

## REVIEW ARTICLE

# Osteoporosis in COPD patients: Risk factors and pulmonary rehabilitation

Yujuan Li | Hongchang Gao | Lei Zhao | Jinrui Wang

Department of Pulmonary and Critical Care Medicine, Shanghai Pudong New Area Gongli Hospital, Shanghai, China

**Correspondence**

Jinrui Wang, Department of Pulmonary and Critical Care Medicine, Shanghai Pudong New Area Gongli Hospital, 219 Miao Pu Road, Shanghai, 200315, China.  
Email: wjr01485@glhospital.com

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**Abstract**

**Objectives:** To present a review on the pathogenesis, risk factor and treatment of chronic obstructive pulmonary disease complicated with osteoporosis and provide new ideas for the diagnosis and treatment.

**Data source:** A systematic search is carried out using keywords as chronic obstructive pulmonary disease, osteoporosis, risk factors, and pulmonary rehabilitation.

**Results:** Patients with chronic obstructive pulmonary disease have a high prevalence of osteoporosis and a high risk of fracture. The mechanisms of osteoporosis in COPD patients are associated with general risk factors, such as smoking, reduced physical activity, low weight, and disease-specific risk factors, such as systemic inflammatory, Vitamin D deficiency, use of glucocorticoid, anemia, hypoxemia, and hypercapnia. The treatment of osteoporosis in COPD emphasizes comprehensive intervention, which mainly include basic treatment and anti-osteoporosis drugs. Noticeably, pulmonary rehabilitation program is an important part of treatment.

**Conclusions:** This work summarizes the pathogenesis, risk factor, prevention, and treatment of chronic obstructive pulmonary disease complicated with osteoporosis, and the latest progress of studies on chronic obstructive pulmonary disease and osteoporosis is discussed.

**KEYWORDS**

chronic obstructive pulmonary disease, fracture, osteoporosis, prevalence, pulmonary rehabilitation, risk factors

**List of Abbreviations:** BMD, bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EP1, prostaglandin E1; GP130, glycoprotein130; HIF-1 $\alpha$ , hypoxia-inducible factor 1 $\alpha$ ; ICS, inhaled corticosteroid; IGF-1, insulin-like growth factor-1; IL, interleukin; MIF, migration inhibition factor; MMP, matrix metalloproteinase; OPG, osteoprotegerin; OR, odds ratio; PTH, parathyroid hormone; RANK, receptor activator of nuclear factor kappa; RCT, randomized controlled trial; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ .

Yujuan Li and Hongchang Gao contributed equally to this work.

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## 1 | BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable condition characterized by progressive, incompletely reversible airflow restriction. According to the epidemiological survey of COPD in China, the prevalence rate of COPD is 8.6% (11.9% for males and 5.4% for females), and the number of patients is nearly 100 million, among which the prevalence rate of COPD in adults over 40 years old is as high as 13.7%.<sup>1</sup> COPD ranks third in the global cause of death<sup>2</sup> and fifth in the global economic burden of disease.<sup>3</sup> In recent years, more and more attention has been paid to its systemic effects,<sup>4</sup> including cardiovascular and cerebrovascular diseases, metabolic syndrome, osteoporosis, malnutrition, skeletal muscle dysfunction, diabetes, anxiety, depression, and so on. Osteoporosis is a significant extrapulmonary effect in COPD.

Osteoporosis is a systemic bone disease characterized by low bone density and microstructure change that increase the risk of fractures.<sup>5–8</sup> Because of the reduction of exercise and long-term bed, osteoporosis-related fractures are associated with several adverse health outcomes in COPD, including deteriorated lung function, poor quality of life, increased hospitalization, and mortality rates. Moreover, the two diseases form a vicious cycle and cause significant burden on these patients.

The presence of osteoporosis in patients with COPD is asymptomatic and often undiagnosed until bone fractures occur. Therefore, it is necessary to explore the pathogenesis of osteoporosis in COPD, and special attention should be paid to early recognition of patients at high risk for osteoporosis in COPD.

In this review, we focus on osteoporosis as an extrapulmonary manifestation of COPD. The prevalence, risk factor and potential mechanism of osteoporosis in COPD are discussed and the treatment of osteoporosis is described, especially emphasize on exercise rehabilitation.

## 2 | PREVALENCE OF OSTEOPOROSIS IN COPD

A review quantitatively synthesized the current evidence on the prevalence and risk factors for osteoporosis in COPD in 58 studies with 8753 participants with COPD to demonstrate a pooled global prevalence of 38%.<sup>9</sup> The prevalence of osteoporosis in COPD is 2-fold to 5-fold higher than in age-matched healthy control subjects.<sup>9,10</sup> A recent study has shown that low volumetric bone mineral density (BMD) is present in 58% of all subjects with COPD, and is even more frequent in those with worse COPD, and has a prevalence of 84% among subjects with very severe

COPD.<sup>11</sup> A meta-analysis that contained the total number of patients with COPD from all studies is 3815, has shown the prevalence of osteoporosis among COPD is higher than that among healthy subjects (osteoporosis, 14%–66% and osteopenia, 18%–65%).<sup>12</sup> The difference depends on the diagnostic methods, the population of study, and the severity of the underlying respiratory disease.

## 3 | RISK FACTORS AND MECHANISMS FOR OSTEOPOROSIS IN COPD

The mechanisms of osteoporosis in COPD patients are mostly unknown. However, clinical evidence indicates that osteoporosis and other systemic comorbidities of COPD are associated with general risk factors and disease-specific risk factors. In the following paragraphs, we briefly discuss general risk factors of osteoporosis in COPD patients as well as disease-associated factors.

### 3.1 | General risk factors for osteoporosis in COPD

#### 3.1.1 | Smoking

Smoking is a common risk factor for COPD and osteoporosis. Patients with COPD tend to have a long history of smoking. Many studies have shown that smokers have decreased BMD with increased risk fracture compared to nonsmokers.<sup>13–15</sup>

Smoking-induced osteoporosis belongs to secondary osteoporosis, which refers to a systemic bone disease caused by long-term smoking, such as reduced bone mass, degeneration of bone microstructure, and increased bone fragility. The pathogenesis of smoking induced osteoporosis mainly has the following aspects. First, nicotine in tobacco directly or indirectly stimulates the activity of osteoclasts and increases the concentration of blood calcium and urine calcium, leading to osteoporosis.<sup>16</sup> Nicotine also induces apoptosis in human osteoblasts via a mechanism driven by H<sub>2</sub>O<sub>2</sub> and entailing Glyoxalase 1-dependent MG-H1 accumulation leading to TG2-mediated NF- $\kappa$ B desensitization.<sup>17</sup> Meanwhile, nicotine reduces estrogen synthesis, promotes estrogen dissociation and metabolism, and makes calcium regulated hormone dysregulation, thus affecting BMD.<sup>18</sup> Besides, smoking destroys the stability of the bone marrow environment maintained by lymphocyte, leading to the reduction of bone marrow lymphocytes and changes in the immune system. The changes in bone marrow environment can induce the occurrence of osteoporosis.

### 3.1.2 | Reduced physical activity

Exercise plays an important role in regulating bone growth and development as well as bone metabolism.<sup>19,20</sup> Patients with COPD often stay in indoors due to dyspnea, respiratory failure and shortness of breath after activity in the later stage. Significantly reduced exercise ability is the most important cause of bone loss. A review by Lau et al.<sup>21</sup> has indicated that “disuse” osteoporosis is the result of failure to achieve the optimal peak bone mass and strength. If disuse occurs during the period of bone mass accumulation, it leads to increased bone resorption and reduced bone formation. In ‘disuse’ osteoporosis, mechanical unloading is assumed to influence bone remodeling via change in insulin growth factor, bone morphogenetic proteins, parathyroid hormone and sclerostin.<sup>22,23</sup> It is reported that cycling power of  $50\% \times 45$  min increases plasma testosterone and free testosterone, which promotes the increase of the total amount of protein synthesis bone substrate, bone deposition, and bone thickening. Studies have shown that exercise also improves nerve and muscle function, muscle strength, weight gain, or maintenance, which is beneficial to promote bone replacement, prevent bone loss, and improve bone density and bone strength.<sup>24</sup>

### 3.1.3 | Low weight and sarcopenia

Body mass index (BMI) is an important physiological index used to judge the nutritional status of people and is closely related to BMD. Many studies have corroborated that low BMI and the presence of sarcopenia are associated with osteoporosis and fractures in COPD.<sup>25–28</sup> Low BMI and muscle wasting frequently present in severe COPD.<sup>27</sup>

Most patients with COPD have low body weight, which may be related to hypoxia, gastrointestinal congestion, reduced appetite and poor digestion and absorption function. A study<sup>29</sup> including 104 patients with COPD has found that BMI less than or equal to  $22 \text{ kg/m}^2$  is associated with the incidence of osteoporosis, which indicates that poor nutritional status of COPD patients is more prone to osteoporosis. A low BMI changes the level of hormone that is responsible for maintaining bone cell metabolism and alter the bone turnover rate.<sup>30</sup> Both fat and muscle mass provide mechanical loading on the weight-bearing bones and facilitate bone formation.<sup>31</sup>

The decrease in BMD caused by malnutrition may be due to systemic inflammatory responses in COPD patients, such as TNF- $\alpha$ , a proinflammatory cytokine, which causes malnutrition in COPD. TNF- $\alpha$  is also an effective inhibitor of collagen synthesis and osteoclast

bone resorption stimulator. On the other hand, adipokines secreted by adipocytes, such as leptin and adiponectin, or from the pancreatic  $\beta$  cells increase the proliferation and differentiation of osteoblasts, promote bone formation and regulate osteoclast development.<sup>32</sup> It is also reported that the subjects of COPD with lower BMD show higher serum levels of RANK ligand and a higher ratio of RANK ligand/osteoprotegerin compared with those with normal BMD.<sup>33</sup>

In addition to low BMI, COPD is related to low fat-free mass, reduced muscle strength and sarcopenia.<sup>34–37</sup> Several studies have shown that low fat-free mass and sarcopenia in COPD patients are related with osteoporosis and increased fall risk, resulting in increased risk of fracture.<sup>38</sup>

## 3.2 | Disease-associated risk factors

### 3.2.1 | Systemic inflammatory

Systemic inflammatory response is considered to be the key to the co-occurrence of COPD and osteoporosis.<sup>39,40</sup> Systemic inflammation in COPD may be the direct consequence of a systemic “spill-over” of the ongoing pulmonary inflammation.<sup>41</sup> Chronic airway inflammation is the characteristic of COPD. Neutrophils, macrophages, T lymphocytes, and other inflammatory cells are involved in the pathogenesis of COPD. Many cytokines induced by inflammatory cells are closely related to the occurrence of osteoporosis. They mainly include IL-6,<sup>42–44</sup> IL-17,<sup>45</sup> TNF- $\alpha$ ,<sup>39</sup> OPG,<sup>35</sup> and MMP.<sup>46,47</sup> These cytokines are well-known inducers of osteoclasts both in vitro and in vivo and are considered to be involved in the pathogenesis of both primary and secondary osteoporosis<sup>39,48</sup> by regulating the RANKL (RANK/RANK ligand) -OPG axis system,<sup>49,50</sup> which leads to osteoporosis. RANK, RANKL, and OPG are members of the tumor necrosis factor receptor superfamily. Various cytokines and calcium-related pathways are involved in bone remodeling and mineral metabolism. Moreover, systemic inflammation, represented by elevated CRP, is linked to osteoporosis in the general population.<sup>51,52</sup>

### 3.2.2 | Glucocorticoid

Osteoporosis caused by long-term use of glucocorticoid is the most common secondary osteoporosis. Its incidence is second only to postmenopausal osteoporosis and senile osteoporosis.<sup>53,54</sup> Glucocorticoid is currently an effective treatment for COPD, but it is associated with a reduction in BMD and an increased risk of fracture.<sup>55,56</sup>

It is found<sup>57</sup> that the fastest rate of bone loss occurred at 3–6 months after glucocorticoid treatment and bone loss increase with the increase of cumulative dose. Inhaled corticosteroid (ICS) is widely used for the regular treatment of COPD. However, studies investigated the effects of ICS on bone in patients of COPD show conflicting results. The difference is caused by dose and follow-up time. Administered during acute exacerbations as GOLD guideline recommendations are relatively devoid of these adverse effects and ICS is not show to aggravate the bone mineral loss in COPD patients.<sup>58</sup> However, according to a recent meta-analysis including 16 RCTs with 17 513 subjects and seven observational studies with 69 000 subjects, ICS has been found to be associated with significant fracture risk (OR = 1.27 for RCTs and 1.21 for observational studies).<sup>59</sup> Some other studies also have shown that ICS increases the risk of osteoporosis<sup>34,60</sup> and the loss of BMD are dose-dependent and time-dependent. Overall effects of ICS depend on the balance between its anti-inflammatory effects and fracture risk.<sup>61</sup> But studies have shown that the use of oral corticosteroids increase the risk of fracture.<sup>55,56</sup>

Bone tissue is in the process of remodeling throughout life. The normal maintenance of this process depends on the balance between the osteogenic function of osteoblasts and the bone resorption function of osteoclasts.<sup>62,63</sup> Glucocorticoid can directly acts on bone tissue, promotes osteoblast apoptosis through WNT signaling and inhibits osteoblast precursor differentiation and osteoblast maturation through IGF-1, MIF, and other cytokines.<sup>64</sup> On the other hand, glucocorticoid also increases the number and the activity of osteoclasts by affecting cytokines such as RANKL/RANK/OPG, PTH, and GP130,<sup>65</sup> thus increasing bone resorption. It also regulates the metabolism of vitamin D by affecting 1,25 (OH) 2D3 and reduces the absorption of intestinal calcium.<sup>66</sup> Glucocorticoid increases serum parathyroid hormone level, reduces calcium transport function of intestinal mucosa, reduces calcium absorption, and inhibits renal calcium ion reabsorption.<sup>67</sup> Inhibition of pituitary secretion of adrenocorticotrophic hormone decreases sex hormone levels, in which the reduction of estrogen level promotes osteoclast formation and increases bone resorption. In conclusion, glucocorticoid affects bone metabolism in a variety of ways, leading to bone loss and inducing osteoporosis.

### 3.2.3 | Vitamin D deficiency

Vitamin D is an essential part of human hormone. It stabilizes concentration of serum calcium phosphate. Low blood calcium concentration induces parathyroid hormone secretion, which is released to the kidney and affects

the absorption and storage of calcium and phosphorus. According to the Endocrine Society Clinical Practice Guideline, vitamin D deficiency and insufficiency are defined as 25-hydroxy Vitamin D levels below 20 ng/ml and 20–30 ng/ml, respectively.<sup>68</sup> Vitamin D deficiency is consistently reported to be more common in patients with COPD than in healthy controls.<sup>69–71</sup> Vitamin D deficiency in patients with COPD may be related to the following factors: poor dietary habits, reduced synthetic ability due to skin aging, decreased sun exposure due to restricted activities, renal dysfunction, and increased vitamin D metabolism due to use glucocorticoid. In summary, the intake, synthesis, storage, and metabolism of vitamin D are all disrupted. The body cannot maintain calcium homeostasis in the low 25(OH)D3 state. The mineralized collagen matrix in bone further decomposes and the beneficial functions of anti-oxidation and anti-infection also lost, which leads to the decrease of bone mass.

### 3.2.4 | Hypoxemia and hypercapnia

The patients with COPD have a large number of loss of alveoli and capillaries, reduced diffusion area, ventilation and blood flow ratio imbalance. Ventilation dysfunction leads to hypoxia and carbon dioxide retention and further causes varying degrees of hypoxemia and hypercapnia. Studies have proved that oxygen concentration has a significant effect on the formation of osteoclasts in mouse bone marrow cells. With the reduction of oxygen concentration, the differentiation of preosteoclasts into osteoclasts significantly increases.<sup>72</sup> Steinbrech et al.<sup>72</sup> have believed that the effect of hypoxia on osteoblasts is mainly through the effect of vascular endothelial growth factor on angiogenesis under the control of hypoxia-inducible factor 1 $\alpha$ (HIF-1 $\alpha$ ). Angiogenesis and bone formation interact and influence each other. HIF-1 $\alpha$  also affects osteoblast formation through bone morphogenetic protein, prostaglandin 2, and its receptor EP1.<sup>73</sup>

The oxidative process of cell metabolism is impaired and ATP synthesis in mitochondria is insufficient in the state of hypoxemia.<sup>74</sup> Collagen synthase function is affected and collagen synthesis and osteoblast activity in vivo are affected. In addition, Knowles et al.<sup>75</sup> have shown that hypoxia stimulate the differentiation of monocyte progenitor cells into osteoclasts, which can stimulates the formation of osteoclasts.

### 3.2.5 | Anemia

Anemia is commonly seen in patients with COPD and is related with a low-grade systemic inflammation. Elevated

osteoclast activity and subsequent accelerated bone resorption are proposed as underlying mechanisms of osteoporosis in anemia patients. The reduced blood volume stimulates the proliferation of hematopoietic cells, including osteoclasts. Proliferated osteoclasts stimulate bone resorption. Although osteoblast formation is also stimulated by blood loss, stimulated bone resorption may hinder bone remodeling cycles and result in osteoblast fatigue.<sup>76</sup>

Hypoxemia in anemic patients mediates the risk of osteoporosis. Chronic hypoxia increases oxidative stress, and acidification of the extracellular matrix impairs bone metabolism.<sup>77,78</sup> Although anemia appears to be linked with bone health, the effects of anemia on bone remodeling are not entirely clear yet. Additional research is necessary to be elucidated whether anemia is an independent factor.

### 3.2.6 | Therapy

The clinical treatment of COPD patients mainly focused on the lung function and oxygenation capacity of patients, but ignores the prevention and treatment of osteoporosis. However, osteoporosis has the same serious consequences as COPD, clinical attention should be paid to it. The treatment of osteoporosis emphasizes comprehensive intervention, which mainly include basic treatment and anti-osteoporosis drugs.

### 3.2.7 | Change lifestyle

On the one hand, excessive use or abuse of alcohol,<sup>15,79–82</sup> caffeine,<sup>83,84</sup> and carbonated drinks<sup>83</sup> should be avoided, which are harmful for both healthy people and patients with osteoporosis. On the other hand, any form of nicotine should be discouraged.<sup>85,86</sup> Besides, patients with COPD and osteoporosis should be given a balanced diet. It is recommended that patients eat foods with high calcium and foods rich in vitamin D, such as egg yolk and liver.<sup>83</sup> Protein and vitamin C increase the absorption of calcium in the body, so patients are recommended to eat lean meat, fish, beans, milk and vitamin-rich vegetables and fruits.<sup>83,87,88</sup> At the same time, sufficient sunshine should be kept to promote the absorption of calcium.<sup>80,89</sup> It is recommended that we can be exposed to the sun for 15 to 30 min from 11:00 AM to 15:00 PM.

### 3.2.8 | Pulmonary/exercise rehabilitation

A sedentary lifestyle and prolonged rest in bed lead to bone loss in the involutional period. Therefore, we encourage

physical activity and implement a moderate exercise program to minimize bone loss in elderly people.<sup>90,91</sup> Exercise shows promise as a non-invasive and non-pharmacological method of regulating both osteoporosis. Physical exercise effectively decreases risk factors for falling and improves balance.<sup>92,93</sup> In the past years, many studies<sup>94,95</sup> have reported consistent results on the beneficial effects of exercise on BMD. Mechanical signals produced by exercise can promote bone and muscle anabolism.<sup>96</sup> In general, therapeutic exercises for osteoporosis can be ranked in two types of activities. One is weight-bearing aerobic exercises, such as walking, stair climbing, jogging, volleyball, tennis, tai chi, and dancing. Walking predominates as the most common form of physical activity in older adults,<sup>97</sup> while daily walking activity is associated with a range of positive health outcomes, its potential for increasing or maintaining BMD is less convincing.<sup>95</sup> Another is strength or resistance training,<sup>98</sup> in which the joints are moved against some kind of resistance, in the form of free weights, machines or one's own body weight and develop muscle hypertrophy and strength.<sup>99–102</sup> Huovinen et al. has demonstrated that a 16-week resistance training intervention, involving exercises such as abdominal crunches, leg presses and other large muscle group exercises improves total hip BMD by 6%.<sup>103</sup>

The international consensus is that rehabilitation programs are an important part of COPD treatment,<sup>3</sup> which follows from the realization that drug therapy for COPD is inadequate. A vicious cycle of deterioration in physical capacity, shortness of breath, anxiety is formed in patients with COPD. Rehabilitation is beneficial in improving health-related quality of life and exercise capacity breaks this cycle by introducing physical training, psychological support and networking with other COPD patients.<sup>35,104</sup> All patients with COPD can benefit from physical training.<sup>105,106</sup>

A study including 65 RCTs and involving 3822 participants has found statistically significant improvement for all included outcomes. In four important domains of quality of life (Chronic Respiratory Questionnaire scores for dyspnea, fatigue, emotional function, and mastery).<sup>104</sup> In particular, physical exercise<sup>105,106</sup> has been shown to improve general conditions of COPD patients and to significantly increase BMD. Evidence has shown that aerobic exercise increases BMD, while a combination of resistance training and balance training prevents the risk of falls and fractures in elderly people.<sup>92,93</sup>

Lacking of time and access to transportation are the most commonly reported barriers to exercise participation in patients with osteoporosis. Thus, clinicians and researchers should explore strategies to facilitate exercise participation in this population, such as the safety and efficacy of home-based impact exercise.

### 3.2.9 | Drug therapy

As for pharmacological intervention, adequate amounts of vitamin D and calcium are first recommended.<sup>107</sup> Osteoporosis guidelines recommend that daily intake is 1000–1200 mg for calcium and 800–1000 units for vitamin D3.<sup>108</sup> However, hydroxylated vitamin D metabolites increase the risk of hypercalcemia and hypercalciuria, they therefore need to monitor with serial serum and urinary calcium measurement.<sup>109</sup> There have many drugs for treatment of primary osteoporosis. However, there are few studies on pharmacological intervention for COPD-associated osteoporosis.<sup>110,111</sup> Because of lacking specific evidence in COPD patients, it is recommended to basically follow general practice guidelines for the treatment of primary osteoporosis.<sup>6,112,113</sup> First-line treatment includes bisphosphonates such as alendronate, risedronate and zoledronate, denosumab, and teriparatide. We use mathematical algorithms that quantify the risk in terms of “10-year fracture risk” such as FRAX. Oral bisphosphonates can be considered if the patient has low to moderate risk of fracture. If patient has high risk of fracture or has osteoporotic fracture, intravenous bisphosphonates are largely recommended.<sup>109,114</sup>

## 4 | CONCLUSIONS

Osteoporosis is very common in patients with COPD and has profound impact on the quality of life in COPD patients, but COPD associated osteoporosis is extremely underdiagnosed and undertreated. Thus, we propose to act immediately to screen every COPD subject for osteoporosis, identify patients at high risk of fracture and treat them with the standard medications.

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### CONFLICT OF INTEREST

The author declare that they have no competing interests.

### ETHICS STATEMENT

Ethics statement is not applicable.

### AUTHOR CONTRIBUTIONS

YJL, HCG, and JRW contributed substantially to the article concept. YJL and HCG retrieved literature and manuscript writing. LZ and JRW revised the manuscript. LZ and JRW reviewed and approved the final version before submission. All the listed authors have participated actively in the study. All authors read and approved the final manuscript.

### DATA AVAILABILITY STATEMENT

Data availability statement is not applicable.

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