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Assessment of Osteoporosis and Osteopenia and its Co-Relation with Disease Severity in Patients of Chronic Obstructive Pulmonary Disease with Respect to Associated Risk Factors: A Case Control Study in India

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is the major cause of morbidity and mortality which results in an economic and social burden. Osteoporosis is considered as one of the major systemic manifestations of COPD.

Aim and Objective: It is to determine the prevalence of osteoporosis in COPD patients and its disease severity and also to evaluate various risk factors involved in reduced bone mineral density in patients with COPD.

Methods: A total of 30 COPD patients and 15 healthy controls were enrolled and all individuals were subjected to pulmonary function test and DEXA scan. Various risk factors for COPD associated with osteoporosis and association of osteoporosis with severity of COPD were studied and analyzed. Statistical analysis was done for parametric data using t-test. p value <0.05 was considered as significant.

Results: The incidence of osteoporosis was found to be significantly higher in COPD patients (60%) compared to healthy adults (20%) (p=0.017). Osteoporosis within the COPD patients of age group of 51-60 was found to be significantly higher compared to other age group in COPD. Obesity, overweight and smoking habit as well as exacerbations may be the risk factors in COPD patients. The average number of exacerbation in COPD patients was 2.13. COPD Patients in Gold Stage 2 had less osteoporosis while majority of patients in stage 3 and stage 4 had osteoporosis. T score and BMD differed significantly between the cases and control (p=0.007). BMD was higher in healthy controls compared to COPD patients (p=0.012). BMD has higher in age group of 41-50 compared to age group 51-60. (p=0.021).

Conclusion: The risk of osteoporosis and osteopenia increases with the increase of COPD severity. There are multiple risk factors which are found to be associated with osteoporosis and osteopenia in COPD. Thus the present study warrants further COPD study.

Keywords: COPD; Osteoporosis; Risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality across the globe which results in substantial economic and social burden [1]. According to World Health Organization estimates, 65 million people have moderate to severe COPD. More than 3 million people died of COPD in 2005 corresponding to 5% of all deaths globally and it is estimated to be the third leading cause of death by 2030 [2]. Jindal in 1993 reported that the prevalence was 6.2% in men and 3.9% in women in rural area, and 4.2% and 1.6%, respectively in urban area [3]. The overall prevalence of chronic bronchitis in adults >35 yr was 3.49% (ranging 1.1% in Mumbai to 10% in Thiruvananthapuram) [4].

Risk factors such as cigarette smoking, genetic risk factor, inhalational exposures such as tobacco smoke and occupational dusts and chemicals (vapors, irritants, and fumes) are commonly encountered risk factor for COPD [5,6]. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin [6]. Indoor air pollution, especially from burning biomass fuels in confined spaces, is associated with increased risk for COPD in developing countries, especially among women.

The most common co morbidities responsible for the clinical manifestations and natural history of COPD co-morbidities are cachexia, skeletal muscle abnormalities, osteoporosis, metabolic syndrome, coronary artery disease, heart failure, pulmonary infections, cancer and pulmonary vascular disease [7].

Osteoporosis, with resulting fractures is one such major co-morbid condition in patients with advanced COPD [8]. The prevalence of osteoporosis in COPD patients is 36% to 60% and that of osteopenia is 35% to 72% [9]. Usually, the loss of bone occurs over an extended period of years. Moreover, COPD patients have a higher risk of osteoporosis compared to healthy subjects [10]. Indeed COPD has been included in the male osteoporosis risk estimation score [11]. The etiology of osteoporosis in COPD is probably complex and various factors may contribute to its pathogenesis. Some of these are consequences of the chronic inflammatory lung disease itself. Lung damage leads to dyspnoea resulting in reduced physical activity, reduced skeletal muscle mass and changes in body composition. The natural changes due to ageing like hypogonadism and inactivity may be the associated risk factors. Environmental factors and habits like smoking also contribute to the pathogenesis of osteoporosis in COPD. Corticosteroid treatment (both inhaled and systemic) therapy used during the COPD or

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LUNG disease may also be considered as important risk factors in the development of osteoporosis. Therefore, awareness amongst health care providers and early diagnosis should trigger preventive and therapeutic measures that could avoid or reduce the consequences of osteoporosis in COPD [12].

Based on the background information this study was designed to determine the prevalence of osteoporosis in COPD patients with correlation of occurrence of osteoporosis with disease severity of chronic obstructive pulmonary disease (COPD) and also to evaluate various risk factors involved in reduced bone mineral density in patients with COPD.

Methods

The study was conducted at the Department of Medicine and Department of Biochemistry, Maulana Azad Medical College, Associated Lok Nayak Hospital, and Institute of Nuclear Medicine and Allied Sciences, Delhi.

Sample size calculation

Sample size was calculated using test of "two proportion method" and "Two means method". A total of 30 chronic obstructive pulmonary disease patients and 15 unrelated healthy controls without any chronic diseases leading to osteoporosis were enrolled for the study. Healthy age and sex matched persons without any chronic diseases leading to osteoporosis were included.

Patients who attended the medicine and respiratory clinic in Lok Nayak Hospital were included in the study after their individual written informed consent. All individuals were subjected to pulmonary function test and DEXA scan to stage the severity of COPD and osteoporosis respectively. Occurrence of osteoporosis and osteopenia in COPD patients was investigated. Various risk factors for COPD associated with osteoporosis such as age, sex, BMI, smoking, number of exacerbations were studied and also association of osteoporosis with severity of COPD were analyzed. Serum vitamin-D-3 levels and PTH level of all the study subjects was done and the subjects with low vitamin-D-3 and high PTH level were excluded to rule out confounding factor for osteoporosis.

Patients were subjected to bone densitometry and muscle mass assessment after explaining the hazards of radiation. Bone densitometry was performed in Institute of nuclear medicine and applied sciences (INMAS), Timarpur, New Delhi. GE Healthcare Lunar Prodigy DEXA machine was used for measuring the bone density at hip and lumbar spine along with muscle mass of patients [8]. A patient's BMD was given a T-score, which was 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 was referred to as a standard deviation (SD) [13].

Statistical analysis

The statistical analysis was done using SPSS version 23.0. The parametric data was expressed as mean ± SD and compared using student t test. Pearson correlation analysis was done for evaluation of statistical association. p value <0.05 was considered as significant.

Results

The mean age of COPD patients and healthy adults was 54.03 ± 5.92 years 53.27 ± 5.36 years respectively. Out of 30 COPD patients, 20 (66.67%) were males and 10 (33.33%) were females. Among the healthy adults males were 10 (66.67%) and females were 5 (33.33%). There was no significant difference for age (p value=0.67) while cases and controls groups were compared using unpaired student 't' test. Male to female ratio were compared using Fisher's exact test and statistically two groups were comparable (p value=1.0). The percentage of GOLD stage 2, stage 3 and stage 4 in COPD patients were 5 (16.67%), 11 (36.67%) and 14 (46.67%) respectively.

The incidence of osteoporosis was found to be significantly higher in COPD patients (60%) compared to healthy adults (20%). Occurrence of osteoporosis within the COPD patients of age group of 51-60 was found to be significantly higher compared to other age group in COPD (Table 1). There was a weak positive correlation between osteoporosis and Body Mass Index.

Comparative analysis of BMI between COPD patients and healthy controls showed that 10% of COPD patients were underweight (BMI <18.5) compared to 13.33% of healthy controls whereas 66.67% of COPD patients were normal (BMI 18.5 to 24.9) compared to 66.67% of healthy controls. Besides, 20% of COPD patients were found overweight (BMI 25 to 29.9) compared to 20% of healthy controls. 3.33% of COPD patients were obese (BMI >30) compared to healthy controls. Therefore, overweight and obesity may be considered as one of the risk of COPD.

Distribution of cases and controls according to smoking status expressed in pack years showed that out of 30 COPD patients, none had smoking of <10 pack years while 5 out of 15 healthy controls had smoking of <10 pack years. Four (04) out of 30 COPD patients had smoking duration of 11-20 pack years while 5 out of 15 healthy controls had smoked for 11-20 pack years. Seven out of 30 COPD patients had smoking of 21-30 pack years while no healthy control had smoking of 21-30 pack years. Nine out of 30 COPD patients had smoking of >30 pack years while no healthy control had smoking of 21-30 pack years. Ten (10) out of 30 COPD patients were exposed to chulha smoke while 5 out of 15 healthy subjects were exposed to chulha smoke during home food preparation.

Distribution of COPD patients according to exacerbations in last one year showed that 17 out of 30 COPD patients had <3 exacerbation in last one year while 13 out of 30 patients had ≥ 3 exacerbation in last one year. The average number of exacerbation in COPD patients was 2.13.

Occurrence of osteoporosis in patients with COPD was observed as high as 60% compared to 20% in healthy adults. Occurrence of osteopenia in COPD patients was 23.33% compared to 33.33% in healthy adults. Normal bone density in patient with COPD was 16.67% compared to 46.67% in healthy adults. The incidence of osteoporosis was found to be significantly higher among COPD patients compared to the control subjects in our study (p value=0.028). Occurrence of osteoporosis in patients of age group of 51-60 was found to be

Age group (yrs)	Copd patients			Healthy controls		
	Normal	Osteopenia	Osteoporosis	Normal	Osteopenia	Osteoporosis
41-50	3	6	2	4	1	0
51-60	2	1	16	3	4	3
Total	5 (16.67%)	7 (23.33%)	18 (60%)	7 (46.67%)	5 (33.33%)	3 (20%)

Table 1: Comparison of osteoporosis with age in chronic obstructive pulmonary disease patients and healthy controls.

significantly higher compared to age group of 41-50 (p=0.012). Correlation of osteoporosis with severity of COPD showed that COPD Patients in Stage 2 had less osteoporosis while majority of patients in stage 3 and stage 4 had osteoporosis (Table 2). As the severity of COPD increased, the risk of osteoporosis also increased (p=0.017). A positive and significant correlation was observed between osteoporosis and severity of COPD (Pearson correlation R=0.453, p=0.012).

Correlation of osteoporosis with number of exacerbations showed that 43.33% of patients who experienced >3 exacerbations in the past one years had osteoporosis compared to 16.67% of patients who had <3 exacerbation in last one year. All the patients with >3 exacerbations in the past one years had osteoporosis (Table 3). A positive and significant correlation was observed between osteoporosis and number of exacerbations (Pearson correlation R=0.810, p=0.0001, n=30).

Comparison of T score and BMD with smoking in COPD patients and healthy controls showed that T score and BMD did not differ significantly in COPD patients who had smoking duration of less than 15 pack years or more (p value 0.096) (Table 4). T score differed significantly between the cases and control using t test with p value of (0.007). T score also differed significantly between the age group 51-60 and age group 41-50 with p value of (0.021) (Table 5). BMD differed significantly between the cases and control using t test with p value of (0.012). BMD was recorded higher in healthy controls compared to COPD patients. BMD was higher in age group of 41-50 compared to age group 51-60 (Table 5). A positive correlation was observed between osteoporosis and Body Mass Index. However the correlation was statistically not significant (R=0.043, p=0.823, n=30).

Discussion

Copd severity	Normal	Osteopenia	Osteoporosis
Stage2	2	2	1
Stage 3	2	4	5
Stage 4	1	1	12
Total	5	7	18

Table 2: Correlation of osteoporosis with severity of COPD.

Exacerbations	Normal	Osteopenia	Osteoporosis	Total
<3	5 (16.67%)	7 (23.33%)	5 (16.67%)	17 (56.67%)
>3	0 (0%)	0 (%)	13 (43.33%)	13 (43.33%)
Total	5 (16.67%)	7 (23.33%)	18 (60%)	30 (100%)

Table 3: Correlation of osteoporosis with number of exacerbations.

Smoking (pack years)	Normal	Osteopenia	Osteoporosis	Total
≤ 10 pack years	4 (8.88%)	1 (2.22%)	0 (0%)	5 (11.11%)
11-20 pack years	2 (4.44%)	4 (8.88%)	3 (6.67%)	9 (20%)
21-30 pack years	2 (4.44%)	3 (6.67%)	2 (4.44%)	7 (15.56%)
≥ 30 pack years	0 (0%)	0 (%)	9 (20%)	9 (20%)
Chulha exposer	4 (8.88%)	4 (8.88%)	7 (15.56%)	15 (33.33%)
Total	12 (26.67%)	12 (26.67%)	21 (46.67%)	45 (100%)

Table 4: Correlation of osteoporosis with smoking.

Age group	T score		Bmd	
	Copd patients	Healthy controls	Copd patients	Healthy controls
41-50	-1.48	-0.28	1.03	1.16
51-60	-3.23	-3.15	0.78	1.03
Total	-2.59 ± 1.60	-1.11 ± 1.66	0.87 ± 0.25	1.07 ± 0.21

Table 5: Comparison of T score and BMD with age group in chronic obstructive pulmonary disease patients and healthy controls.

COPD is a chronic inflammatory disorder of the airways with significant extra-pulmonary involvement indicating that it is a systemic disease. One of the major systemic manifestations of COPD is osteoporosis. Osteoporosis is more prevalent among COPD patients compared to healthy subjects. In the present study, the risk of osteoporosis increased with the increasing severity of COPD. The prevalence of osteoporosis was found to be higher in COPD patients compared to healthy subjects. Graat-Verboomet et al. suggested that 21%, 41% and 38% of COPD patients had osteoporosis, osteopenia and normal DEXA scan respectively which was found in a large cohort of population of 554 patients with moderate to severe COPD subjected to whole body DEXA scan for screening of osteoporosis [10]. In another study, Jorgenson et al. described that out of 62 patients 26 (44.8%), 13 (22.4%) and 15 (25.9%) of COPD patients had osteoporosis, osteopenia and normal bone mass respectively where the diagnosis of osteoporosis was based on both bone mass measurements and the knowledge of previous low energy fractures of individual patients [14]. Vriezeet et al. described that out of 115 COPD patients (GOLD stage 2 to stage 4) 10 (8.7%), 47 (40.9%) and 58 (50.4%) patients had osteoporosis, osteopenia and normal DEXA scan respectively [15]. Bhattacharya et al described that out of 37 COPD patients, the BMDs of the left heel bone (calcaneus) of the patients using a broadband ultrasound bone densitometer was done. Eight patients (21.62%) had osteoporosis, 19 (51.35%) had Osteopenia while 10 patients (27%) had normal BMD [16]. So, the prevalence of osteoporosis in COPD patients in our present study was found to be higher compared to other studies (9% to 69% in COPD versus 0% to 13% in healthy subjects). The varied difference in different study groups can be attributed to the methodological differences in the assessment of BMD and also may be due to the characteristics of patient population chosen for the study such as age, sex, past use of calcium, vitamin-D, stable COPD. Standard DEXA scan method for diagnosing osteoporosis which is considered to be the gold standard method was used for our study.

In the present study majority (66.67%) of patients who had osteoporosis were in stage 4 category (Very Severe). So the risk of osteoporosis increased with the increasing severity of COPD. Graat-Verboom et al. found in his study that 25% of osteoporosis patients were in stage 4 COPD [10]. Jorgenson et al. also observed that there was an increased incidence of osteopenia and osteoporosis with advancing COPD stage while looking into the relationship between the severity of COPD and osteoporosis [14]. 68% of GOLD stage 3 and 4 COPD patients had either low bone mass (osteopenia or osteoporosis) or a previously undiagnosed vertebral fracture with 25% of the included patients having a vertebral fracture. Vrieze et al. found and described that 75% of osteoporosis patients were in stage 4 where patients in stage 4 had 7.6 times greater risk of low BMD compared to the patients with stage 2 [15]. In Indian scenario, study done by Hattiholi et al. found the majority of the patients who had osteoporosis had grade 4 COPD (93.7%) [17].

In the present study, comparison of BMD with severity of COPD was done and observed that there was inverse relation of BMD with severity of COPD. Patients of stage 4 COPD had low BMD while patients of stage 2 had high BMD. Consistent with our study Vrieze et al. also observed that the risk of osteoporotic fracture was increased in patients with COPD due to low BMD. Vrieze et al. also observed that the patients with more severe airway obstruction in COPD had increased risks of osteoporosis and thus fractures compared to patients without COPD [15]. They also observed higher prevalence of low BMD in stage 3 and stage 4 COPD disease compared to stage 1 and stage 2. Graat-Verboom et al. observed that as severity of COPD increases, the

BMD also decreases [10]. In Indian scenario, study done by Hattiholi et al. observed that there was no difference in BMD between stage 1 and stage 2 COPD patients while there was a significant difference between stage 1 and 2 compared to stage 3 and 4 patients. There is a difference of BMD as the severity of COPD increases [17].

In the present study, incidence of osteoporosis in patients of age group of 51-60 was significantly higher compared to the 41-50 age group (p=0.012). Graat-Verboom et al. suggested the similar results where higher the age group more risk of osteoporosis and osteopenia. Bhattacharya et al reported no significant difference in BMD with respect to age of the patients [16]. Osteoporosis and osteopenia patients had mean age of 66.07 ± 9.62 years and normal BMD patients had mean age of 63.30 ± 9.53 years [10].

In the present study, majority of patients were not on long term inhaled steroid. Study by Mathioudakis et al. on long term administration of low dose inhaled corticosteroids decelerates the annual BMD loss in bronchitic patients, possibly by reducing both pulmonary and systemic chronic inflammation caused by COPD. So long term inhaled steroid was certainly a risk for osteoporosis [18].

Many risk factors have been evaluated in the development of osteoporosis in COPD. Smoking has been shown to be an independent risk factor for osteoporosis in both men and women. Smoking for less than 10 years had practically no osteoporosis while all patients who smoked for more than 30 years were found to have osteoporosis. There was a positive and significant correlation observed between osteoporosis and smoking duration (R=0.542, p=0.014). The clinical significance of these individual risk factors varies in different studies [19-25]. In the present study, it was observed that in stage IV COPD patients, repeated exacerbation ≥ 3 and longer smoking pack years were significant risk factors for the development of osteoporosis. Similar findings have been observed by Indian studies done by Hattiholi J, Gaude GS and Bhattacharya et al. [17,24]. Bolton et al. observed that low BMI and lower percentage of ideal body weight were significant risk factors for osteoporosis [25]. Vrieze et al. analyzed quantitative USG of the calcaneus in these COPD patients and they observed that stage 3, 4 of COPD, lower fat free mass and lower BMI were significantly associated with higher prevalence of osteoporosis [15]. Graat-Verboom et al. has observed age > 65 years and generalized cachexia to be the significant risk factors to be associated with osteoporosis in COPD patients [10].

Conclusion

As the severity of COPD increased, the risk of osteoporosis and osteopenia also increased. There are multiple factors which are found to be associated with osteoporosis and osteopenia in COPD. A weak but positive and significant correlation was observed between osteoporosis and severity of COPD. A very strong positive and significant correlation was observed between osteoporosis and number of exacerbations. A very strong and significant correlation was observed between osteoporosis and smoking duration. It is important to recognize the risk factors and strategies to manage osteoporosis in COPD patients in order to avoid osteoporotic fractures that deteriorate quality of life and prognosis. Thus the present study warrants further COPD study.

Informed Consent

Informed consent was obtained from all individual participants included in the study. All the study subjects had given written informed consent for the interview and blood sample collection.

Ethical Approval

The study was approved by the local ethical committee of Maulana Azad Medical College, New Delhi, and all the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest

None to be declared

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