principal governing the treatment of osteoporosis is preventing fractures, and can be divided into pharmacological and non-pharmacological interventions.

Non-pharmacological management. COPD is a lifestyle-related disease, and several lifestyle-related factors such as smoking, physical inactivity, and poor diet have been linked to osteoporosis development. A systematic review by Howe et al. revealed that exercise had a relatively small, but statistically significant positive effect on BMD in postmenopausal females. Cigarette smoking is a reversible risk factor for osteoporosis, and smoking cessation results in the improvement in BMD. Active smoking cessation should be instituted at the earliest. Patients should be counseled on fall prevention. 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.

Leuppi et al. in a randomized, non-inferiority multicenter trial showed that a five-day course of oral prednisone (at 40 mg daily) was similar to conventional 14-day course of prednisone with regard to re-exacerbation within six months of follow-up. Therefore, most patients with AEs-COPD can be treated with a five-day course of prednisone or equivalent (40 mg daily).

Pharmacological management. Pharmacological interventions consist of calcium and vitamin D supplementation and anti-resorptive therapy. Vitamin D and calcium supplementation is an integral part in the prevention and treatment of osteoporosis. Tang et al. evaluated the effects of calcium alone or in combination with Vitamin D on osteoporotic fractures and BMD in adults aged 50 years or older in a systematic review of 29 randomized controlled trials. In all, 17 trials reported fracture as an outcome, and treatment was associated with a 12% risk reduction in fractures of all types, whereas in the 24 trials that reported BMD as an outcome, treatment resulted in reduced bone loss of 0.54% at the hip and 1.19% at the spine. The treatment effects was found better with good adherence to therapy and with calcium dosages of 1200 mg or more or vitamin D dosages of 800 IU or more. The populations that gained maximum benefit from calcium supplementation in terms of reduction in fracture risk were older, institutionalized, low baseline calcium intake (<700 mg/day), and low serum 25(OH)D <25 nmol/L levels. Vitamin D also influences the fracture risk by decreasing falls and increasing the BMD, and these benefits are dose dependent. Vitamin D doses below 700 IU a day has no effect on the prevention of falls. Vitamin D deficiency causes falls because of the development of muscle weakness. Vitamin D binds to its nuclear receptor in muscle tissue and increases de novo protein synthesis in the muscles. This effect precedes the effect of vitamin D on bone. In a pooled analysis of several randomized controlled trials, reduction in the risk of fractures was noted only with 800 IU daily doses, with a 30% reduction in the risk of hip fracture and a 14% reduction in the risk of any non-vertebral fractures. Combination therapy is the best for fracture prevention. Vitamin D without calcium supplementation is ineffective in preventing fractures.

Bisphosphonates. Bisphosphonates are the most commonly prescribed drugs for the prevention and treatment of osteoporosis. Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate (PPi), but contain a carbon in the backbone of the molecule (P-C-P), instead of oxygen (P-O-P in pyrophosphate). The P-C-P configuration makes the molecules chemically stable by conferring resistance to chemical and enzymatic hydrolysis.

Bisphosphonates have a very high skeletal retention because of their avidity to hydroxyapatite crystals. They are internalized by endocytosis and inhibit bone resorption by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. Bisphosphonates also inhibit osteoblasts and osteocytes apoptosis, but the importance of this function is currently unclear. Bisphosphonates inhibit the osteoclast functions by inhibiting farnesyl pyrophosphate synthase (FPPS), an essential enzyme of mevalonate pathway within osteoclasts, resulting in reduced formation of prenylated GTP-binding proteins. The prenylated GTP-binding protein is an important signal in osteoclasts, and lack of these proteins produce altered membrane trafficking, lack of cellular morphology control, disruption of integrin signaling, loss of membrane ruffling, and ultimately apoptosis. The ranking of bisphosphonates from the highest to lowest hydroxyapatite affinity is as follows: zoledronate > pamidronate > alendronate > ibandronate > risedronate > etidronate > clodronate. Bisphosphonates tend to bind more avidly to trabecular bone, as trabecular bone is more accessible.
and metabolically active than cortical bone. It explains the greater reduction of the vertebral fracture risk compared to reduction in non-vertebral fracture risk, as the vertebrae are enriched with trabecular bone.\textsuperscript{200} Bisphosphonates are classified into two major groups: nitrogen-containing (NC) and non–nitrogen-containing (NNC) bisphosphonates. The NC group contains zoledronic acid, pamidronate, alendronate, and risedronate.\textsuperscript{201} A protective effect of bisphosphonates has been reported in postmenopausal and glucocorticoid-induced osteoporosis in many large randomized controlled trials.\textsuperscript{202} Smith et al.\textsuperscript{203} evaluated the role of daily alendronate on BMD in patients with airways disease with low BMD. They reported a significant improvement in the lumbar spine, but not hip, BMD with daily alendronate for 12 months. Zoledronic acid has the best overall fracture protection among the available bisphosphonates for osteoporosis.\textsuperscript{204} Maximum effect of bisphosphonates becomes obvious in three to six months, and with continued treatment, it is maintained in a new steady state for 10 years.\textsuperscript{205} Toxicities reported with bisphosphonates therapy are low. Patients may develop mild gastrointestinal complaints. Orally administered drugs may irritate the esophagus and should be avoided in the following groups: inability to stand or sit upright for at least 30 minutes, active upper gastrointestinal symptoms, or have delayed esophageal emptying (eg, strictures, achalasia, or severe dysmotility).\textsuperscript{206} Other side effects are acute phase reaction in patients treated with intra-venous bisphosphonates, nephrotoxicity, osteonecrosis of the jaw, and atrial fibrillation.

Teriparatide is the 1–34 N-terminal active fragment of endogenous PTH and is effective in women with postmenopausal osteoporosis, men with idiopathic or hypogonadal osteoporosis, and patients with glucocorticoid-induced osteoporosis.\textsuperscript{207} The skeletal effect of PTH depends on the nature of exposure. Continuous exposure results in an increased differentiation of osteoclasts, and intermittent exposure preferentially stimulates osteoblasts, resulting in new bone formation.\textsuperscript{208} In corticosteroid-induced osteoporosis, teriparatide was found to be more effective than alendronate. Saag et al.\textsuperscript{209,210} in a randomized controlled trial compared the effects of teriparatide (20 µg/day) and alendronate on BMD in patients with corticosteroid-induced osteoporosis. BMD of the lumbar spine increased significantly after 18 months follow-up in the teriparatide group than in the alendronate group (7.2 vs. 3.4%; \( P < 0.001 \)). They also had fewer new vertebral fractures. BMD of the total hip increased from baseline by 3.8% and 5.2%, respectively, at 18 and 36 months follow-up in the teriparatide group.

Denosumab is a promising new anti-resorptive drug. It is a fully humanized recombinant monoclonal antibody that binds to the RANKL. Denosumab decreases bone resorption by binding to the RANKL and inhibiting the RANKL/RANK interaction on the surface of osteoclasts and osteoclast precursors. It results in inhibition of osteoclast differentiation, activity, and survival.\textsuperscript{196,211} Denosumab is administered at a dosage of 60 mg as a single subcutaneous injection into the thigh, abdomen, or upper arm once every six months for up to three years. Patients must be given calcium and vitamin D supplements as denosumab is contraindicated in patients with hypocalcemia. In several international phase III trials involving more than 12,000 women with postmenopausal osteoporosis or low BMD, denosumab reduces the incidence of vertebral, non-vertebral, and hip fractures relative to placebo. It also increases BMD at all skeletal sites evaluated, including the lumbar spine and total hip, and increases the BMD significantly compared to that by oral alendronate, ibandronate, or risedronate.\textsuperscript{212} Combined effect of teriparatide and denosumab on the spine and hip BMD is significantly more than either drug alone. In the Denosumab and Teriparatide Administration (DATA) study, Tsai et al.\textsuperscript{213} demonstrated that 12 months of combined denosumab and teriparatide therapy increase areal BMD at the spine and hip more than either treatment alone and more than what has been reported with any currently recommended treatment. The same authors also studied the effect of this combination on bone microarchitecture by HR-pQCT study.\textsuperscript{214} The combination therapy improved the bone microstructure more as compared to either drug alone. These superior effects of combination therapy may result in greater resistance to fracture and their potential role in patients with severe osteoporosis. Denosumab by reducing the osteoclast function also reduces osteoblastic bone formation. Therefore, it may further reduce bone formation in patients with corticosteroid-induced osteoporosis.

All symptomatic COPD patients should be evaluated for the presence of following minor criteria: BMI \(< 21\, \text{kg/m}^2\), current smoking, use of ethanol \(> 3\, \text{units/day}\), age \(> 65\) years, parent hip fracture, rib fracture, menopause, inactivity, FEV\(_1\) <50% predicted, and major criteria: systemic corticosteroids (three months/year) and major fragility fracture (spine/hip).

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:\textsuperscript{215}

1. COPD with documented fragility hip or vertebral fractures,
2. \( T \)-score below \( -2.5\, \text{SD} \), and
3. \( -2.5 < T \)-score \( < -1 \) and one major criterion.

However, there is a practical problem with this approach as it will impose a huge economic burden, particularly in developing countries with high burden of COPD. We need more research in this field to develop a COPD-centric evidence-based guideline suitable for mass implication.

Fracture risk in corticosteroid-associated osteoporosis is mostly independent of BMD; therefore, the American College of Rheumatology (ACR) guideline recommends estimation of patient’s overall clinical risk by FRAX score instead of \( T \)-scores alone for pharmacologic intervention.\textsuperscript{216}
Anti-resorptive therapy should be started early during corticosteroid treatment as the bone loss starts quite early and fracture risk is independent of BMD. Alendronate, risedronate, and zoledronic acid are normally used; however, in severe osteoporosis, teriparatide is recommended.\textsuperscript{217} Monitoring. In otherwise healthy individuals treated for osteoporosis, repeat DEXA scan is usually recommended after a minimum of two years of anti-resorptive treatment, as it takes minimal two years to have a least significant change in BMD.\textsuperscript{218} COPD patients treated with oral corticosteroids develop osteoporosis at an accelerated pace and is recommended to have annual repeat DEXA scans, and corticosteroids-treated COPD patients should be monitored in the same fashion.\textsuperscript{219}

Conclusion

Comorbidities are common in COPD patients, and their assessment should be done routinely. Osteoporosis is a common comorbidity in COPD patients and is associated with significant morbidity. Various factors implicated in the pathogenesis of osteoporosis are systemic inflammatory, physical inactivity, body composition changes, tobacco exposure, corticosteroids use, hypogonadism, anemia, COPD exacerbation, and hypoxia. DEXA scan is the gold standard for the diagnosis of osteoporosis. Early diagnosis and treatment prevents future fracture risk. However, in developing countries with insufficient resources, there is a practical problem of applying screening procedure to all COPD patients. We definitely need a COPD–specific guideline for osteoporosis in the future.

Abbreviations

COPD: Chronic obstructive pulmonary disease
GOLD: Global Initiative for Chronic Obstructive Lung Disease
WHO: World Health Organization
BMD: Bone mineral density
DEXA: Dual-energy X-ray absorptiometry
FFMI: Fat-free mass index
OPG: Osteoprotegerin
RANK: Receptor activator of nuclear factor–κB
RANKL: RANK-ligand

Author Contributions

Conceived and designed the experiments: MS. Analyzed the data: MS, JK. Wrote the first draft of the manuscript: MS, RB. Contributed to the writing of the manuscript: MS, IM, JK. Agree with manuscript results and conclusions: MS, IM. Jointly developed the structure and arguments for the paper: MS, RB. Made critical revisions and approved final version: MS. All authors reviewed and approved of the final manuscript.

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