ORIGINAL ARTICLE

Bone mineral density among elderly patients with chronic obstructive pulmonary disease patients in India

Jyothi Hattiholi, Gajanan S. Gaude

Departments of Pulmonary Medicine, Karnataka Lingayat Education University's Jawaharlal Nehru Medical College, Belgaum, Karnataka, India

ABSTRACT

Background: Osteoporosis is one of the major extra-pulmonary manifestations of chronic obstructive pulmonary disease (COPD), which limits the physical activity. The present study was undertaken to study the bone mineral density (BMD) and osteoporosis in the elderly COPD patients. **Materials and Methods:** This was a cross-sectional study carried out among elderly COPD patients. After a detailed clinical history spirometry was done to stage the severity of COPD. DEXA scan of the lumbar spine was performed using bone densitometer to determine osteoporosis. Statistical analysis was based on Chi-square test. Risk factors were identified by univariate and multivariate logistic regression analysis. **Results:** A total of 70 elderly COPD patients were included. Fourty-six patients (65.7%) had osteoporosis and 13 (18.6%) had osteopenia. Majority of the osteoporosis patients had stage III or stage IV COPD disease (77.2%). As the severity grade of COPD increased, the risk of osteoporosis also increased. Also, with the increasing severity of COPD, BMD decreased. Patients with lower body mass index (BMI) had higher prevalence of osteoporosis (45.7%). Using multivariate regression analysis, stage IV COPD, number of acute exacerbations >3 and steroid cumulative dose >1000 mg were independent risk factors for osteoporosis in elderly COPD patients. **Conclusions:** The prevalence of osteoporosis was 65.7%, and 18.6% had osteopenia. Stage III and IV patients had significantly lower BMI in elderly COPD patients. High clinical suspicion and early diagnosis and treatment are required in the evaluation of osteoporosis in elderly COPD patients.

Key words: Bone mineral density, osteoporosis, risk factors

Address for correspondence:
Dr. Gajanan S. Gaude,
Department of Pulmonary Medicine,
Karnataka Lingayat Education University's Jawaharlal Nehru Medical College,
Belgaum - 590 010, Karnataka, India.
E-mail: gsgaude922@gmail.com

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a syndrome of progressive airflow limitation caused by the abnormal inflammatory reaction of the airway and lung parenchyma. It is now considered as a systemic disease with widespread extra-pulmonary manifestations.[1] The prevalence rates of COPD in males varied from 2.12% to 9.4% in studies conducted in north India and from 1.4% to 4.1% in south India, and the rate is projected to increase by nearly 50% by the year 2016.[2]

The most common co-morbidities responsible for the clinical manifestations are cachexia, skeletal muscle abnormalities, osteoporosis, metabolic syndrome, coronary artery disease, heart failure, pulmonary infections, cancer and pulmonary vascular disease.[3] Osteoporosis is a systemic skeletal disease characterized by a low bone mineral density (BMD) and microarchitectural changes in bones, leading to increased bone fragility and, increased fracture risk.[3] The prevalence of osteoporosis in COPD patients is 36% to 60%.[4] COPD patients have a higher risk of osteoporosis as compared to healthy subjects, and the loss of bone occurs over an extended period of years.[5] When fractures occur as a complication of osteoporosis, the quality of life is further reduced. Kado *et al*.[6] reported increased mortality in elderly women with vertebral. The management of COPD patients with osteoporosis poses a clinical challenge. Therefore, early diagnosis of COPD, with preventive and therapeutic measures that could avoid or reduce the consequences of osteoporosis is imperative.

This study compared the degree of osteoporosis and bone metabolism markers among elderly patients with COPD; the factors influencing bone metabolism in these patients were determined.

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MATERIALS AND METHODS

This was a cross-sectional questionnaire-based study conducted in the department of Pulmonary Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum elderly patients with COPD, between January 2010 and December 2011. The study was approved by the Institutional Ethical Committee and all the patients gave informed consent.

All the patients diagnosed as a case of COPD, based on GOLD guidelines,[2] were included in the study. Persons of >60 years were considered as elderly group as per WHO definition of this group.[7]

Bronchogenic carcinoma, untreated thyroid dysfunction, rheumatic diseases, diseases affecting bone or calcium homeostasis, primary or secondary hyperparathyroidism, Cushings syndrome, established osteoporosis and patients taking treatment with bone active agents and oral corticosteroids.

After a detailed demographic and clinical history, a post-bronchodilator spirometry was performed using RMS Helios 702 Spirometer (Recorders and Medicare Systems Pvt., Ltd, MEDSPIROR, India) in all patients and FVC and FEV1 were expressed as a percentage of predicted. Staging of COPD was according to GOLD criteria.[2] Peripheral blood was collected in the morning under fasting conditions, and the plasma concentrations of calcium, phosphate, total protein, albumin, BUN, creatinine, alkaline phosphatase, and urinary concentration of calcium, phosphate and creatinine were measured by routine assays. Bone mineral content (grams) and BMD (grams per centimeter squared) were measured with dual-energy X-ray absorptiometry using Lunar DPX densitometer DEXA Scan (Dual Energy X-Ray Absorptiometry) (GE Healthcare Lunar prodigy advance, scanner serial no. PA + 302343, software version-ENCORE 2008 version 12.2, Germany). Regions of interest that were assessed included femur and lumbar spine (L2-L4). Lumbar BMD was also expressed as a Z score and T score. The Z score is a SD from the weight-adjusted average BMD for each age. A patient's BMD was given as a T-score, which is derived by comparing it to an average score for a healthy 30-year-old of the same sex and race. The difference between the "normal young" score and the patient's score is referred to as a standard deviation (SD).[8] Using DEXA scan, osteoporosis was defined by a T-score of ≤−2.5, osteopenia as T-score between −1 and −2.5, and normal BMD-T score >−1. To analyze the risk factors for osteoporosis in the elderly COPD patients, we divided groups into osteoporosis and no osteoporosis (osteopenia and normal BMD combined), because only patients with osteoporosis need to be treated pharmacologically. Body mass index (BMI) was defined as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (>25-29.9 kg/m^2) and obese (>30 kg/m^2).

Statistical analysis

Discrete variables were compared with Chi-square test and presented as percentages. Continuous variables were compared with independent *t* test and presented as means ± SD. Relationships between the variables were assessed with Pearson correlation coefficients. To estimate the relative risk, a McNemars test was used. A *P*-value of <0.05 was considered significant. Relative risk of individual risk factors was analyzed by using univariate and multivariate logistic regression analysis. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 16.0.

RESULTS

A total of 70 patients were included in the study. There were 45 male patients (64.3%) and 25 female patients (35.7%). The baseline patient characteristics are shown in Table 1. A total of 46 patients had osteoporosis (65.7%), 13 patients (18.6%) had osteopenia, while the rest 11 patients (15.7%) had normal bone densitometry. Mean age of the male patients was 69.6 ± 5.7 years and that of female patients was 67.4 ± 4.3 years. Nearly half of the patients (45.7%) were underweight (BMI <18.5). More than two-thirds of

Table 1: Baseline characteristics of the patients

	Men (*n*=45)	Women (*n*=25)	Total (*n*=70)
Age, years	69.6±5.7	67.4±4.3	69.2±5.3
FEV_1%, Predicted	43.3±17.7	40.7±17.3	42.7±16.9
Stage I	6.6	4.0	5.7
Stage II	15.6	20.0	17.1
Stage III	42.2	40.0	41.5
Stage IV	35.6	36.0	35.7
Smoking			
Current smoker	22.2	—	14.3
Ex-smoker, %	64.4	—	41.4
Pack years	15±9	—	15±9
BMI, kg/m^2	22.7±4.4	20.1±5.4	21.4±4.7
Low, %	44.4	48.8	45.7
Normal, %	24.5	32.0	27.1
High, %	22.2	12.0	18.6
Obese, %	8.9	8.0	8.6
DEXA Scan, Hip and LS			
BMD, g/cm^2	1.112±0.114	1.078±0.125	1.117±0.114
T-Score	−2.6±1.5	−2.7±1.9	−2.6±1.8
Normal BMD, %	17.8	12.0	15.7
Osteopenis, %	17.8	20.0	18.6
Osteoporosis, %	64.4	68.0	65.7
Duration of illness (%)			
<5 years	11.1	16.0	12.8
5–10 years	66.7	56.0	62.8
>10 years	22.2	28.0	24.4
Inhaled Steroids, %	32.6	33.4	32.5
Complications, if any (*n*)	3	1	5
Deaths (*n*)	2	1	3

Results are presented as means±standard deviation, unless otherwise indicated, LS – Lumbar spine, BMI – Body mass index, BMD – Bone mineral density

the male patients were smokers, while none of the women patients were smokers.

Majority of the elderly patients who had osteoporosis had stage III and stage IV COPD disease (77.2%). Stage I and stage II COPD disease had less prevalence of osteoporosis. It was observed that, as the severity grade of COPD increased, the risk of osteoporosis had also increased. Almost 85% of the patients who had suffered ≥3 exacerbations in the past 3 years had osteoporosis, while all the patients with >5 exacerbations in the past 3 years had osteoporosis.

The BMD of the hip and lumbar area of the spine were significantly lowered in elderly patients with COPD [Table 2]. BMD showed a significant difference ($P < 0.0001$) among the different stages of COPD [Table 3]. As the severity of stage of COPD increased, the BMD decreased.

The various risk factors for osteoporosis in COPD such as BMI, smoking and use of corticosteroids in elderly COPD patients were analyzed. It was observed that underweight patients had higher prevalence of osteoporosis (45.7%) as compared to overweight patients. Obese individuals had protective effect against development of osteoporosis (8.6%). But, this association was not statistically significant ($P < 0.073$). In this study, all female patients were non-smokers. Smoking was found to have no association with COPD. Comparing only among smokers, osteoporosis was observed to be more prevalent in those with >10 pack years smoking history (24.6%) as compared to the patients having pack year history of ≤10 (11.8%) ($P < 0.3$).

Most of the patients with COPD are prescribed steroids during any exacerbations, and the use of steroids may increase with the number of exacerbations and hospitalizations. All the patients were categorized as those not on any steroids, those who used only inhaled steroids, those who used <1000 mg of steroids (cumulative dose; equivalent of prednisolone) and those who used >1000 mg (cumulative dose; equivalent of prednisolone). Osteoporosis was observed to be high in those using >1000 mg (cumulative dose, prednisolone) ($P < 0.0001$). It was also observed that the risk of developing osteoporosis in COPD patients using inhaled corticosteroids was almost the same as those not using inhaled corticosteroids (3.9% versus 6.8% respectively).

The various factors were analyzed to evaluate the role of each factor in the predisposition for osteoporosis in elderly COPD patients. By performing simple univariate analysis, it was observed that the risk factors for osteoporosis in COPD were female sex, number of exacerbations, BMI and severity of COPD. After using multivariate logistic regression analysis, the significant risk factors observed for the development of osteoporosis in elderly COPD were the number of acute exacerbation of COPD ≥3, COPD stage IV disease and the use of steroids >1000 mg (cumulative dose; equivalent of prednisolone) [Table 4].

Table 2: Bone densitometry data

Bone data	Men	Women	Total
Total body BMD, gm/cm²	1.112±0.114	1.078±0.124	1.111±0.121
Spine BMD gm/cm²	0.98±0.06	0.86±0.15	0.92±0.10
Z score	−0.33±0.27	−0.31±0.19	−0.33±0.27
T score	−2.6±1.5	−2.7±1.9	−2.6±1.8

Table 3: Bone mineral density and severity of COPD

COPD severity	Normal (BMD) (gm/cm²)	Osteopenia (BMD) (gm/cm²)	Osteoporosis (BMD) (gm/cm²)	Mean±SD
Stage I	1.239	1.172	0.892	1.114±0.202
Stage II	1.145	1.118	0.824	0.975±0.213
Stage III	1.393	0.971	0.73	0.852±0.225
Stage IV	0	0.983	0.713	0.717±0.141
Mean±SD	1.215±0.183	1.013±0.103	0.744±0.124	

COPD – Chronic obstructive pulmonary disease

DISCUSSION

Osteoporosis is more prevalent among COPD patients than among healthy subjects.[9] Thus, it is important to recognize the risk factors and strategies to manage osteoporosis in elderly COPD patients in order to avoid osteoporotic fractures, since it deteriorates the quality of life and prognosis. In this study, we compared the degree of BMD among COPD patients in the elderly patients and determined the factors that influence bone metabolism in these patients. This study has clearly shown that, in elderly patients with COPD, the lumbar and hip BMD was much lower.

In the present study, the prevalence of osteoporosis in elderly COPD patients was 65.7% and that of osteopenia was 18.6%. Various studies done in different parts of the world showed prevalence of osteoporosis to be 9%-69% in COPD patients versus 0%-13% in healthy individuals.[5] Katsura and Kida have observed the prevalence of osteoporosis in patients with COPD to be 50%, and this was significantly higher than that of bronchial asthma. The prevalence of osteoporosis was reported to be 24% among postmenopausal women in Japan,[10] and the prevalence of osteoporosis in women with COPD was almost two-fold higher than that in the general population. Among various studies done, study by Verboom *et al*.,[11] and TORCH trial[10] were landmark studies. They found prevalence of osteoporosis to be 21% and 65% and that of osteopenia to be 41% and 65%, respectively. An Indian study[12] recently done among 37 patients showed a prevalence of osteoporosis to be 21.6% and that of osteopenia to be 27%. But, this study had used calcaneal USG for the diagnosis of osteoporosis, which is not a standard test. We used DEXA scan for the diagnosis of osteoporosis, which is considered as a gold standard test, and

Table 4: Univariate and multivariate analysis of various risk factors for osteoporosis in COPD

Risk Factors	Univariate analysis			Multivariate analysis		
	Unadjusted odds ratio	95% CI	*P* value	Adjusted odds ratio	95% CI	*P* value
Sex (F/M)	4.25	1.52-11.30	0.005	1.30	0.22-7.78	0.771
No of Exacerbations						
<3	Reference population			Reference population		
3-5	35.71	30.36	30.36	30.36		
>5	125	85.33	85.33	85.33		
BMI						
Normal	Reference population			Reference population		
Underweight	2.95	2.62	0.034	2.62	0.39-17.54	0.661
Overweight	1.32	3.10	0.660	3.10	0.34-27.02	0.416
Obese	1.96	0.34-11.23	0.453	3.64	0.12-111.11	0.649
COPD Severity						
Stage I	Reference population			Reference population		
Stage II	2.81	Stage II	2.81	1.50	0.07-31.25	0.552
Stage III	6.25	1.09-35.71	0.039	2.11	0.10-40	0.350
Stage IV	41.70	4.9-333.33	0.001	13.61	0.48-333.33	0.024
Steroid Use (Cumulative Dose)						
No Steroids	Reference population			Reference population		
ICS	5.30	ICS	5.30	10.15	0.63-166.66	0.101
<1000 mg	2.20	<1000 mg	2.20	1.98	0.22-17.85	0.545
>1000 mg	35.75	>1000 mg	35.75	7.38	0.92-58.52	0.05

COPD – Chronic obstructive pulmonary disease

the patients were classified according to the WHO criterias.[8] The varied difference in the prevalence of osteoporosis in different studies can be attributed to the methodological differences in the assessment of BMD and also the characteristics (age, sex, past use of bone medications, stable COPD patients) of patient population chosen for the study. The higher prevalence of osteoporosis in the present study may be due to varied reasons. These includes higher age group, presence of altered vitamin D homeostasis, repeated exacerbations leading to higher cumulative dose of parental steroids, immobility due to advanced disease and physical inactivity.

In the present study, higher prevalence of osteoporosis was observed in female COPD patients ($P < 0.005$), as females are at increased risk for development of osteoporosis. A recent Japanese study[11] observed two-fold higher prevalence of osteoporosis in female COPD patients. In a meta-analysis, it was observed that the prevalence of osteoporosis varied from 9% to 69%, and that there was higher proportion of women patients with COPD. There is a definite relation between the severity of COPD disease and the risk of development of osteoporosis. In the present study, majority of patients who had osteoporosis had grade IV COPD (93.7%). Also, BMD reduced as the severity of the disease progressed ($P < 0.004$). In a study by Stevenson *et al*.,[13] it was observed that there was increased incidence of osteopenia and osteoporosis with advancing COPD stage. They observed that 68% had either low bone mass (osteopenia or osteoporosis) or a previously undiagnosed vertebral fracture, with 25% of the included patients having a vertebral fracture. Consistent with the above studies, another study by de Vries *et al*.,[14] observed that the risk of osteoporotic fracture increased in patients with COPD (OR 1.61; 95% CI 1.52-1.71). It was also observed that patients with more severe airway obstruction in COPD had increased risks of osteoporosis and bone fractures as compared with patients without a history of obstructive airway disease. Three cross-sectional observational studies described an independent association between osteoporosis with poor pulmonary function (FEV_1 predicted). In these studies, BMD decreased approximately 0.02 g/cm^2 for every 1 L/s decrease in FEV1 and had a 2.4 increased risk of osteoporosis. COPD patients are associated with a 1.2- to 1.3-fold higher risk of fractures.[15] Graat-Verboom *et al*.,[3] observed that, as severity of COPD increased, the prevalence of osteoporosis also increased. In another study, similar findings of higher prevalence of osteoporosis in stage III and stage IV COPD disease as compared to stage I and stage II COPD were observed.[16] The TORCH study[10] demonstrated a higher prevalence of osteoporosis and osteopenia at baseline in COPD patients, but there was no association between FEV_1 impairment and BMD when adjusted by age and gender.

Smoking is a well-known cause of COPD, and it has also been found to be an independent risk factor for osteoporosis in both men and women.[17,18] Slemenda *et al*.,[19] reported that lumbar spine BMD was 12% lower in smokers who have smoked 20 pack-years as compared to non-smokers. Both vertebral fractures and hip fractures were found to be higher in smokers. The pathophysiologic mechanism for the lower bone mass and increased fracture risk in smokers is unclear. A study[20] showed evidence of decreased calcium absorption in the gastrointestinal

tract (GI) tract in smokers as compared to non-smokers. In the present study, all female patients were non-smokers; among male smokers, it was observed that the prevalence of osteoporosis was more in those with >10 pack-years. Prevalence of osteoporosis in patients with smoking >10 pack-years was 19.6%, while it was 10.8% in those with smoking of ≤10 pack-years.

Elderly COPD patients with lower BMI had higher prevalence of osteoporosis (45.7%) as compared to overweight patients. Bisboking *et al*.,[21] observed that bone mass was directly correlated with BMI. Body weight has previously been shown to be closely related to BMD in both men and women.[22] It is well recognized that patients with chronic lung disease such as COPD occasionally show a malnourished status or so-called pulmonary cachexia. A similar relationship between malnutrition and low BMD has been reported in adult patients with cystic fibrosis.[23] Both men and women with high BMIs have higher BMD. This is believed to be partially due to the effect of the greater weight-bearing load on the bones. In addition, estrogen levels tend to be higher in obese people due to the increased aromatization of testosterone to estrogen in adipose tissue. The resulting higher estradiol levels may help to explain the higher BMD in obese persons, since estradiol levels in both men and women correlates with BMD.[21] Many patients with end-stage COPD lose weight as the disease progresses due to decreased intake and increased energy requirements, especially more in the elderly patients due to the long standing nature of the disease. Furthermore, low bone mass was correlated with low fat free mass (FFM) in stage IV patients, and FFM could thus be used as a determinant of bone loss in this population. These findings were supported by a case-control study,[24] in which patients with COPD were found to have lower bone mass than controls, and decreasing BMD was found with increasing GOLD COPD stage. Another study[25] also found that BMI was the strongest predictor of osteoporosis in COPD, with a BMI ≤22 having an odds ratio of 4.18 (95% CI, 1.19 to 14.71, $P < 0.026$). Since, in COPD, there is systemic inflammation, there is a release of proinflammatory cytokines such as TNF-α, which may cause peripheral muscle dysfunction and malnutrition. Studies have shown that serum TNF-α level and the lipopolysaccharide-stimulated TNF-α production by peripheral blood monocytes was significantly higher in patients with COPD who are losing weight as compared with that in weight-stable patients with COPD and normal subjects.[26] TNF-α is also known as a potent inhibitor of bone collagen synthesis and a stimulator of osteoclastic bone resorption, suggesting that systemic inflammatory response and increased production of TNF-α causes weight loss as well as bone loss in patients with COPD.[27] However, other inflammatory cytokines other than TNF-α are also known to affect BMD, which may contribute to osteoporosis.[11]

Corticosteroids, commonly prescribed to patients with COPD or asthma, are known to reduce bone formation and increased bone resorption. As the number of exacerbations of COPD increases, the cumulative dose of parental steroids also increases. The dose of steroids during exacerbation of COPD is much higher, which may contribute to the higher incidence of reduced BMD. Also, the number of exacerbations is affected by prolonged immobilization. In the present study, majority of the patients with COPD were prescribed steroids during exacerbations, and the use of steroids increases with a number of exacerbations and hospitalizations. Osteoporosis was observed to be high in those using >1000 mg (cumulative dose, prednisolone) ($P < 0.0001$). Normal bone metabolism is a result of the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts. The mechanism of bone loss induced by glucocorticoids is two-fold, with decreased bone formation and increased bone resorption.[28] Similar findings have been observed by Bhattacharya *et al*.,[12] in Indian COPD patients.

The risk of developing osteoporosis in COPD patients using inhaled corticosteroids was observed to be almost the same as those not using inhaled corticosteroids in the present study (3.9% versus 6.8% respectively). Similar results were observed in a study by Canalis *et al*.[29] They studied patients with more severe COPD and found that they had higher risks of fracture and that these risks were comparable between users and nonusers of inhaled corticosteroids. TORCH study[10] investigated the long-term effects of therapy with inhaled steroids on BMD and bone fractures in patients with moderate-to-severe COPD. No significant differences were observed between placebo and inhaled steroids group. The incidence of fractures also was low and was similar for all treatments (5.1% to 6.3%). Whether ICS therapy produces adequate blood levels that can adversely affect BMD is not certain, but even a small effect over an extended period of time may produce serious side effects.[29] Also, a Cochrane review[30] of randomised clinical trials found no evidence of effect of inhaled-corticosteroid exposure on BMD in COPD patients. Thus, this trend is consistent with the current hypothesis that underlying disease severity is important in the aetiology of reduced BMD in COPD patients rather than using inhaled corticosteroids.[31,32]

We hypothesized that corticosteroids, smoking, physical inactivity, low body weight and/or malnutrition can explain the lower BMD and higher rates of osteoporosis in elderly patients with COPD. Elderly patients with moderate to severe COPD have advanced nature of the disease, which predisposes them to osteoporosis by virtue of being elderly or chronically disabled and having chronic systemic inflammation. Low-grade systemic inflammation persists even in non-smoking subjects with chronic airflow limitation, suggesting that smoking cessation does not

eliminate ongoing inflammation and that inflammation is not due to tobacco alone.[33] Another potential mechanism could be due to hypercapnia, which has been associated with increased bone resorption.[34] Dimai *et al*.,[35] showed that lower arterial pH and higher arterial carbon dioxide levels were correlated with lower BMD in COPD patients. Finally, hormonal levels may be another mechanism. Hormone replacement therapy and increased circulating estrogen levels had a protective effect on pulmonary function in pre- and postmenopausal women.[36] Further studies to examine whether inflammation, hypercapnia or sex hormones mediates the relationship between COPD and BMD are needed.

In summary, it is now established that osteoporosis in COPD is multifactorial. It is evident from the present study that COPD is now increasingly being recognized as an inflammatory condition of the lung, and, over the past decade, it has been recognized for its systemic inflammation and having extra-pulmonary manifestations. Patients with COPD are often treated with oral or parenteral glucocorticoids during exacerbations. Such oral or parenteral glucocorticoid therapy along with various other risk factors clearly increases the risk for the development of osteoporosis.

This study has certain limitations. First, data on physical activity and exact smoking status were limited. Second, there were no data on the loss of fat-free mass. Loss of fat-free mass has been associated with reduced BMD and more severe COPD and might be a more concise marker of severity of COPD as compared with BMI. Third, there was no control group. This becomes difficult when the test is costly, making it difficult for a normal person to affirm it. Lastly, among patients who used inhaled steroids, about 40% were using oral corticosteroids during exacerbations. Therefore, it may be difficult in this patient group to separate the effects of oral and inhaled corticosteroids.

In conclusion, the results of our study demonstrated that osteoporosis is common among elderly COPD patients even if these patients did not receive systemic corticosteroids. The development of osteoporosis in COPD is muti-factorial, but preventive strategies to decrease osteoporotic fractures should be added to the management of elderly patients with COPD. Hence, in an ideal set-up, all patients with COPD should be screened for osteoporosis using BMD measurements made by DEXA for the early diagnosis, and proper therapy of this condition can be advised at the earliest.

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