

COPD and Osteoporosis: Associated Factors in Patients Treated with Inhaled Corticosteroids

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Purpose: Osteoporosis is a systemic skeletal disease with a consequent increase in fractures rates. Osteoporosis may be primary which is related with normal aging, or secondary which occurs in the presence of an underlying disease or medication. Osteoporosis is one of the significant comorbidities in chronic obstructive pulmonary disease (COPD). In this study, we aimed to investigate the presence of osteoporosis and the influencing factors in COPD patients.

Patients and Methods: This is a two-group comparison study that was conducted among 30 COPD patients on inhaled corticosteroid (ICS) and 33 controls. It was conducted in the outpatient clinics at the Departments of Physical Medicine and Rehabilitation and Pulmonary Diseases in Bursa Uludag University Hospital, a tertiary reference center, in the northwest region of Turkey. For both groups, demographic variables, osteoporosis risk questioning, body mass index (BMI), bone mineral density (BMD), biochemical blood tests, vertebral fractures on lumbar and thoracic x-rays were recorded. COPD patients were also evaluated for lung functions via spirometry.

Results: Thirty patients with COPD (Group 1) and 33 controls (Group 2) were included in the study. Comparing the demographic and biochemical data, no difference was found between the groups except smoking (pack/year) ($p < 0.001$) and erythrocyte sedimentation rate ($p < 0.001$), which were significantly high in COPD group. BMD in the COPD group was significantly lower in both hip and lumbar regions compared with the controls. There were significant correlations between L2 BMD values and pulmonary function tests. BMI was significantly low in osteoporotic COPD patients when compared with the non-osteoporotic COPD patients ($p = 0.002$).

Conclusion: In patients with COPD using inhaled corticosteroids, BMD was significantly low compared with the controls. Osteoporotic COPD patients had significantly lower BMI than non-osteoporotic. These findings suggest that pulmonary dysfunction and low BMI are associated with osteoporosis in COPD patients.

Keywords: BMD, BMI, COPD, osteoporosis

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.¹

Chronic obstructive pulmonary disease (COPD) is one of the secondary causes of osteoporosis. The pooled global prevalence for osteoporosis among individuals with COPD is 38%.² Osteoporosis is one of the common comorbidities affecting the cost of hospital-treated COPD.³ Osteoporotic fractures are associated with decreased quality of life and increased mortality in patients with COPD.^{4,5}

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Although osteoporosis is a well-known complication of COPD it is usually underestimated and undertreated.⁶

Mechanisms by which osteoporosis occurs in COPD patients are mostly unknown. General risk factors like older age, smoking, low body mass index (BMI), reduced physical activity and disease-specific risk factors like systemic inflammation, pulmonary dysfunction, glucocorticoid use and vitamin D insufficiency/deficiency can be listed.^{7,8}

Osteoporosis is diagnosed when bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is 2.5 standard deviations or more below the young adult mean (T-score is equal to or less than -2.5) according to the World Health Organization criteria.⁹

Disease-specific factors like systemic inflammation and reduced pulmonary function have significant impacts on bone metabolism and may predispose osteoporosis.¹⁰ Decreased FEV1 (forced expiratory volume in 1 second) and/or advanced GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages have been demonstrated to be correlated with lower BMD.^{11,12}

Glucocorticoids are the most important group of drugs that cause osteoporosis.¹³ Glucocorticoid-induced osteoporosis develops in a time- and dose-dependent manner, but even at low doses, an increased risk of fragility fracture may be observed even within the first month of treatment.¹⁴ Glucocorticoid-induced osteoporosis is mediated by multiple pathophysiologic mechanisms resulting in an inhibition of bone formation and an increase in bone resorption.¹⁵ Inhaled corticosteroids (ICS) and bronchodilators are frequently used drugs for the treatment of bronchial asthma and COPD. The independent role of ICS is difficult to discern since most COPD and asthma patients receive periodic bursts of oral or parenteral glucocorticoids.⁷ A Cochrane systematic review on the effect ICS on bone metabolism showed neither evidence of increased risk of fracture nor loss of BMD with conventional doses of inhaled glucocorticoids given for 2 or 3 years.¹⁶ However, a longer duration of treatment (>8 years) and greater mean daily dose (>600 µg/day) of inhaled and nasal corticosteroid use and the risk of fracture.^{17,18} On the other hand, ICS was shown to reduce annual BMD loss in COPD patients most likely due to ameliorated inflammation.¹⁹

In a recent meta-analysis investigating prevalence and risk factors of osteoporosis in COPD patients, pooled global prevalence from 58 studies was 38% and the

patients with sarcopenia and BMI<18.5kg/m² were at high risk for osteoporosis.²

In this study, we aimed to investigate the presence of osteoporosis and the factors associated with low BMD in COPD patients.

Patients and Methods

Patients

This is a two-group comparison study that was conducted among 30 COPD patients and 33 controls. It was conducted in the outpatient clinics at the Departments of Physical Medicine and Rehabilitation and Pulmonary Diseases in Bursa Uludag University Hospital, a tertiary reference center, in the northwest region of Turkey. Entry period of this study was January 2018 to December 2018. Thirty COPD patients from the Pulmonology Outpatient Clinic who were on inhaled corticosteroid (ICS) treatment were included in the study (Group 1). Twenty-five of the patients were male and 5 were female. Exclusion criteria were history of systemic glucocorticoids, osteoporosis treatment (calcium, vitamin D, bisphosphonates, selective estrogen receptor modulators, teriparatide, denosumab), chronic disease leading to secondary osteoporosis, immobilization, tuberculosis, asthma, compromised immune system, metabolic disorders, hormonal disorders, genetic disorders, malignant diseases. End-of-life or palliative care and older patients (above 90 years) were also excluded.

Control group was created among the patients who were admitted to the Physical Medicine and Rehabilitation Outpatient Clinic (Group 2) for any musculoskeletal complaints. Patients with diagnosis of COPD and the above exclusion criteria were not allowed. A total of 33 patients, 24 males and 9 females, were included in the control group.

COPD patients were diagnosed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.²⁰ COPD exacerbation was defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that was beyond normal day-to-day variations and that required treatment with systemic steroids or antibiotics, and/or a visit to the emergency room or admission to hospital.²¹ Acute COPD exacerbations in the previous 12 months and oral steroid use were assessed using medical records of the patient. The diagnosis, treatment and the follow-up for COPD patients were all done by the pulmonologist and the eligible patients were included in the study.

The study was conducted in accordance with the Declaration of Helsinki. All subjects signed an informed consent prior to enrollment and the protocol was approved by the Institution's Ethics Committee (Bursa Uludag University Medical Faculty Clinical Research Ethics Committee).

Assessments

All patients were questioned for age (year), height (cm), weight (kg) and body mass index (BMI) (kg/cm^2). COPD patients were also questioned for disease duration (years), duration of ICS use (months), daily dose of ICS (μg) and cumulative dose of ICS. Different active ingredients were recorded by calculating the equivalent dose. Cumulative ICS doses were calculated using the formula of "daily ICS dose \times 365 \times years used"¹⁷ Pulmonary functions of COPD patients were evaluated via spirometry and FVC (Forced vital capacity) (%), FEV1 (Forced expiratory volume in the first second) (%), FEV1/FVC, PEF (Peak expiratory flow) (lt) were recorded.

Bone densitometry of all patients was studied with dual-energy x-ray absorptiometry, DXA (Hologic QDR 1000). Lumbar spine L1-L4 anterior, left hip femoral neck, trochanter and ward triangle BMD and T scores were recorded. Patients with T-score equal to or less than -2.5 were classified as osteoporotic.

Lateral dorsal and lumbar spine radiographs were taken for vertebral fracture evaluation. The presence of vertebral fracture was evaluated by Genant's semi-quantitative scale.¹⁸ Patients were classified as "fracture present" or "not present".

In order to exclude other possible secondary causes of osteoporosis serum parathormone (PTH), thyroid-stimulating hormone (TSH), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) levels and erythrocyte sedimentation rate (ESR) were studied.

Statistical Analysis

The statistical analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp). Continuous variables were given as mean and standard deviation or median and minimum–maximum values. The consistency of continuous variables to normal distribution was examined with the Shapiro Wilk test and according to the test result, Mann Whitney *U*-test or independent sample *t*-test was used for comparison between two independent groups. Chi-square test was used to compare categorical variables between groups and these

variables were presented with *n* (%) values. Correlations analysis was conducted to examine the relationships between continuous variables. Statistical significance was accepted when $p < 0.05$.

Results

A total of 63 people, 30 patients with COPD (Group 1) and 33 controls (Group 2) were included in the study. In the first group, median age was 65 (min-max: 41–79) years. Twenty-five (83.33%) of the patients were male and 5 (16.67%) were female. There was no statistically significant difference in age, height, weight, BMI values between two groups (Table 1).

History of fracture was present in 2 (6.67%) cases in the first group and 1 (3.03%) in the second group. There was no difference between the two groups in terms of fracture history ($p=0.601$). There was no difference between the two groups when evaluated for the vertebral compression fracture detected on radiographs (group 1: $n=13$ (43.33%), group 2: $n=24$ (72.73%); $p=0.412$). Disease duration, ICS duration, daily and cumulative ICS doses are given in Table 2. ICS use among patients was as follows: five patients budesonide 800 $\mu\text{g}/\text{day}$, ten patients budesonide–formoterol fumarate 800/24 $\mu\text{g}/\text{day}$, seven patients budesonide–formoterol fumarate 320/9 $\mu\text{g}/\text{day}$, 3 patients budesonide–formoterol fumarate 640/18 $\mu\text{g}/\text{day}$, one patient budesonide–formoterol fumarate 160/4,5 $\mu\text{g}/\text{day}$, three patients budesonide–formoterol fumarate 400/12 $\mu\text{g}/\text{day}$, one patient salmeterol–fluticasone propionate 100/1000 $\mu\text{g}/\text{day}$. Median

Table 1 Comparison of Demographic and Biochemical Data Between the Two Groups

Variables	Group 1	Group 2	p-value
Age (years) [#]	65 (41–79)	61 (44–76)	0.202
Height (cm) [*]	167.43 \pm 7.32	167.58 \pm 8.98	0.946
Weight (kg) [*]	74.07 \pm 8.73	78.80 \pm 12.74	0.088
BMI (kg/cm^2) [*]	26.46 \pm 3.16	27.99 \pm 3.72	0.085
Smoking (pack/year) [#]	32.50 (0–140)	6 (0–50)	<0.001
ESR (1 hour) [#]	29 (8–99)	9 (2–42)	<0.001
Ca [*]	9.49 \pm 0.45	9.46 \pm 0.42	0.835
P [#]	3.20 (2.30–4.40)	3.00 (2.20–4.80)	0.214
ALP [#]	73 (48–151)	79 (44–145)	0.558
T3 [#]	2.92 (0.85–3.58)	2.75 (1.02–3.38)	0.421
T4 [#]	1.11 (0.69–2.96)	1.08 (0.78–1.30)	0.591
TSH [#]	1.06 (0.09–4.94)	1.00 (0.09–4.31)	0.901

Note: Data were given as ^{*}mean \pm standard deviation or [#]median (minimum–maximum) value.

Abbreviations: PTH, parathormone; TSH, thyroid-stimulating hormone; Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; ESR, erythrocyte sedimentation rate.

Table 2 Disease-Related Variables and Pulmonary Function Test Results in COPD Patients

Variables	Descriptive Value
Disease duration (year) [#]	5.50 (2–20)
ICS duration (month) [#]	60 (12–132)
Cumulative ICS dose (µg) [#]	700,800 (233,600–3,212,000)
Daily ICS dose (µg) [#]	800 (160–1000)
FVC (%)*	57.28±15.63
FEV1 (%)*	51.85±14.60
FEV1/FVC*	67.69±9.91
PEF (%)*	39.85±14.85

Note: Data were given as *mean±standard deviation or [#]median (minimum–maximum) value.

disease duration was 5.50 years (min–max: 2–20), median time on ICS use was 60 months (min–max: 12–132) and median ICS dose was 800 µg (min–max: 160–1000). Cumulative ICS doses were calculated as 700,800 (min–max: 233,600–3,212,000) µg. Spirometric tests of Group 1 revealed that the average of FVC was 57.28±15.63%, average FEV1 was 51.85±14.60%, average FEV1/FVC 67.69±9.91% and average PEF was 39.85±14.85% (Table 2).

Both groups were compared in terms of lumbar and femur T score and BMD values. There was a statistically significant difference in all lumbar and hip T scores and BMD values except fourth lumbar vertebra (Table 3).

Laboratory tests like ESH (1 hour), Ca, P, ALP and TSH of both groups are given in Table 1. In comparison between the groups, only ESH ($p < 0.001$) was found to be significantly higher in Group 1.

According to the percent of predicted FEV1 values, COPD severity was classified as mild ($\geq 80\%$), moderate (≥ 50 – 80%), severe (≥ 30 – 50%) and very severe ($< 30\%$).¹⁹ Accordingly, 1 (3.33%) patient was very severe, 13 (43.33%) were severe, 15 (50.00%) were moderate and 1

(3.33%) was mild-grade COPD. No significant correlation was found between the severity of the disease determined according to this classification and the BMD and T scores.¹⁹

Correlations of t scores with disease duration (years), ICS duration (months), daily ICS dose (µg), cumulative ICS dose (µg) and pulmonary function test parameters were calculated. There were significant correlations between L2 t scores and FEV1 (L) ($p = 0.009$, $r = 0.468$), FVC (L) ($p = 0.032$, $r = 0.391$), PEF (L) ($p = 0.025$, $r = 0.431$), PEF (%) ($p = 0.026$, $r = 0.436$), MVV (L) ($p = 0.027$, $r = 0.442$) and MVV (%) ($p = 0.018$, $r = 0.479$) (Table 4).

When COPD patients were divided into two groups as “osteoporotic” and “non-osteoporotic” according to the lumbar total and femur neck t scores, only BMI was found to be significantly low in osteoporotic patients (Table 5).

Discussion

This study suggests that COPD patients are significantly more osteoporotic than the controls and BMD was significantly lower in low BMI COPD patients. Correlations with second lumbar BMD scores and pulmonary function tests were statistically significant.

It is a well-known fact that the presence of COPD increases the likelihood of having osteoporosis. In a recent meta-analysis investigating prevalence and risk factors of osteoporosis in COPD patients, pooled global prevalence from 58 studies was 38% and the patients with sarcopenia and low BMI were at high risk for osteoporosis.² Although there is no doubt that COPD increases the risk of osteoporosis, there are different results about the osteoporosis risk factors in COPD patients. It is also well known that corticosteroid use leads to osteoporosis. However, data on whether inhaled corticosteroid used in COPD treatment poses a risk of osteoporosis is contradictory. In the TORCH (Towards a Revolution in COPD Health) study, no significant effect on BMD was detected for ICS therapy compared with placebo.²² Similarly, in a large group of patients with COPD, long-term treatment with ICS had no clinically significant effects on bone mineral density or fracture rates.²³

In another study long-term administration of low-dose-inhaled corticosteroids was shown to decelerate the annual BMD loss in bronchitic patients, possibly by reducing both pulmonary and systemic chronic inflammation caused by COPD.¹⁹ Contrarily, in a randomized double-

Table 3 Comparison of BMD Values Between the Two Groups

BMD	Group 1	Group 2	p-value
L1 [#]	0.75 (0.63–1.31)	0.94 (0.45–1.38)	0.014
L2*	0.87±0.15	0.98±0.17	0.010
L3 [#]	0.86 (0.69–1.22)	0.97 (0.71–1.63)	0.018
L4*	0.95±0.17	1.02±0.19	0.125
L total [#]	0.83 (0.67–1.20)	0.98 (0.64–1.51)	0.017
Femur neck [#]	0.73 (0.56–1.06)	0.79 (0.58–1.00)	0.004
Femur trochanter [#]	0.63 (0.53–0.87)	0.73 (0.48–1.91)	0.002
Femur Ward's [#]	1.11 (0.12–1.59)	1.22 (0.28–1.47)	0.007
Femur total [#]	0.92 (0.71–1.30)	1.02 (0.09–1.29)	0.033

Note: Data were given as *mean±standard deviation or [#]median (minimum–maximum) value.

Table 4 Correlations Between BMD and Pulmonary Function Tests in COPD Patients

BMD		FEV1 (L)	FEV1%	FVC (L)	FVC %	FEV1/FVC	PEF (L)	PEF %	IC (L)	IC %	MVV (L)	MVV %
L1	r	0.134	-0.141	0.055	-0.147	0.046	0.119	0.068	0.059	-0.497	0.100	0.072
	p-value	0.482	0.459	0.775	0.447	0.813	0.554	0.742	0.774	0.050	0.634	0.738
L2	r	0.464	0.135	0.400	0.207	0.116	0.418	0.416	0.215	-0.040	0.449	0.503
	p-value	0.010	0.477	0.028	0.281	0.548	0.030	0.034	0.292	0.884	0.024	0.012
L3	r	0.298	-0.022	0.264	0.095	0.072	0.135	0.153	0.209	-0.180	0.249	0.321
	p-value	0.110	0.910	0.158	0.624	0.710	0.502	0.455	0.306	0.506	0.231	0.127
L4	r	0.154	-0.111	0.200	0.075	0.124	0.152	0.185	-0.053	-0.303	0.143	0.212
	p-value	0.417	0.559	0.290	0.698	0.520	0.450	0.366	0.796	0.254	0.496	0.319
L total	r	0.286	-0.051	0.238	0.063	0.134	0.179	0.172	0.108	-0.305	0.262	0.309
	p-value	0.125	0.789	0.205	0.746	0.490	0.371	0.400	0.599	0.251	0.206	0.142
Femur neck	r	0.001	-0.143	0.131	-0.067	-0.171	-0.077	-0.175	-0.037	-0.362	-0.056	0.005
	p-value	0.996	0.449	0.490	0.729	0.376	0.702	0.393	0.858	0.168	0.790	0.982
Femur trochanter	r	-0.010	-0.317	0.173	-0.011	-0.158	-0.022	-0.035	-0.029	-0.465	-0.102	-0.037
	p-value	0.956	0.088	0.362	0.956	0.413	0.912	0.864	0.887	0.070	0.629	0.864
Fem inter	r	-0.010	-0.242	0.087	-0.002	-0.063	-0.119	-0.019	-0.205	-0.411	-0.034	0.068
	p-value	0.956	0.198	0.648	0.993	0.745	0.554	0.926	0.315	0.114	0.872	0.754
Femur total	r	0.022	-0.238	0.134	-0.045	-0.111	-0.022	0.011	-0.073	-0.350	-0.045	0.027
	p-value	0.908	0.206	0.479	0.816	0.565	0.912	0.959	0.722	0.184	0.831	0.902
ICS duration (ay)	r	0.219	0.106	0.082	-0.007	-0.180	0.034	0.106	0.273	-0.187	0.048	0.010
	p-value	0.244	0.576	0.668	0.971	0.351	0.865	0.608	0.177	0.487	0.821	0.963
ICS dose (mcg)	r	-0.277	-0.109	-0.159	-0.124	-0.117	0.128	-0.004	-0.337	-0.297	0.129	0.089
	p-value	0.139	0.567	0.401	0.520	0.546	0.524	0.983	0.093	0.263	0.540	0.681
B agonist dose (mcg)	r	0.036	0.201	-0.072	-0.132	0.324	0.233	0.145	-0.129	-0.121	0.268	0.261
	p-value	0.851	0.286	0.705	0.495	0.086	0.241	0.480	0.529	0.655	0.196	0.219
Disease duration (year)	r	0.209	0.340	0.028	0.091	-0.135	0.054	0.085	0.367	-0.157	0.187	0.160
	p-value	0.267	0.066	0.882	0.641	0.486	0.789	0.681	0.065	0.562	0.370	0.455

blind, placebo-controlled trial at seven centers, the use of ICS was associated with loss of BMD at the femoral neck and lumbar spine after 3 years of treatment.²⁴ A recent review analyzing 17 randomized controlled trials found no difference in the number of bone fractures among patients receiving ICSs versus placebo across the six identified RCTs reporting fracture data.²⁵ In this study, we excluded patients with the history of systemic glucocorticoid use in order to minimize the negative effects on bone mineral density. Inhaled corticosteroid dose and duration were not correlated with BMD in COPD patients. Our results were compatible with the studies suggesting that osteoporosis in COPD patients was not related with ICS use.

Systemic inflammation may be involved in the pathogenesis of the COPD associated complications including osteoporosis. In this study, erythrocyte sedimentation rate between the osteoporotic and non-osteoporotic COPD patients were not significantly different. Inflammatory cytokines such as TNF- α and IL-6 which were previously reported as independent predictors for osteoporosis in COPD patients.¹⁰ Since our study did not include extensive inflammatory markers, it is not possible to compare the results. Reduced lung function is associated with increased levels of systemic inflammatory markers which may have important pathophysiological and therapeutic implications for subjects with stable COPD.²⁶ In a study assessing the association between airflow limitation and

Table 5 Comparison of Osteoporotic and Non-Osteoporotic COPD Groups

Variables	Osteoporotic COPD Patients (n= 12)	Non-Osteoporotic COPD Patients (n=18)	p-value
Age [#]	65.00 (41–79)	65.00 (44–78)	0.723
BMI [#]	24.69 (19.66–29.38)	27.07 (24.91–34.11)	0.002
Smoking: pack/year [#]	37.75 (0–128)	27.50 (0–140)	0.285
ESH [#]	25.50 (8–53)	31.50 (11–99)	0.267
ICS duration (month) [#]	36.00 (12.00–120.00)	60.00 (24.00–132.00)	0.305
ICS dose (µg) [#]	720 (320–800)	800 (160–1000)	0.917
Cumulative dose	642,400 (292,000–292,000)	788,400 (233,600–3,212,000)	0.305
Disease duration (year) [#]	5 (2–10)	6 (2–20)	0.415
FEV1 (L) [#]	1.28 (0.55–2.35)	1.52 (0.75–2.16)	0.491
FEV1 (%) [#]	51.00 (30.00–85.00)	48.50 (28.00–75.00)	0.573
FVC (L) [#]	2.03 (0.70–2.70)	2.08 (0.9–3.20)	0.950
FVC (%) [#]	57.00 (33.00–72.00)	55.00 (31.00–88.00)	0.642
FEV1/FVC [#]	63.90 (43.00–85.80)	68.65 (47.30–84.30)	0.642
PEF (L) [#]	3.13 (0.88–4.75)	2.43 (1.43–5.87)	0.790
PEF (%) [#]	40.00 (19.00–61.00)	33.00 (18.00–77.00)	0.799
IC (L) [#]	2.32 (1.44–3.15)	2.52 (1.15–3.01)	0.897
IC (%) [#]	75.00 (53.00–122.00)	61.00 (46.00–116.00)	0.252
MVV (L) [#]	31.30 (18.80–56.70)	37.60 (17.10–92.10)	0.767
MVV (%) [#]	30.00 (21.00–50.00)	41.00 (18.00–53.00)	0.494

Note: Data were presented as [#]median (minimum–maximum).

bone mineral density, prevalence of reduced BMD in subjects with moderate-to-severe airflow limitation was significantly higher than in those without limitation.²⁷ In our study, there was no significant correlation between the severity of the lung function and BMD. This might be due to low number of patients in the “mild” and “very severe” groups according to GOLD classification. On the other hand, correlations between pulmonary function tests and BMD scores revealed that only the second lumbar vertebra BMD was significantly and positively correlated with pulmonary functions. Vertebral compression fractures are the most common fractures associated to osteoporosis and due to the peculiar kinetic of the spine and 80% of pathological vertebral fractures are located at the dorsal-lumbar passage. Most frequent sites of osteoporotic vertebral fractures are lumbar 1, dorsal 12 and lumbar 2.^{28,29} Studies investigating vertebral compression or BMD in COPD patients usually make the comparisons regarding lumbar total scores (L1-4). In this study, we analyzed the correlations between pulmonary functions and BMD of each lumbar vertebra. The results revealed that BMD of second lumbar vertebra which is the common compression site was correlated with the pulmonary functions. On the other hand, we found no significant differences between the number of the vertebral fractures between the COPD and control groups. These results may be due

to the exclusion of patients on systemic glucocorticoids or very few number of patients in the very severe group. Additionally, vertebra compressions were recorded as “present” or “not present” according to the dorsal and lumbar column radiographs. More detailed compression measures like number of the compressed vertebrae or the detailed compression degree according to the Genant’s classification may have led to different results.

Some life style parameters like smoking may be linked with osteoporosis. Combined analysis of studies shows that the smoking habit increases the risk of hip fracture by 1.5 times, but it has only a modest effect on BMD.^{30,31} In our study, smoking (pack/year) was significantly high in COPD patients; however, there was no statistical difference between BMD scores of osteoporotic and non-osteoporotic COPD patients.

Low BMI is one of the well-recognized modifiable risk factors for both osteoporosis and fracture.³² In a recent meta-analysis investigating prevalence and risk factors of osteoporosis in COPD patients, pooled global prevalence from 58 studies was 38% and the patients with sarcopenia and BMI<18.5kg/m² were at high risk for osteoporosis.² Similarly, in a study evaluating risk factors of osteoporosis in COPD patients BMI and FEV1 were found to be independent risk factors.⁴ In another study, osteoporosis was significantly more common in non-obese COPD patients.³³ The results in our study were found to be compatible with

the above data while BMI was found to be significantly lower in osteoporotic COPD patients compared with non-osteoporotic COPD patients. Other than BMI, lean body mass and sarcopenia were also found to be low in COPD patients.³⁴ COPD patients over 50 years of age lose their %1–2 muscle mass each year which is an important indicator of frailty syndrome. In overweight patients, sarcopenia measurements instead of BMI are suggested in order to avoid misdiagnosis.³⁵

In conclusion, COPD patients are at high risk for osteoporosis compared with the controls. Low BMI, a modifiable risk factor for osteoporosis, should not be underestimated in COPD patients.

Disclosure

The authors report no conflicts of interest in this work.

References

- Consensus A. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94(6):646–650. doi:10.1016/0002-9343(93)90218-E
- Chen YW, Ramsdook AH, Coxson HO, Bon J, Reid WD. Prevalence and risk factors for osteoporosis in individuals with COPD: a systematic review and meta-analysis. *Chest.* 2019;156(6):1092–1110. doi:10.1016/j.chest.2019.06.036
- Deniz S, Sengul A, Aydemir Y, Celdir Emre J, Ozhan MH. Clinical factors and comorbidities affecting the cost of hospital-treated COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11:3023–3030. doi:10.2147/COPD.S120637
- Lin CW, ChenYY, ChenYJ, LiangCY, LinMS, Chen W. Prevalence, risk factors, and health-related quality of life of osteoporosis in patients with COPD at a community hospital in Taiwan. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1493–1500.
- Pascual-Guardia S, Badenes-Bonet D, Martin-Ontiyuelo C, et al. Hospital admissions and mortality in patients with COPD exacerbations and vertebral body compression fractures. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1837–1845. doi:10.2147/COPD.S129213
- Graat-Verboom L, Spruit MA, van den Borne BE, et al. Correlates of osteoporosis in chronic obstructive pulmonary disease: an underestimated systemic component. *Respir Med.* 2009;103(8):1143–1151. doi:10.1016/j.rmed.2009.02.014
- Okazaki R, Watanabe R, Inoue D. Osteoporosis Associated with chronic obstructive pulmonary disease. *Chron Obstruct Pulmon Dis.* 2016;23(3):111–120. doi:10.11005/jbm.2016.23.3.111
- Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. *Int J Chron Obstruct Pulmon Dis.* 2016;11:637–648. doi:10.2147/COPD.S79638
- Kanis JA, Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int.* 1994;4(6):368–381. doi:10.1007/BF01622200
- Liang B, Feng Y. The association of low bone mineral density with systemic inflammation in clinically stable COPD. *Endocrine.* 2012;42(1):190–195. doi:10.1007/s12020-011-9583-x
- Watanabe R, Tanaka T, Aita K, et al. Osteoporosis is highly prevalent in Japanese males with chronic obstructive pulmonary disease and is associated with deteriorated pulmonary function. *J Bone Miner Metab.* 2015;33(4):392–400. doi:10.1007/s00774-014-0605-7
- Ogura-Tomomatsu H, Asano K, Tomomatsu K, et al. Predictors of osteoporosis and vertebral fractures in patients presenting with moderate-to-severe chronic obstructive lung disease. *COPD.* 2012;9(4):332–337. doi:10.3109/15412555.2012.667850
- Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine.* 2018;61(1):7–16.
- Hayat S, Magrey MN. Glucocorticoid-induced osteoporosis: insights for the clinician. *Cleve Clin J Med.* 2020;87(7):417–426. doi:10.3949/ccjm.87a.19039
- Adami G, Saag KG. Glucocorticoid-induced osteoporosis: 2019 concise clinical review. *Osteoporos Int.* 2019;30(6):1145–1156. doi:10.1007/s00198-019-04906-x
- Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2002;1:CD003537.
- Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med.* 2004;169(1):83–88. doi:10.1164/rccm.200305-640OC
- Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of fracture. *Chest.* 2006;130(4):1082–1088. doi:10.1378/chest.130.4.1082
- Mathioudakis AG, Amanetopoulou SG, Gialmanidis IP, et al. Impact of long-term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? *Respirology.* 2013;18(1):147–153. doi:10.1111/j.1440-1843.2012.02265.x
- Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187(4):347–365. doi:10.1164/rccm.201204-0596PP
- Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl.* 2003;41:46s–53s. doi:10.1183/09031936.03.00078002
- Ferguson GT, Calverley PMA, Anderson JA, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the Towards a revolution in COPD Health study. *Chest.* 2009;136(6):1456–1465. doi:10.1378/chest.08-3016
- Johnell O, Pauwels R, Lofdahl CG, et al. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. *Eur Respir J.* 2002;19(6):1058–1063. doi:10.1183/09031936.02.00276602
- Scanlon PD, Connett JE, Wise RA, et al. Loss of bone density with inhaled triamcinolone in Lung Health Study II. *Am J Respir Crit Care Med.* 2004;170(12):1302–1309. doi:10.1164/rccm.200310-1349OC
- Caramori G, Ruggeri P, Arpinelli F, Salvi L, Girbino G. Long-term use of inhaled glucocorticoids in patients with stable chronic obstructive pulmonary disease and risk of bone fractures: a narrative review of the literature. *Int J Chron Obstruct Pulmon Dis.* 2019;14:1085–1097. doi:10.2147/COPD.S190215
- Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.* 2004;59(7):574–580. doi:10.1136/thx.2003.019588
- Watanabe K, Onoue A, Kubota K, et al. Association between airflow limitation severity and reduced bone mineral density in Japanese men. *Int J Chron Obstruct Pulmon Dis.* 2019;14:2355–2363. doi:10.2147/COPD.S213746
- Masala S, Magrini A, Taglieri A, et al. Chronic obstructive pulmonary disease (COPD) patients with osteoporotic vertebral compression fractures (OVCFs): improvement of pulmonary function after percutaneous vertebroplasty (VTP). *Eur Radiol.* 2014;24(7):1577–1585. doi:10.1007/s00330-014-3165-2
- Wu SS, Lachmann E, Nagler W. Current medical, rehabilitation, and surgical management of vertebral compression fractures. *J Womens Health.* 2003;12(1):17–26. doi:10.1089/154099903321154103

30. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int.* 2005;16(2):155–162. doi:10.1007/s00198-004-1640-3
31. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int.* 2001;68(5):259–270. doi:10.1007/BF02390832
32. Jiang X, Good LE, Spinka R, Schnatz PF. Osteoporosis screening in postmenopausal women aged 50–64 years: BMI alone compared with current screening tools. *Maturitas.* 2016;83:59–64. doi:10.1016/j.maturitas.2015.09.009
33. Zewari S, Hadi L, van den Elshout F, Dekhuijzen R, Heijdra Y, Vos P. Obesity in COPD: comorbidities with practical consequences? *COPD.* 2018;15(5):464–471. doi:10.1080/15412555.2018.1509951
34. Spelta F, Fratta Pasini AM, Cazzoletti L, Ferrari M. Body weight and mortality in COPD: focus on the obesity paradox. *Eat Weight Disord.* 2018;23(1):15–22. doi:10.1007/s40519-017-0456-z
35. Costa TM, Costa FM, Moreira CA, Rabelo LM, Boguszewski CL, Borba VZ. Sarcopenia in COPD: relationship with COPD severity and prognosis. *J Bras Pneumol.* 2015;41(5):415–421. doi:10.1590/S1806-37132015000000040

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