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Chronic obstructive pulmonary disease and bone health: A review on possible links and follow up studies

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a common multisystem disease mostly affecting the respiratory system. Despite the well-known pulmonary manifestations of COPD, the extrapulmonary complications are mainly demonstrated in clinical studies, and the exact mechanisms behind the relationship between COPD and some extrapulmonary manifestations are still unclear. Many case-control studies reported osteoporosis as a common complication of COPD. However, the possible causality between COPD and osteoporosis is not clearly understood, and a lack of follow-up studies on COPD patients is an important issue addressed in the literature. In the present review, we discussed the common molecular pathways in COPD and osteoporosis and summarized the follow-up studies on COPD patients evaluating the possible changes in bone mass density or the development of fractures in COPD patients.

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Introduction

Chronic respiratory diseases are one of the main leading causes of death worldwide. Among the chronic respiratory diseases, most of the disability-adjusted life-years (DALYs) in both genders are due to chronic obstructive pulmonary disease (COPD) (1). COPD is a chronic disease with a considerable burden in every country, and most COPD-related deaths happen in low to middle-income countries (2). The estimated global prevalence of COPD has been estimated to be more than 328 million people (2), and the total mortality rate has been reported as 41.9 deaths per 100000 individuals (1). Many COPD patients have comorbid illnesses, including diabetes, lung cancer, psychological disorders, including depression and anxiety disorder (3). Among these comorbid diseases, osteoporosis is an important disease addressed in many clinical studies. However, there is conflicting evidence indicating a cause and effect relationship between osteoporosis and COPD. Moreover, it is not clearly understood whether osteoporosis in COPD patients is caused by their medications

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Or is a consequence of their underlying lung disease. Therefore, the present review discusses the available evidence about the possible relation between these diseases and the available follow-up clinical studies on COPD patients developing osteoporosis to determine osteoporosis's potential risk factor in COPD patients.

COPD and Respiratory Symptoms

The human respiratory system consists of various cells with specialized function enrolling in oxygen exchange and immunologic responses (4). Most of the chronic respiratory diseases including COPD are caused by the disruption of these complex systems in the lungs. During COPD, reversible airflow obstruction and disrupted inflammatory responses in the lungs are considered as the main underlying pathology (4). Mucus hypersecretion and lung tissue destruction, known as chronic bronchitis and emphysema, are the main pathologic findings in COPD patients (4). Such pathologic changes result in increased air-trapping and small airways resistance leading to progressive airflow obstruction (4). The progressive airflow obstruction results in respiratory symptoms, including sputum production, cough, dyspnea, breathlessness, and chest tightness (5). The progressive nature of the COPD results in restricted daily physical activities and decreased quality of life (5).

Moreover, COPD patients face various exacerbation episodes directly related to worse survival (6). COPD exacerbations trigger by several risk factors, including infections and the development of bronchiectasis (6). Therefore, controlling the COPD exacerbation factors by simple lifestyle modifications, including smoking cessation and adhesion to the treatment regimens and pulmonary rehabilitation, is considered the best approach in managing the COPD symptoms and exacerbations (6). Regardless of the COPD exacerbations requiring appropriate management, some other extra pulmonary complications of COPD need special consideration. Osteoporosis is one common complication in COPD patients' requiring specific consideration in these patients.

COPD and Bone Mass Density

The adverse effects of COPD are not restricted only to the respiratory system. Extrapulmonary complications are another complicating issue in the management of COPD patients. Decreased bone mass density (BMD) is among the important extrapulmonary complications of COPD, and the annual economic burden of osteoporosis-related fractures is $17.9 and £4 billion per year in the US and the UK (7). Despite the significant burden of osteoporosis and osteoporosis-related fractures, only a minority of at-risk populations receive treatment (7). Age and body mass index for both genders is the main risk factors of osteoporosis and menopausal age and years since menopause are the main risk factors among female patients (8). It has been demonstrated that COPD patients, especially those at the end stages of the disease waiting for transplantation, have an increased risk of osteoporosis and fractures (9).

Nevertheless, the causal relationship between COPD and osteoporosis development is not addressed in the literature. COPD patients receive various long-term medications, including different corticosteroids, considered a known risk factor of osteoporosis (10). Moreover, these patients deal with other disabilities and comorbidities, reducing their physical activities and affecting their body mass index (BMI), which are essential role players in osteoporosis development (10). To date, there is not enough clinical evidence regarding the relationship between osteoporosis and COPD. The only available systematic-review study by Graat-Verboom et al. evaluating the possible relationship between osteoporosis and COPD evaluated 775 COPD patients (11). They revealed a significant relationship between osteoporosis prevalence among COPD patients and healthy individuals (11). They demonstrated that the prevalence of osteoporosis and osteopenia among COPD population is 35.1% and 38.4%, respectively, and patients with low BMD are mostly females (11). Even more, receiving corticosteroids, disease severity, and body composition were the main correlates of osteoporosis (11). However, Graat-Verboom et al. study could not establish the causality based on the available reviews and lack of prospective ones (11). Table 1 summarizes

the follow-up studies evaluating the possible relationship between COPD and osteoporosis.

Follow Studies on Bone mass densities and fractures in COPD patients

Among the studies summarized in Table 1, two studies evaluated the prevalence of bone fractures on different sites, and four studies evaluated BMD among COPD patients during specific follow-up periods. Only one follow-up case-control study assessed the osteoporosis in these patients. Graat-Verboom et al. study evaluated COPD subjects with different severity for 3 years and demonstrated that the prevalence of osteoporosis increased from 47% to 61%, according to DXA-scan and X-spine studies (12). Moreover, they reported that the prevalence of osteoporosis among patients with newly diagnosed osteoporosis is 33% during the three years of follow up. Patients who developed osteoporosis showed a significant decrease in FEV1, while patients' lung function without osteoporosis remained stable (12). Based on their results, vitamin D deficiency and low T-scores at trochanter were both independent risk factors for osteoporosis (12). Among COPD patients, various risk factors, including smoking, increased age, inactivity, low BMI, systemic inflammation, and using corticosteroids, had controversial associations with osteoporosis or bone fractures (13, 14). Although the lack of case-control studies similar to Graat-Verboom et al. research is evident in the literature; however, other studies evaluating the risk of fractures in COPD patients provide valuable clues about the possible relationship between osteoporosis and COPD. COPD patients deal with an increased risk of severe vertebral fractures, and unfortunately, the treatment of osteoporosis is somehow neglected in these patients (15). Liao et al. study demonstrated that vertebrae and femur are the most common fracture sites among hospitalized COPD patients and the female population had higher fracture risks (16). Moreover, they reported an increase in COPD patients' age significantly elevates fractures' risk (16). Patients who were younger than 64 years did not increase fracture risk than non-COPD patients of similar age (16). The Liao et al. study did not consider the COPD disease severity and enrolled the younger population. Besides, they did not evaluate the patients' previous smoking history or pulmonary function tests (16).

Moreover, more than half of their study population was receiving oral corticosteroids (16). Regardless of the smoking history and pulmonary function tests that significantly affect osteoporosis, corticosteroids are among the most controversial drugs commonly used in COPD. McEvoy et al. study evaluated the relationship between receiving corticosteroids and bone fracture in COPD patients (17). They compared vertebral fractures among COPD male patients receiving oral or inhaled corticosteroids with those who do not use steroids (17). This study proved that using corticosteroids increases the likelihood of fractures in COPD patients, and using long-term oral corticosteroids strongly correlated with fractures (17). Dam et al. demonstrated that older males had lower spine bone BMD (18). After 4.5 years of follow-up, they reported that COPD patients have a 2.6 fold increase in the risk of vertebral fractures and a 1.4 fold increase in non-vertebral fractures after six years (18). Although they did not consider the duration of corticosteroid use and COPD; however, those receiving oral or inhaled corticosteroids had 2 fold increased risk of osteoporosis at the spine (18). The results of the Dam et al. study on the male COPD patients contrast with previous studies demonstrating a protective role for inhaled corticosteroids (19). Mathioudakis et al. reported that long-term administration of inhaled corticosteroids reduces the BMD loss in bronchitis males (19). Moreover, another study demonstrated that using inhaled corticosteroids in females has a dose-dependent protective effect on osteoporosis development (20). Liu et al. hypothesized that using corticosteroids reduces systemic inflammation in COPD patients (20). Moreover, it has been demonstrated that using inhaled corticosteroids can reduce COPD exacerbations. Kiyokawa et al. demonstrated that only COPD exacerbations and baseline PaO2 are associated with decreased thoracic BMD (21).

Table 1. Follow up studies evaluating osteoporosis or bone fracture in COPD patients

Author, year	Study characteristics	Mean age (years)	COPD Population (male (%))	Follow up duration	Results	Comments
J Van Dort et al., 2018 (22)	Smokers and subjects with COPD (GOLD II-IV)	61	999 (61%)	3 years	21.6% of the COPD subjects had more than one vertebral fracture at baseline and 33.5% at a 3-years follow-up.	The study population was not using oral corticosteroids at baseline. Baseline bone attenuation and BMI were the only significant determinant for the risk of incident vertebral fracture.
Liao et al., 2016 (16)	Hospitalized COPD	-	11312 (68.05%)	Up to 3.6 years	The vertebrae and femur were the most common fracture sites.	Half of the population received oral corticosteroid.
					Females had a higher fracture risk.	The female population had a higher fracture risk. An increase in COPD patients' age significantly increases the risk of fractures.
Liu et al., 2016 (20)	COPD without osteoporosis and aging > 40 years	-	10723 (0%)	Up to 15 years	Corticosteroid users had a lower risk of osteoporosis.	Female patients receiving inhaled corticosteroids are less likely to have osteoporosis.
Graat-Verboom et al., 2012 (12)	subjects with COPD (GOLD I–IV)	71.7	90 (60%)	3 years	Osteoporosis prevalence increased from 47% to 61%.	Patients who developed had a significant decrease in FEV_1, while patients' lung function without osteoporosis remained stable after three years.
					33% of patients developed osteoporosis during follow up.	Vitamin D deficiency and low T-scores at trochanter were both independent risk factors for osteoporosis.
Kiyokawa et al., 2012 (21)	COPD receiving oral systemic corticosteroid	70	42 (93%)	2 years	A decrease in thoracic vertebral BMD was greater in those who had exacerbations.	A decrease in thoracic vertebral BMD was associated with baseline PaO2.The exacerbation correlated with decreased BMD.
Dam et al., 2010 (18)	COPD or asthma ageing over 65 years	-	714 (100%)	4.5 years	BMD increased at the spine.	Males receiving inhaled or oral corticosteroids had lower BMD. Males receiving oral or inhaled corticosteroids had a two-fold increased risk of osteoporosis at the spine.

BMD: Bone Mineral Density, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Chronic Obstructive Lung Disease.

This study failed to establish a significant relationship between other osteoporosis risk factors and thoracic BMD (21). In this regard, the authors concluded that factors involved in COPD exacerbations could be a critical precipitating factor (21). The Kiyokawa et al. study did not consider confounding factors affecting BMD, including daily diet and physical activity (21).

Regarding the result of Liu et al. and Kiyokawa et al. studies demonstrating exacerbations as the only risk factor of decrease in thoracic BMD, we might conclude that inhaled corticosteroids might reduce osteoporosis by reducing the exacerbations (20, 21). Van Dort et al. conducted the most recent follow-up study (22). Van Dort et al. used bone attenuation measurement by computed tomography among their study population and demonstrated that this method could be a potential screening method for fracture risk as well as osteoporosis (22). They showed that among subjects without prevalent vertebral fractures, the body mass index and baseline bone attenuation are associate with increased risk of vertebral fractures within one year of follow-up (22). This study demonstrated that evaluation of bone attenuation and the presence of vertebral fractures on computed tomography scans are essential factors in identifying high-risk heavy smokers with or without COPD for vertebral fractures (22).

Common Underlying Molecular Etiologies, Two Different Diseases

The possible relationship between COPD and osteoporosis development is not clearly understood, and most of the available data is related to case-control studies. Although many clinical studies evaluated COPD's possible causality for osteoporosis; however, the multifactorial nature of COPD made it challenging to compare the available studies. COPD is somehow considered a chronic systemic inflammatory syndrome, and as Fabbri et al. stated, COPD should be viewed as a chronic disease not only limited to the pulmonary system (23). COPD patients have increased C reactive protein (CRP), leucocytes, fibrinogen, and tumour necrosis factor-alpha (TNF-a) compared to the healthy population. Even non-smoker COPD patients have low-grade systemic inflammation. Increased systemic inflammatory markers are associated with reduced lung function in COPD patients (24). Moreover, many inflammatory mediators increase during COPD exacerbation and remain elevated even in the disease's stable phase (20). Among inflammatory markers related to the development of osteoporosis, CRP, interleukin-6, and TNF-α are the inflammatory markers that are also elevated in COPD patients (20, 25). Liang et al. demonstrated that TNF-α and IL-6 are independent predictors of low BMD in COPD patients (25). These markers are associated with increased osteoclast bone resorption following increased osteoclast activity (26, 27). TNF-α has a potent synergic relationship with RANKL activity is a well-known osteoclastogenic cytokine (26). However, it has been suggested that TNF-a might activate differentiated osteoclasts independent of RANKL (26). Chen et al. studied the possible association between COPD and osteoporosis (28). They demonstrated that cigarette smoke extract increases RANKL expression in CD^{4+} T lymphocytes (28).

Moreover, COPD patients had an increased percentage of RANKL positive CD4 lymphocytes (28). These cells' frequency was inversely correlated with vertebrae and femoral neck bone mineral density (28). Therefore, RANKL positive CD4 lymphocytes could be a mechanistic link between lung disease and bone quality in COPD patients (28). Osteoclast genesis can be up regulated by macrophage colony-stimulating factor (M-CSF) releasing in an inflammatory environment (27). Along the side of the effect of inflammation on the development of osteoporosis in COPD patients, the role of vitamin D deficiency should be considered as an essential factor in these patients. Patients with variable COPD severity exhibit vitamin D deficiency compared to a healthy population (29). Vitamin D plays a vital role in bone hemostasis. This fat-soluble vitamin stimulates osteoclast genesis by regulating the RANKL signaling and enhancing bone resorption (29). Moreover, vitamin D can strengthen osteoprotegerin, reducing osteoclast genesis in mature osteoblasts (29). Regardless of the effect of the inflammatory environment and abnormal vitamin D levels in COPD patients accounting as common

etiologies in COPD and osteoporosis, other influential factors in developing osteoporosis, including steroid hormones, have not been widely studied in the literature.

COPD and Osteoporosis; A Mutual Communication

Regardless of the effect of molecular mediators on osteoporosis in COPD patients, other underlying mechanisms may predispose COPD patients to bone loss. Diami et al. evaluated hypercapnia and respiratory acidosis in COPD patients (30). They revealed that untreated COPD patients with hypercapnia and respiratory acidosis have lower BMD compared with matched healthy subjects (30). Hypercapnic COPD patients who lost more BMD than eucapnic patients had significantly increased bone resorption (30). This study did not find any correlation between any inflammatory cytokines and indicators of bone resorption in COPD patients and therefore suggested that the inflammatory cytokines may not be a significant contributor to osteoporosis in COPD patients (30). Other clinical studies, including Ohara et al. demonstrated similar findings indicating that BMD significantly correlates with the severity of pulmonary emphysema (13). COPD patients developing osteoporosis during 3-years follow-up shows reduced FEV1 level, while lung function of patients without osteoporosis remains stable (12). Such reports emphasize mutual communication between COPD and bone health. Regardless of COPD's respiratory complications, these patients also suffer from other complications negatively affecting bone health. Low BMI is a common finding in COPD patients related to poor prognosis (31). Cachectic COPD patients have significantly greater inflammatory markers and oxidative stress, and there is a possible link between low BMI and osteoporosis in clinical studies (31-33). Moreover, almost half of COPD patients have at least a component of metabolic syndrome that is considered as risk factor of osteoporosis (23).

The last and the most controversial issue regarding the mutual communication between COPD and osteoporosis is the effect of corticosteroids. Glucocorticoids suppress inflammatory cytokines and, therefore, suppression of the osteoclasts has been demonstrated in the literature (26). However, the Impact of chronic use of corticosteroids in chronic pulmonary diseases may have adverse effects on bone health. Earlier studies suggested that 20mg/day of prednisolone for 14 days provides detectable alterations in bone resorption markers and formation (34). Moreover, a recent meta-analysis by Van Staa et al. revealed a significant relationship between the total cumulative dose of corticosteroids and decreased BMD in those receiving corticosteroids for treating their chronic diseases (35). Iqbal et al. evaluated the effect of corticosteroid use among patients with chronic lung diseases and reported that receiving glucocorticoids are associated with a nine-fold increase in having osteoporosis (36). Moreover, patients who were not receiving glucocorticoids were associated with a five-fold increase in having osteoporosis (36). However, it seems that inhaled corticosteroid use might not be as harmful as oral corticosteroids. As mentioned earlier, Liu et al. demonstrated that female COPD patients using inhaled corticosteroids are less likely to have osteoporosis. Liu et al. explained their findings based on the anti-inflammatory effects of inhaled corticosteroids (20). Lau et al. demonstrated that using inhaled corticosteroids is not related to hip fracture in older females, and Sin et al. study confirmed the effect of inhaled corticosteroids on the inflammatory markers of COPD patients (37). They revealed that C-reactive protein increases in COPD patients and decreases as they become retreated by inhaled corticosteroids (37). Lau et al. and Vestergaard et al. revealed that using inhaled corticosteroids or B-agonists after adjustment for obstructive airway disease were not associated with increased risk of osteoporosis and fracture (38, 39).

Limitations and future perspective

The association between COPD and bone health has been demonstrated in many case-control studies, and the increased incidence of osteoporosis is highlighted in the literature; however, the heterogeneity among the available studies complicates the relationship's interpretation. COPD affects other body systems except for the lungs. These patients experience many complications, such as limited physical activities and abnormal weight gain or weight

loss that are the main risk factors for osteoporosis. Moreover, other confounding factors, including age, female gender, cigarette smoking, and disease severity, complicate the interpretation of the relation between COPD and osteoporosis (25). Even more, using different medications, including corticosteroids, is variable among the studies. Another limitation of the available studies is the method of evaluating bone health. The other point is using BMD as an indicator of bone health. As BMD determines the bone quality, one may not consider the BMD as a predictor of bone fracture in COPD patients. Therefore, researchers should focus their effort on conducting clinical studies with more restricted study designs comparing the effect of different COPD stages on bone health in follow-up studies with participants matched controlled for osteoporosis risk factors.

Conclusion

COPD is a chronic pulmonary disease with extrapulmonary complications. Osteoporosis is an extrapulmonary complication in COPD patients with considerable burden mostly induced because of bone fractures. COPD and osteoporosis may share a typical molecular relationship, while inflammation and vitamin D deficiency are etiologies for both diseases. Regardless of the shared molecular mechanism, the main risk factors presented in the limited available follow up studies include gender, increased age, COPD exacerbations, and BMI. Corticosteroids are still a controversial risk factor for osteoporosis in COPD patients. However, inhaled corticosteroids may be associated with lesser adverse effects on BMD during short-term follow-up studies.

Conflict of interest

The authors declare that they have no competing interest.

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