Original Article

Journal of Iranian Medical Council, Volume 6, Issue no. 1
http://dx.doi.org/10.18502/jimc.v6i1.11846

Prevalence and Associated Factors of Osteoporosis in Chronic Obstructive Pulmonary Disease Patients

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Received: Feb 28 2022
Accepted: May 25 2022

Citation to this article:

Eslaminejad AR, Sharifi H, Sadr M, Dastan F, Fakharian A, Heshmatnia J, et al. Prevalence and Associated Factors of Osteoporosis in Chronic Obstructive Pulmonary Disease Patients. *J Iran Med Counc.* 2023;6(1):82-91.

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a lifestyle-related chronic inflammatory pulmonary disease and a major cause of morbidity and mortality globally. In this study, we evaluated the prevalence and associated factors of osteopenia and osteoporosis in COPD patients.

Methods: A total of 91 COPD patients were recruited from October 2017 and December 2018. Lung function test, CAT score, 6-minutes' walk test, Modified Medical Research Council (MMRC) dyspnea score and body mass index, air flow obstruction, dyspnea, and exercise capacity (BODE index) were evaluated in the patients. Bone Mineral Density (BMD) measurements of the femoral neck, total femur (including femoral neck, trochanter, and intertrochanter area), and lumbar spine were conducted using dual-energy X-ray absorptiometry. A T-score which was 2.5 standard deviations (SDs) below the average value was indicative of osteoporosis, in accordance with the World Health Organization criteria. We excluded COPD patients who had asthma, malignancy, and fracture.

Results: There were 86 males (mean age±SD: 66.49±9.40 years) and 5 females (mean age±SD: 65.40±12.40 years). Among all the patients, 46 (51.1%) patients had osteopenia and 36 (40%) had osteoporosis. Comparing COPD grades showed grade 2 was a more prevalent grade (41.1%). There was no statistically association between femoral neck T score (mean±SD: -2.21±0.89) and COPD grade (P=0.58), while lumber spine T score (mean±SD: -2.13±1.11) was statistically decreased with increasing severity of COPD (p= 0.02).

Conclusion: The results of our study demonstrated that osteoporosis is common among COPD patients. Moreover, we found significant correlations between BMI, walking test, FEV1, MMRC, and BODE index.

Keywords: Bone density, Chronic obstructive pulmonary disease, Iran, Osteoporosis

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a syndrome of progressive airflow limitation with an increasing prevalence worldwide, especially in developing countries (1). Globally, COPD was reported as the fourth leading cause of death (5.1%) in 2004 and predicted to occupy the third position (8.6%) in 2030 (2). A majority of COPD-related deaths occurs in low and middle-income countries (3).

COPD is now regarded as a heterogeneous disease with different comorbidities and systemic manifestations, such as skeletal muscle weakness, reduced Bone Mineral Density (BMD), osteoporosis, metabolic diseases (diabetes mellitus, metabolic syndrome, and obesity), cardiovascular disorders (coronary artery disease, chronic heart failure, and hypertension), pulmonary infections, cancer, anemia, depression, cognitive decline, and pulmonary vascular disease (4,5). Osteoporosis is considered as one of the major systemic comorbidities of COPD (6). Although the relationship between COPD and osteoporosis remains to be fully recognized, epidemiological data clearly demonstrate that in COPD patients, osteoporosis is highly prevalent (7-9). It is believed that the prevalence of osteoporosis in COPD patients is observed from 36% to 60% (5). Ohara *et al* (10) revealed that severity of COPD was related to loss of vertebral BMD evaluated by Computed Tomography (CT) scan. These findings were subsequently proved by other scientists using conventional osteoporosis indices (dual-emission X-ray absorptiometry) (11). Osteoporotic fractures may further deteriorate pulmonary function, leading to reduced quality of life, and impair activities of daily life of COPD patients. Thus, it seems that the vicious cycle made by two diseases, have significant effects on burden of patients. Moreover, osteoporosis in COPD patients is extremely undertreated (7,8,12).

Exacerbation is a crucial factor in both COPD and osteoporosis. In COPD, exacerbation has negative impressions on health status, survival, FEV_1, the body mass index, air flow obstruction, dyspnea, and exercise capacity (BODE index) (13-16). On the other hand, exacerbations normally cause risk factors, such as inactivity, systemic inflammation, and use of systemic corticosteroids during these conditions leading to BMD loss (17,18). All these risk factors are highly important in osteoporosis (19). It seems that early diagnosis of COPD especially in elderlies, with preventive and therapeutic measures that could avoid or reduce the consequences of osteoporosis is essential.

The present study was done to evaluate the prevalence of osteopenia and osteoporosis in COPD patients, and to determine the various risk factors contributing to the development of osteoporosis and osteopenia in these patients.

Materials and Methods

This was a cross-sectional questionnaire-based study conducted in the department of pulmonary medicine, Masih Daneshvari Hospital, Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Iran, between October 2017 and December 2018.

Diagnosis of COPD

A diagnosis of COPD was established based on spirometry using the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (20). According to the GOLD criteria and our previous studies (21), diagnosis of COPD was based on documentation of FEV1/FVC below the fixed ratio of 0.7.

We divided severity of airflow limitation according to the GOLD criteria (stage I, mild $FEV_1 \geq 80\%$; stage II, moderate FEV_1 50–80%; stage III, severe FEV_1 30–50%; stage IV, very severe $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure) (20).

All patients diagnosed as a case of COPD, based on GOLD guidelines were included in the study.

Measurements

BMD measurements of the femoral neck, total femur (including femoral neck, trochanter, and intertrochanter area), and lumbar spine were conducted using dual-energy X-ray absorptiometry. A T-score (the lowest T-score of the three measured locations; lumbar, total femur, and femur neck) that was 2.5 standard deviations (SDs) below the average value was indicative of osteoporosis, in accordance with the World Health Organization criteria (22). We evaluated the following variables in patients with

COPD: age, sex, Body Mass Index (BMI), tobacco smoking, Steroid use, complications, T-score, Z-score, BMD, predicted FEV_1%, COPD Assessment Test (CAT) score, and serum Phosphorus, Alkaline Phosphatase, Calcium, Vitamin D, TSH level.

Several covariates were considered as potential confounders of osteoporosis and used as the exclusion criteria, including prior asthma, malignancy, and fracture.

Ethical considerations

The study was approved by the Ethics Committee of National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Tehran, Iran, and the patients' satisfaction was documented. The study objectives and procedures were explained to the subjects and their written informed consents were obtained. Data confidentiality of the individuals was observed during the study.

Statistical analysis

All statistical analyses were done using SPSS 21 software and statistical significance level was considered as 0.05. For describing data, we used number and percent, median and IQR or mean±standard deviation (SD). For comparing scores among groups, one-way ANOVA and Kruskal Wallis tests were used. For evaluating the relation between qualitative variables Chi- square test was done. Factors associated with osteoporosis were evaluated with the aid of logistic regression method.

Results

Main characteristics

A total of 91 patients were included in the study. There were 86 males (mean age±SD: 66.49±9.40 years) and 5 females (mean age±SD: 65.40±12.40 years). More than 50% of all the patients had BMI between 18.5, 24.9 *Kg/m2*. Most patients were Ex-smoker (55.6%) or current smokers (28.9%), and also 15.6% were alcohol consumer. Among all the patients, 46 (51.1%) patients had osteopenia and 36 (40%) had osteoporosis. Comparing COPD grades showed grade 2 was more prevalent grade (41.1%). Diabetes and kidney diseases were other more prevalent comorbidities. Important characteristics are shown in table 1.

Bone density results:

The results of bone density tests are presented in table 2. Comparing BMD among COPD grades demonstrated that BMD (mean±SD: -2.28±1.00 *gm/cm²*) had a significant difference among various grade of COPD (p=0.01) and the BMD decreased with increasing COPD grade (Table 2).

There was no statistically association between femoral neck T score (mean±SD: -2.21±0.89) and COPD grade (p=0.58), while lumber spine T score (mean±SD: -2.13±1.11) was statistically decreased with increasing severity of COPD (P= 0.02).

Relation between pulmonary function and BMD level:

FEV1 had a significant difference among tree levels of BMD (p=0.02). Additionally, BODE index for osteoporosis patients was higher than others (p=0.001). 6-minute walk test and COPD grade had no statistical difference among BMD levels (p>0.05). Details are shown in table 3.

Factor associated with osteoporosis:

The risk factors of osteoporosis were evaluated by logistic regression model in table 4. Among all variables, BMI (OR: 16.33; 95% CI (1.35-19.76), p=0.02), walking test (OR: 0.996; 95% CI (0.991-0.999), p= 0.04), FEV1 (OR:0.96; 95% CI (0.94- 0.99), p=0.01), Modified Medical Research Council (MMRC) dyspnea score (OR: 1.73; 95% CI (1.20- 2.49), p=0.003) and BODE (OR: 1.48; 95% CI (1.19-1.85), p<0.001) had a significant association with the risk of osteoporosis in the univariate model. In the multivariate model, controlling for significant variables, there is not any significant association.

Table 1. Main characteristics of the participants

	Number	Percent
Age, year; mean (SD)	66.43	(9.50)

Sex, men	86	94.5
BMI (Kg/m^2)		
<18.5	10	11.1
18.5- 24.9	51	56.7
25- 29.9	21	23.3
>30	8	8.9
FEV1%, predicted		
Grade 1	6	6.7
Grade 2	37	41.1
Grade 3	33	36.7
Grade 4	14	15.6
Smoking		
No smoker	14	15.6
Current	26	28.9
Ex- smoking	50	55.6
Pack- year; mean (SD)	48.42	(35.43)
Bone Mineral Density (BMD)		
Normal	8	8.9
Osteopenia	46	51.1
Osteoporosis	36	40
Steroid use		
Inhaled steroids	90	98.9
Oral steroids	15	16.7
Injection steroids	19	21.1
Complications		
Diabetes	2	2.2
Kidney diseases	3	3.3
Hyperthyroidism	3	3.3
Alcohol	14	15.6
Heparin consumption	1	1.1

Table 2. Bone densitometry results

Bone data	Mean	SD
Total body BMD, *gm/cm²*	-2.28	1.00
Spine T- score	-2.44	1.28
Total Z- score	-0.85	1.40
Total T- score	-1.97	1.03

Table 3. Pulmonary function relative to osteoporosis, osteopenia, and normal bone mass

Variables	Osteoporosis (n =36)	Osteopenia (n =46)	Normal bone mass (n=8)	p-value
FEV1 (*L*); mean, SD	41.94±18.31	51.15±16.98	57.88±24.23	0.024
6-min walk distance (*m*); mean, SD	340.64±102.45	384.20±92.22	374.25±101.96	0.135
BODE index, median (IQR)	4(3-6)	2(1-4)	2(1.25-3.75)	0.001
GOLD COPD grade, no. (%)				0.229
Grade 1	1(2.8)	3(6.5)	2(25.0)	
Grade 2	12(33.3)	22(47.8)	3(37.5)	
Grade 3	15(41.7)	16(34.8)	2(25.0)	
Grade 4	8(22.2)	5(10.9)	1(12.5)	

Table 4. Factor associated with osteoporosis

Variables	Univariate		P-value
	OR	95% CI	
Sex, male	0.42	0.06-2.67	0.366
Age	1.007	0.96- 1.05	0.753
BMI			0.027*
<18.5	16.33	1.35-19.76	
18.5- 24.9	6.22	0.71-54.29	
25- 29.9	1.65	0.15-17.47	
>30	1		
FEV1	0.96	0.94-0.99	0.018*
COPD grade			0.251
1	1		
2	2.40	0.25-22.87	
3	4.16	0.44-39.68	

Cont Table 4.

	4	6.67	0.61- 73.03	
	MMRC	1.73	1.20- 2.49	0.003*
	BODE	1.48	1.19- 1.85	<.001*
	CAT score			0.203
	Low	1		
	Medium	2.5	0.61- 10.19	
	High	-		
	Steroid use (eating or injection)			0.234
	No	1		
	yes	0.56	0.22- 1.44	
	Smoking			0.456
	No smoker	1		
	Current	1.38	0.42- 4.53	
	Ex-smoking	0.61	0.22- 1.67	
	Onset of smoking	1.009	0.95- 1.06	0.753
	Cigarette / daily	0.99	0.96- 1.02	0.678
	Walking test	0.996	0.991- 0.999	0.047*
	Calcium			0.363
	No	1		
	Yes	0.67	0.27- 1.63	
	Does not know	0.33	0.06- 1.76	
	Vitamin D			0.641
	No	1		
	Yes	0.98	0.39- 2.49	
	Does not know	0.55	0.14- 2.01	
	Serum Phosphorus	0.93	0.75- 1.15	0.525
	Serum ALK phosphatase	1.002	0.99- 1.009	0.518
	Serum Calcium	0.67	0.34- 1.33	0.253
	Serum Vitamin D	0.98	0.96- 1.01	0.288
	Serum TSH			0.894
	TSH < 0.27 *mIU/L*	-		
	TSH 0.27–4.20 *mIU/L*	0.92	0.26- 3.17	
	TSH > 4.2 *mIU/L*	1		

*Significant.

Discussion

This study is to demonstrate the prevalence of osteopenia and osteoporosis among COPD patients. COPD is a chronic inflammatory pulmonary disease with significant extra pulmonary complications. One of the main systemic manifestations of COPD is low BMD (1,23,24). In this study, the prevalence of osteoporosis in COPD patients was 40% and that of osteopenia was 51.1%. It is showed in different studies that the prevalence of osteoporosis in COPD patients varies from 9 to 69% and that of osteopenia vary 27–67%. The prevalence of osteoporosis proved to be higher in COPD patients than in healthy subjects (25). This figure for osteoporosis vary 0-13% in healthy individuals (26).

Consistent with the above rates, the prevalence of osteoporosis was high in Towards a Revolution in COPD Health (TORCH) study which was done amongst 658 patients in 88 US health centers. Although, bone density measurements were being done annually, at baseline the overall prevalence of both osteoporosis and osteopenia was high at 65% (27). Jørgensen NR *et al* conducted a study on 62 patients with COPD, with the use of Dual-energy X-ray absorptiometry (DEXA) scan of hip and lumbar spine. Diagnosis of osteoporosis was based on bone mass measurements and the knowledge of previous low-energy fractures of individual. It was detected that 26 patients (44.8%) had osteoporosis while 13 patients (22.4%) had osteopenia and 15 patients (25.9%) had normal bone mass (28). An Indian study by Hattiholi and Gaude in 2010 measured the BMD in COPD patients by DEXA scan. They reported osteoporosis in 68 patients (66.6%) and osteopenia in 20 patients (19.6%) (29). It seems that the prevalence of osteopenia and osteoporosis in COPD patients in our study were consistent with other studies which varied from 9%–69% compared to 0-13% in healthy population for osteoporosis, and that of 27% to 67% for osteopenia.

There is a clear relation between severity of COPD and risk of osteoporosis both in terms of T-score and BMD. In the present study, comparing BMD among COPD grades showed that BMD had a significant difference among various grade of COPD (p=0.01) and the BMD decreased with increasing COPD grade. Stevenson JC *et al* demonstrated that there was increased incidence of osteopenia and osteoporosis with advancing COPD stage. They observed that there were other factors decreasing bone density, and increasing risk for osteoporosis, such as low body weight, alcohol and cigarette consumption, nulliparity, lack of previous use of oral contraceptives, and lack of regular exercise (30). Another study was conducted by Vries F *et al* observed that patients with more severe airway obstruction in COPD had increased risks of osteoporosis and bone fractures as compared with patients without the history of obstructive airway disease (31). Similar findings have been observed by other researchers (8,27,32).

In this study, it was observed that patients with lower BMI had higher prevalence of osteoporosis, and BMI (OR: 16.33; 95% CI (1.35-19.76), p=0.02), had a significant association with the risk of osteoporosis in the univariate model. It is proved by Biskobing DM *et al* that bone mass was directly correlated with BMI. In their study, both men and women with high BMIs have higher BMD (33). Aloia JF *et al* reported that the lowest BMD was seen in a group of patients with BMI below the normal median and reported an independent correlation between BMI and BMD ($r = 0.34$; $p<0.05$) (34). Another study conducted by Seeman on osteoporosis in COPD patients proved that BMI was the strongest predictor of osteoporosis, with a BMI ≤ 22 having an odds ratio of 4.18 (95% CI: 1.19-14.71, $p<0.026$) (35).

Hattiholi *et al* observed that elderly COPD patients with lower BMI had higher prevalence of osteoporosis (45.7%) as compared to overweight patients (36). It is proved that patients with chronic lung disease such as COPD, and cystic fibrosis occasionally show a malnourished status or so-called pulmonary cachexia (37).

In current study, the BODE index was higher in the osteoporosis patients than osteopenia and normal-bone-mass patients ($p<0.01$). In a study conducted by Silva *et al* it was proved that there was a significant inverse relationship between femoral-neck T-score and BODE index, and significant correlations between T-score (both femoral-neck and lumbar-spine) and pulmonary function test results (38). In another recent study by Rubinsztajn, it was mentioned that the number of comorbidities (bone density abnormalities including osteoporosis and osteopenia)

was related to the BODE index (39). Actually, the risk of osteoporosis in COPD patients seems to be higher in severe COPD, as demonstrated previously.

Conclusion

The results of our study demonstrated that osteoporosis is common among COPD patients. Moreover, we found significant correlations between BMI, walking test, FEV1, MMRC, and BODE index. We did not find an association between bone mineral density and age, sex, and smoking or number of daily cigarettes. These data suggest that osteoporosis should be evaluated in all COPD patients, where osteoporosis treatment improves the prognosis of COPD patients. We also recommend that all patients with COPD should be screened with DEXA scan, which is considered gold standard for the diagnosis of osteopenia and osteoporosis.

Acknowledgements

The authors thank all the study participants. This study was supported by Masih Daneshvari Hospital, Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Iran. The study protocol was approved by the hospital ethics committee (IR.SBMU.NRITLD.REC.1394.173).

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