A REVIEW OF REDUCED BONE HEALTH IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT

The chronic obstructive pulmonary disease is a progressive inflammatory disease of the airways with high morbidity and mortality worldwide. COPD is associated with various comorbidities of which osteoporosis is a significant one. Reduced bone health (osteoporosis or/and osteopenia) is very common in COPD patients and has a significant impact on morbidity, mortality and economic burden. However such reduced bone health is often undiagnosed in COPD patients. Decreased bone mineral density and bone quality contribute to fragility fractures that worsen the respiratory function and further reduce the quality of life of the COPD patients. Routine screening of bone health enables the physician to identify osteoporosis and osteopenia at an early stage and can reduce the chance of osteoporotic fractures. Thus management of comorbidities should be incorporated into the management of COPD which will improve the outcome in COPD patients. Various risk factors, such as tobacco smoking, older age, low physical activity, vitamin D deficiency, low Body Mass Index (BMI) and use of oral or inhaled corticosteroids are considered to be responsible for osteoporosis or/and osteopenia in COPD patients. This review focuses on the prevalence of reduced bone health in COPD patients and some of the risk factors involved in the development of such reduced bone health.

KEYWORDS: Chronic Obstructive Pulmonary Disease (COPD), Osteoporosis, Osteopenia, Bone Mineral Density (BMD).

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by persistent airflow limitation that is progressive in nature and is
associated with abnormal inflammatory response in the airways and lungs to noxious particles and gases. COPD is a systemic disease with high morbidity and mortality worldwide and is considered to be the third leading cause of death by 2020. COPD is often complicated with various comorbidities such as cardiovascular disease, lung cancer, osteoporosis, diabetes, anxiety/depression and obstructive sleep apnoea.\cite{1} Such comorbidities and exacerbations contribute to overall severity in COPD patients and its management has clinical importance as they can cause hospitalization, increased mortality and can diminish the quality of life of COPD patients.\cite{2}

Reduced bone strength (osteoporosis or/and osteopenia) is one among the major comorbidities in COPD. Osteoporosis is a disease with low bone mass and micro architectural deterioration of bone tissue that may lead to increased bone fragility which in turn increases the fracture risk\cite{3}, while osteopenia is a medical condition in which protein and mineral content of the bone are reduced, less severely than in osteoporosis.\cite{3} The prevalence of osteoporosis and osteopenia are found to be in between 24 -44% of COPD patients.\cite{5}

Osteoporosis is a silent disease that often remains untreated in COPD patients unless complicated by fractures.\cite{1} Fractures tend to occur mainly in the hip, vertebrae, and forearm. Hip fractures demand more home care, can cause increased hospitalization and reduced life span. Vertebral fractures are associated with back pain, increased dyspnoea and decreased rib mobility that further restrict their lung disease. Such osteoporotic fractures further worsen the respiratory function in COPD patients.\cite{1,2} Various risk factors such as older age, tobacco smoking, low physical activity, Vitamin D deficiency, low BMI, COPD exacerbation and use of corticosteroids can contribute to the development of osteoporosis or osteopenia in COPD. The severity of the disease can also be considered as a risk factor.\cite{1,2,6,7} This review is meant to assess the prevalence of osteoporosis and/or osteopenia in COPD patients, and to analyze the factors that can contribute to reduced bone mass in COPD.

**PREVALENCE OF LOW BMD IN COPD**

The actual cause of osteoporosis in COPD patients is unknown, although several factors contribute to its development. Graat –Verboom et al (2009) in an ordered 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%) in COPD. According to this review, the important correlates of osteoporosis in COPD include low BMI, low fat-free mass, the
severity of COPD and treatment with corticosteroids. In a cross-sectional study, Silva et al evaluated BMD on 95 clinically stable COPD patients and reported the presence of osteopenia and osteoporosis each in 40 patients (42%). The study showed a significant correlation between BMD and level of physical activity, BMI, and BODE index (Body-mass index, airflow Obstruction, Dyspnoea, and Exercise). They also found the presence of altered pulmonary function tests in patients with reduced BMD than in patients with normal BMD. The National Health And Nutrition Examination Survey (NHANES), which included 14,828 subjects aged 45 yrs and above, reported the prevalence of osteoporosis of 16.9% in patients with COPD, compared to 8.5% in subjects without coexisting COPD. Jorgensen et al by combining the data of vertebral fracture and bone mass found that out of 58 evaluable patients, 44.8% were osteoporotic, 22.4% were osteopenic and 25.9% had normal bone mass.

Fragility fracture is one of the main burdens of osteoporosis in COPD. Fracture risk depends on bone strength, which is determined by bone mineral density and bone quality. As there is less number of clinical tools for the precise evaluation of bone quality, measurement of bone mineral density can be used for the diagnosis of osteoporosis and can be measured by Dual-energy X-ray absorptiometry (DXA) which is the gold standard for diagnosis of osteoporosis. BMD is reported as the SD of means, i.e., T-score and Z-score. The T-score is the difference in the number of SDs between the mean BMD value of the patient and mean BMD of a young sex-matched adult control population. The Z-score is the difference in the number of SDs between mean BMD of the patient and mean BMD of a race-, sex-, and age-matched reference population. According to WHO, T-score for normal individuals is within 1 SD of the mean value for young adults (-1 to +1), for osteopenia between -1 to -2.5 and for osteoporosis ≤2.5. BMD is reported as Z-score in children, premenopausal women, and younger men. Z-score higher than -2.0 indicate normal BMD for age and Z-score -2.0 or lower indicate low BMD for age.

There are only a few studies related to the prevalence of osteoporosis in COPD patients in India. Hattiholi and Gaude by using DEXA scan measured the BMD of COPD patients and they reported osteoporosis in 66.6% patients and osteopenia in 19.6% patients. From the study, independent predictors of low BMD in COPD patients are a number of exacerbations, the severity of COPD and steroid cumulative dose > 1000mg. Bhattacharya et al conducted a study on advanced COPD patients and evaluated the BMD of the patients using ultrasound.
bone densitometer. They reported osteoporosis in 21.62% patients. There were few limitations with Bhattacharya et al study. First, the study included only advanced COPD patients (GOLD Stage III, IV), second most of the volunteers were male and third, BMD was measured by Ultra Sound bone densitometer and not by DEXA scan.\[13\]

Gupta et al, in a retrospective study of patients with COPD, have reported low bone mass in 90% of their study population.\[5\] The multicentre TORCH (Towards a Revolution in COPD Health) study, which included 658 COPD patients, had reported osteoporosis in 23% patients through DEXA scan.\[14\] Jorgensen and Schwartz reported a higher prevalence of low BMD among COPD patients since they found a decline in BMD in about 50% of COPD patients.\[15\] S.M. Abu-Bakr et al in a study on 60 male subjects reported an increased prevalence of low BMD (56.6%) among men with COPD (Gold stage III- IV) than healthy individuals of same age and sex. They noted a threefold increase in fracture risk in COPD patients with low BMD than COPD patients with normal BMD\[16\]. Another study by A. Godah EL-Gazzar et al demonstrated abnormal BMD in 80% of the COPD patients of moderate to the very severe stage.\[17\]

Different investigators have reported the different prevalence of osteoporosis in COPD. This may be referred to different study population characteristics (smoking index, age, sex, GOLD stages), different methods of diagnosis of BMD, or variable genetic susceptibility to osteoporosis.\[14,18,19\] Shepherd et al concluded that the prevalence of reduced BMD in COPD patients varies between 9-69% and 27-67% respectively, depending on the diagnostic methods used, the population used for study and also the severity of COPD.\[20\]

**RISK FACTORS OF LOW BMD IN COPD**

The actual cause or mechanism of osteoporosis in COPD patients is mostly unknown. However, clinical evidence indicates that certain risk factors are associated with osteoporosis and other comorbidities of COPD.

**Smoking**

Smoking is a common risk factor for COPD and osteoporosis. A meta-analysis by Ward and Klesges, demonstrated that tobacco smoking had a cumulative, dose–dependent effect on bone mass. Compared to non-smokers, smokers show a significant reduction in bone mass at major sites including hip, lumbar spine and forearm. Smokers are estimated to have 32% greater risk of suffering a hip fracture compared with individuals who have never smoked.\[21\]
Jorgensen et al in a cross-sectional study found no difference in smoking habits between osteoporotic and non-osteoporotic patients.\textsuperscript{[9]} One study reported an increased risk of hip fracture in smokers.\textsuperscript{[22]} Baldock PA et al has shown evidence of decreased calcium absorption in the gastrointestinal (GI) tract in smokers compared to non-smokers.\textsuperscript{[23]} It is also considered that several mechanisms can contribute to osteoporosis: altered calcitropic hormone mechanism, dysregulation in production, metabolism, and binding of estradiol, altered metabolism of the hormone of the adrenal cortex.\textsuperscript{[1]}

**Low Body Mass Index (BMI)**

Biskobing D M observed a direct correlation between bone mass and BMI. The review says that both men and women with high BMI have a higher value of BMD. This is partially considered to be the effect of greater weight-bearing load on the bone. Along with this the presence of high levels of estrogen in obese persons increase the aromatisation of testosterone and is converted to estrogen in the adipose tissue. The resulting increased estradiol level may explain the higher BMD in obese persons.\textsuperscript{[6]} In a study in India, Hattiholi and Gaude observed that patients with lower BMI had a higher prevalence of osteoporosis (37.3\%) when compared to overweight patients.\textsuperscript{[12]} A.Godah EL-Gazzar et al, in a study, showed a significant decline in BMI in COPD group compared to the control group and had demonstrated low BMD in 80\% of the patients.\textsuperscript{[17]}

**Low physical activity**

Physical activity scores have been found to be correlated with BMD in patients with COPD. Liu et al in a study on the relationship between low daily physical activity (DPA) and low BMD in COPD, noted significantly lower DPA in COPD patients with low BMD than those without osteoporosis. They found significant positive correlation between daily physical activity and BMD of lumbar spine, femoral neck and total hip.\textsuperscript{[24]} Various studies have shown that exercise can prevent bone loss. Patients with advanced COPD are often associated with decreased mobility.\textsuperscript{[6]} Daisuke Inoue et al found a negative correlation between hip BMD and COPD Assessment Test scores.\textsuperscript{[2]} Decreased muscle strength and activity may increase the risk for falls and fracture in COPD patients.\textsuperscript{[6]}

**Age and Sex**

Older age is found to be an established risk factor for both COPD and osteoporosis. Thus, older patients with COPD show a high prevalence of osteoporosis compared to younger patients. Females are considered to be at an increased risk for osteoporosis. This is due to the
effect of estrogen in women. A study by Hattiholi and Gaude agree with a high prevalence of osteoporosis in females (p<0.005).\[12\]

**Severity of COPD**

Several studies prove the relationship between severity of COPD disease and risk of development of osteoporosis. In a cross-sectional study Jorgensen et al observed increased incidence of osteoporosis and osteopenia with an advanced stage of COPD. They included COPD patients of GOLD stage III & IV and found that 68% had either low bone mass or a previously undiagnosed vertebral fracture.\[9\] Graat-Verboom et al used whole body and local DEXA scan in the evaluation of osteoporosis in COPD patients and observed an increase in the prevalence of osteoporosis with increasing severity of COPD.\[25\] Bolton et al in a study of 58 patients reported a prevalence of osteoporosis in 20% of GOLD stage II patients\[26\], while T.Schopp et al found that 69% of their patients in GOLD stage II were osteoporotic.\[27\]

**COPD exacerbation**

In a longitudinal study, Kiyokawa et al noted an independent association between COPD exacerbation and progression of osteoporosis.\[28\] Another study showed a mechanistic link between COPD exacerbation and osteoporosis. Hypoxia, inflammation, use of steroids, physical inactivity and oxidative stress during exacerbation can all contribute to increased bone loss in COPD patients.\[29\]

**Use of Corticosteroids**

Oral and inhaled corticosteroids are frequently used in COPD patients. Inhaled corticosteroids (ICS) are used in moderate to severe COPD patients in order to reduce the frequency of exacerbation and improving the quality of life.\[30\] A Meta analysis of randomized controlled trials and observational studies found that ICS use was associated with a modest but statistically significant increase (>20%) in the risk of fractures in patients with COPD.\[31\] Osteoporosis induced by glucocorticoids mainly depend on daily dose of the drug.\[32\] Jorgensen et al noted that high percentage of patients in glucocorticoid treatment belong to the fracture group compared to the non-fracture group.\[9\] The increasing prevalence of glucocorticoid induced bone loss is so common that the National Osteoporosis Foundation formulated a guideline and recommended that all patients receiving chronic glucocorticoid treatment (>1 month) with 7.5 mg/day of prednisone or equivalent should undergo screening for osteoporosis.\[12\]
Vitamin D deficiency

Vitamin D deficiency is found to be prevalent in COPD patients. Vitamin D and Parathyroid hormone play a major role in Calcium and bone hemostasis. Romme et al reported Vitamin D deficiency in 58% of patient with moderate to very severe COPD and they observed a positive correlation between Vitamin D and BMD. Vitamin D deficiency in different stages of COPD was reported as 43% in GOLD stage II, 50% in GOLD stage III, and 76% in GOLD stage IV patients.[33] Another longitudinal study by Graat-Verboom et al reported 7.5 fold increased the risk of osteoporosis development in COPD patients with baseline Vitamin D deficiency.[34] Various factors that can cause Vitamin D deficiency in COPD include poor diet, less sunlight exposure, smoking (accelerated skin aging), depression, renal dysfunction.[1]

CONCLUSION

Reduced bone health is a common problem in COPD which is often undiagnosed. This impaired bone health raise the problem of fragility fractures that increase the morbidity and reduce the quality of life in COPD patients. Smoking, low BMI, older age, decreased physical activity, severity of the disease, Vitamin D deficiency, exacerbation and use of corticosteroids can contribute to the decline in BMD in COPD patients. Early diagnosis and detection of low bone mineral density and prevention of the risk factors may help to reduce the incidence of reduced bone health in COPD patients.

BIBLIOGRAPHY


