EVALUATION OF BONE DEMINERALIZATION IN COPD PHENOTYPES

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ABSTRACT

Objective*: Diminished bone mineral density in patients with chronic obstructive pulmonary disease have increased risk for osteoporosis and its associated fractures. Even though the relationship between different phenotypes of chronic obstructive pulmonary disease and bone mineral density was not fully understood. The aim of this study was to evaluate bone mineral density in different phenotypes of chronic obstructive pulmonary disease and compare these outcomes with an age-correlated control group.*

Methods*: In this retrospective study 100 patients (emphysematous, chronic bronchitis and healthy control group) were participated. Participants underwent DXA absorptiometry to evaluate bone mineral density. Spirometric pulmonary function tests, 6-minute walk test, bode index, and modified medical research council dyspnea score, body mass index and levels of calcium, vitamin D and parathormone were also evaluated. Comparative assessment of the findings was performed and statistical analysis was applied in present study.*

Results*: Patients with the emphysematous phenotype had significantly lower femur bone mineral density (P = 0.05), body mass index (P< 0.05), than chronic bronchitis phenotype. Inverse correlations were revealed between lumbar bone mineral density and modified medical research council dyspnea score. Statistical analysis was performed by the multivariate logistic regression analysis model test and Tukey tests (p<0.05). On ANOVA analysis, the emphysematous group have two fold higher risk of osteoporosis and lower bone mineral density detected than other groups(OR 1.947, 95%CI (1.009-3.792), P=0.081; OR, 1.863 ,95%CI (1.027-3.274), P =0.037).*

Conclusion*: The evaluation of bone loss rate among groups, emphysematous phenotype had more risk in developing osteoporosis, low bone mineral density and a little less osteopenia than other groups.*

Keywords*: Bone Mineral Density, Body Mass index, Osteoporosis, phenotype,COPD.*

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Introduction

Chronic obstructive pulmonary disease is interrelated with many comorbidities, osteoporosis has more importance in this disease group. Decrease in bone mass density (BMD) and the presence of possible fracture risk is a common symptom in patients with chronic obstructive pulmonary disease. Risk factors interrelated with these complications including smoking, Calcium deficiency, and treatment with corticosteroids. Also osteoporosis and its related fractures are common and significantly destroy the quality of life and even respiratory function in patients with chronic obstructive pulmonary disease[1,2,3].

The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease is higher than healthy individuals. This difference has been related with the use of corticosteroids and lower ability to exercise in this population. The National osteoporosis risk assessment study has confirmed that the risk of fracture increases with decreasing of BMD, some

recent studies reported a rate of osteoporotic fracture of 18 % and a small number of osteoporotic fracture cases can be occurred in the osteopenia group with long follow up periods . Also these studies have suggested that decreased bone mineral density (BMD) and destroyed bone quality lead to fractures in patients with Chronic obstructive pulmonary disease. The gold standard for measuring bone density is dual energy X-ray absorptiometry (DXA). DXA is a two-dimensional method of measuring BMD; therefore, superimposed tissue can cause artifacts and inaccurate measurements. Osteoporosis is diagnosed when BMD is in standard deviations or more below the young adult mean (*T*-score ≤ −2.5), according to the evaluation criteria of World Health Organization (WHO)[3,4].

Chronic obstructive pulmonary disease is related to decreased BMD and increased risk of fracture, and also most related studies have been conducted on this disease. Individuals with Chronic obstructive pulmonary disease has many risk factors for osteoporosis disease, including sedentary lifestyle, older age, vitamin D and calcium (Ca) deficiency. It is important for pulmonologist to be aware of prevalence in osteoporosis among Chronic obstructive pulmonary disease patients and to evaluate these patients for possible fracture risk. Osteoporosis and other comorbidities can be overlooked when chronic obstructive pulmonary disease is evaluated only as a pulmonary disease[5-8].

In present study we evaluated the prevalence of osteoporosis in patients with two different phenotypes of Chronic obstructive pulmonary disease (emphysematous versus chronic bronchitis) and compared these groups with an age-matched control group.

Material and methods

Diagnostic criteria

The diagnosis of osteoporosis was based on WHO-recommended criteria: *T*-score less than -2.5 for bone density of the lumbar vertebrae on DXA [*T* = standard deviation of (measured value - peak bone mass)/(normal adult bone density)][9].

Patient selection

This study was performed on followed Chronic obstructive pulmonary disease (COPD) patients and healthy volunteers in the department of chest disease. Participants were divided into three groups: emphysematous, chronic bronchitis, and control.

We were defined these phenotypes by applying high resolution CT (collimation of 1 to 2 mm) which have greater sensitivity and specifity.

Subjects and sample collection

Serum samples and DXA results were obtained from consecutive patients in the department of chest disease at the tertiary care Hospital from January 2011 through May 2014. All participants provided informed consent (n=100: 30 in the healthy control group, 30 in the emphysematous group, and 40 in the chronic bronchitis group.

Inclusion criteria

Inclusion criteria were determined before review of abstracts and articles. The inclusion criteria for the present study were as follows: female sex, post-menopausal ,age over 40 years, and diagnosis of COPD (with the exception of the control group) as per to the criteria of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and DXA examinations. Sixty patients had received inhaled steroids for more than 2 years as part of their therapy and 40 had not received inhaled steroids. All patients were ex-smokers and Turkish.

Exclusion criteria

Patients were excluded from the study based for the following criteria: (i) known co-morbidity affecting bone mineral status, such as hemiplegia resulting from stroke, severe diabetes mellitus, and endocrinopathies such as thyroid and parathyroid disease, (ii) known malignancy with long-standing systemic steroid therapy, and (iii) autoimmune disease such as rheumatoid arthritis. Antiosteoporotic treatment was not given to any of the patients.

Ethical review

The present study was approved by the local Ethics Committee. The patients and volunteers provided by written informed consent for their attendant before enrollment.

DXA examination

DXA examination of the lumbar spine(L1-L3) was performed in a Hologic discovery QDR series densitometer (Hologic Inc., Bedford, MA). Patients were scanned in the supine position, with their knees held high and bent at a right angle and their calves resting on a cushion to reduce normal spinal lordosis, as proposed by the manufacturer. Patients wore light clothing during the examination. The device was cal-

ibrated daily, according to the manufacturer's instructions for quality control, and had a coefficient of variation of 1.0% for the spine phantom.

The examinations were reviewed by an experienced radiologist. Zones of sclerosis or wide osteophytes were excluded from the analysis. BMD was expressed in gr/cm2, and patients' *T*-scores were estimated using the national health and nutrition evaluation survey database, provided by the manufacturer. Vertebrae were classified by the WHO classification as normal if the *T*-score was -1.0 or higher, as osteopenic between -1.0 and -2.5, and as osteoporotic -2.5 or lower.

Clinical and functional assessment

Pulmonary function tests (spirometry)

Pulmonary function tests (PFTs) were done for all patients in the clinic. FEV1 and FVC were evaluated by a calibrated spirometer, PFTs were evaluated by an experienced technician in pulmonary laboratory with a ZAN500 spirometry device (SpireHealth GmbH, Oberthulba, Germany).

All pulmonary function tests were performed with patients seated upright. Patients were directed by trained staff on proper use of the spirometer. Each measurement was repeated three to five times, with at least 1 min between inhalations. The best value from three successive tests was sustained. FEV1, FVC, and FEV1/FVC were measured by ATS criteria. COPD staging was done by GOLD criteria.

All participants with a forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC) ratio < 0.70 at screening spirometry underwent a bronchodilatation reversibility test performed with 0.4 mg of inhaled salbutamol (or equivalent) followed by spirometry 15 minutes later. The spirometry variables evaluated included FEV1(%, L), FVC(%, L), and FEV1/FVC(%) after this period.

COPD was diagnosed according to internationally recognized guidelines based on clinical history, symptoms, and a FEV1/FVC ratio<0.70. The patient's disease status was classified according to predictive FEV1 values as mild (FEV1≥80%), moderate (50%≤ FEV1< 80%), severe (30%≤ FEV1< 50%), or very severe (FEV1<30%).

Six-Minute Walking Test (6MWT)

All patients applied the 6MWT by current guidelines. Heart rate proportion (HR) and instant oxygen saturation (SpO_2) evaluated by pulse oximetry (Nellcor™ , N-65™ , Covidien AG, USA) were evaluated in baseline and repeated every minute until minute 6. The pulmonary therapist checked that the pulse oximeter device had an inception signal before beginning the tests. Patients already taking oxygen support in rest time after performing the 6MWT. 6MWT was defined as the maximal reached walking distance in room air[10].

Modified Medical Research Council (mMRC) dyspnea score

The mMRC, is a scale that rating by a patient, include five stages that describe the total range of respiratory disability from none (Grade 0) to almost complete (Grade 4). For the aim of this study, symptom evaluation to determine GOLD groupings (A-D) was carried out in each patients.

Measurements of BODE index for patients with COPD

The multidimensional BODE parameters (body mass index, degree of obstruction, dyspnea, exercise capacity) were calculated. Total score was evaluated, with 0 to 3 points assigned for each parameter.

Biochemical analyses

Venous blood samples were collected and centrifugated for PTH and Ca level testing. PTH levels were evaluated with an immulite 2000 systems device and Ca levels with an advia 1800 chemistry device. The average values were standardized and accepted (10-65 pg/mL for PTH and 8.60-10.00 mg/dL for Ca).

Statistical analysis

ANOVA analysis of variance was used to measure the overall differences between groups and Tukey's test was used to detect which differences were significant. The X2 test was performed to confirm the prevalence rates of osteopenia and osteoporosis in each group. A multiple logistic regression analysis model was used to compare the risk of developing osteopenia and osteoporosis in study groups according to age, BMI, Weight, pulmonary function results, smoking pack years, Ca, PTH, physical activity, Length of hospital stay, Number of hospital visits, Inhaled and systemic corticosteroid.

Statistical analyses were performed with SPSS, version 20.0 (Statistical Package For The Social Sciences, Apple OS). Data are expressed as mean ± SD unless otherwise stated. All hypothesis tests were two sided. P values less than 0,05 were considered statistically significant.

Results

Subject characteristics

One hundred participants were enrolled in this study, and underwent DXA examination of the lumbar vertebrae (L1-L3). The mean age ± standard deviation of our patients was 63.1 ± 8.4 years (age range: 42-66 years). Based on FEV1, five patients were classified as GOLD stage I, 35 as stage II, 18 as stage III, and 2 as stage IV (Table 1).

BMD and T-scores and differences in prevalence rates of osteopenia and osteoporosis in groups

The mean femur, femur neck and lumbar BMD values were lower in the emphysematous phenotype than other groups (Table 2), T-scores (femur, lumbar) were used to diagnose osteopenia and osteoporosis.

Table 1. Demographic and clinical data according to COPD phenotype

	Emphysematous n:30	ChronicBronchitis n:30	Control n:40	P Value
Age* (years)	65,3±10,13	63,13±9,62	63,10±7,54	0,836
BMI* (kg/m²)	22,6±4.32	26,7±4,09	27,7±4,39	0,028
Weight,kg	60.4±7.91	61.8±10.47	60.72± 9.34	0,691
FEV1(%)	88,2±16,42	89,8±17,82	98,5±17,77	0,034
FVC (%)	92.2± 8.34	90.7±12.64	82.75±15.99	0,027
FEV1/FVC*(%)	58,6±11,27	58,4±8,63	79,3±6,94	0,041
Smoking pack years (pear year)*	42,06±18,83	35,16±16,50	13,12±10,46	0,758
Ca (mg)	8,96±0,46	9,42±0,63	9,15±0,42	0,592
PTH (pg/ml)	58,66±27,98	62,65±19,15	65,14±20,55	0,707
Vitamin D, ng/ml	18.44± 4.97	20.82± 7.68	24.19± 6.53	0.375
Physical activity (MET-hours/week)*	8.7 (4.4-17.5)	11.2 (6,7- 23.7)	15,3(8,4-28,6)	0,037
Length of hospital stay (days) ± SD	51.4 ± 22.5	41.4 ± 16.2		0,035
Number of hospital visits ± SD	48.2 ± 25.7	35.8 ± 15.4		0,024
Inhaled corticosteroid(ICS)	25 (28.3%)	42 (43.7%)	21 (23,4%)	0.42
Systemic corticosteroid(SCS)	2 (2.4%)	4 (4.2%)	3 (3.5%)	0,69
COPD/Stage 1(mild)	2 / 6,6 %	3 / 30 %		
Stage 2(moderate)	17/ 56,6%	18 / 60 %		
Stage 3 (severe)	10/ 33,3%	8 / 26,6 %		
Stage4(very severe)	1 / 3,3 %	1 / 3,3 %		

$p < 0.05$, statistically significant
BMI: Body mass index; Ca: Calcium; PTH, Parathormone,MET = Metabolic equivalent hours,

Table 2. Bone mineral density of COPD patients and controls

	Emphysematous n:30 mean ± SD	Chronic Bronchitis n:30 mean ± SD	Control n:40 mean ± SD	P value
Femur BMD	0,86±0,18	0,91±0,12	0,94±0,16	0, 329
Femur neck BMD	0,72±0,15	0,78±0,10	0,75±0,15	0,034
Lumbar BMD	0,84±0,17	0,90±0,14	0,87±0,17	0,294
Femur BMD Tscore	-0,67±0,39	-0,46±0,92	0,41±0,15	0,117
Femur neck BMD T score	-1,37±1,18	-0,98±0,79	-1,31±1,08	0,027
Lumbar BMD T score	-1,24±1,12	-1,22±0,81	-1,04±1,05	0, 324

Significant differences in, and FEV1(%), FEV1/FVC, were observed among the groups. Although it was not statistically significant, patients in the emphysematous group also had lower Ca and PTH levels, tended to be older, longer smoking history and statistically significantly poorer pulmonary function results than chronic bronchitis and control groups ((p= 0,034, p= 0,027 and p= 0,041, respectively), P<0,05). Differences in other characteristics among the groups are shown in (Table 1).

The emphysematous group had lower T-scores in mostly parts (femur, lumbar areas), and tended to have lower T-scores in mostly parts than other groups. The osteopenia prevalence rates in the control, emphysematous and chronic bronchitis roups were respectively 48.7%, 49.1% and 55.3%; the osteoporosis prevalence rates were respectively 14.2%, 26.4% and 21.7% (P <0.05) (Figure).

Table 3 ORs for osteopenia and osteoporosis among the obstructive lung disease groups

	Osteopenia		Osteoporosis	
	OR(95%CI)	P value	OR(95%CI)	P value
Model 1				
Control	1		1	
Chronic bronchitis	0.584 (0.252–1.250)	0,115	0.432 (0.246–1.083)	0,077
Emphysematous	1.561 (0.918–2.861)	0,082	1.267 (0.657–2.766)	0,482
Model 2				
Control	1		1	
Chronic bronchitis	0.689(0.348–1.386)	0.348	0.691 (0.277–1.712)	0.394
Emphysematous	1.931 (1.095–3.344)	0.047	1.677 (0.733–3.574)	0.202
Model 3				
Control	1		1	
Chronic bronchitis	0.728 (0.345–1.384)	0.343	0.797 (0.355–2.023)	0.569
Emphysematous	1.946 (1.112–3.402)	0.038	1.892 (0.854–4.276)	0.148
Model 4				
Control	1		1	
Chronic bronchitis	1.152 (0.326–3.921)	0.837	0.342(0.038–4.497)	0.397
Emphysematous	2.067 (1.047–3.842)	0.046	2.045 (1.076–3.829)	0.041
Model 5				
Control	1		1	
Chronic bronchitis	1.181 (0.327–4.039)	0.784	0.349 (0.024–4.995)	0.349
Emphysematous	2.081 (1.071–3.828)	0.048	1.931 (0.661–5.486)	0.257
Model 6				
Control	1		1	
Chronic bronchitis	1.232 (0.347–4.286)	0.757	0.264 (0.034–3.948)	0.364
Emphysematous	1.947(1.009–3.792)	0.043	2.283 (0.761–7.343)	0.157

Odds ratios of osteopenia, osteoporosis and low BMD among the groups

The chronic bronchitis phenotype group had more risk in developing osteopenia than other groups. The odds ratio (OR) for osteoporosis tended to be high in all models. No difference in the risk of developing osteoporosis was observed between the control and chronic bronchitis groups, However significant difference detected between the emphysematous and chronic bronchitis groups (Table 3). The emphysematous group had a higher risk of low BMD than other groups, even after adjusting for age, smoking pack year history,vitamin D, Ca, PTH and FEV1 (OR 1.863, 95% confidence interval [CI] 1.027-3.274, P = 0.037).

There is no difference in risk was detected between the control and chronic bronchitis groups and between the emphysematous and chronic bronchitis groups for low BMD (Table 4).

On a per-patient basis, according to the mean *T* value of the DXA measurements for lumbar, femoral neck, and femur, the emphysematous phenotype group had significantly higher prevalence of osteoporosis than the other groups. In contrast, the chronic bronchitis phenotype group had the same higher prevalence in osteopenia than the other groups ($p < 0.05$; Table 2).

Our analysis showed a relationship between demographic and clinical measurements in COPD phenotype. There were no significant differences in patient age or blood Ca levels among the groups. However there were statistically significant differences in BMI, FEV1, and FEV1/FVC results among the groups (Table 1).

Table 4 ORs for low BMD among the obstructive lung disease groups

	OR (95%CI)	P value
Model 1 Control	1	
Chronic bronchitis	0.547 (0.286–1.052)	0,142
Emphysematous	1.561 (0.894–2.481)	0,167
Model 2 Control	1	
Chronic bronchitis	0.632 (0.341–1.320)	0.271
Emphysematous	1.892 (1.077–3.281)	0.045
Model 3 Control	1	
Chronic bronchitis	0.671 (0.317–1.369)	0.324
Emphysematous	1.928 (1.103–3.422)	0.042
Model 4 Control	1	
Chronic bronchitis	1.137(0.311–3.486)	0.881
Emphysematous	1.976 (1.101–3.859)	0.041
Model 5 Control	1	
Chronic bronchitis	1.117 (0.358–3.813)	0.864
Emphysematous	2.145 (1.077–3.901)	0.048
Model 6 Control	1	
Chronic bronchitis	1.203 (0.317–4.131)	0.801
Emphysematous	1.863(1.027–3.274)	0.037

Model 1*Adjusted for PFT

Model 2* Adjusted for PFT,6MWT

Model 3* Adjusted for PFT,6MWT,mMRC

Model 4* Adjusted for PFT,6MWT,mMRC,BODE

Model 5* Adjusted for PFT,6MWT,mMRC,BODE, Vitamin D, PTH

Model 6* Adjusted for PFT,6MWT,mMRC,BODE, Vitamin D, PTH, DEXA

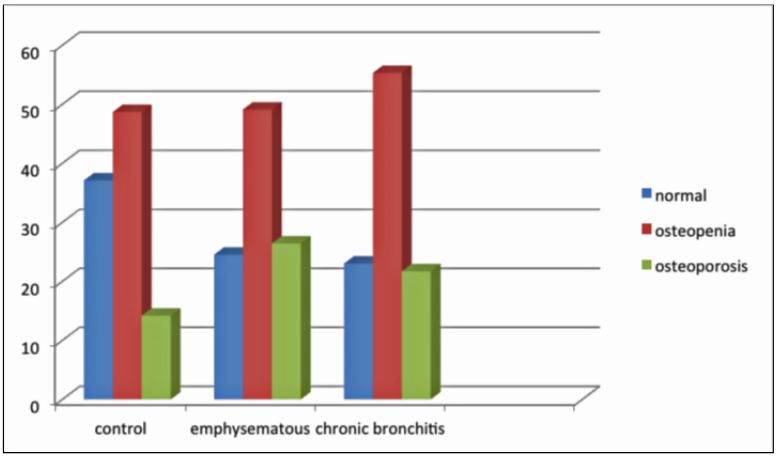

Figure: Prevalence rates of osteopenia and osteoporosis in obstructive lung diseases. COPD=chronic obstructive pulmonary disease.

Discussion

In the present study, we aimed to investigate the prevalence of osteoporosis in patients with two different phenotypes of COPD. We correlated our findings with DXA measurements, which are considered the gold standard for osteoporosis diagnosis[11-13].

Patients with the emphysematous phenotype had a higher proportion of prevalence in osteoporosis than osteopenia. On the other hand the prevalence of osteopenia was higher in chronic bronchitis phenotype. These results are in accordance with a published meta-analysis, which reported an osteoporosis prevalence of 43.7% and an osteopenia prevalence of 56.3% among patients with COPD. Most of the studies included in that meta-analysis used DXA measurements. A recent publication by Jaramillo et al. confirms our finding that COPD and smoking-pack years are combined risk factors that may influence negatively affect BMD[14-16].

According to our results, there is a high prevalence of low BMD according to DXA measurement among our patients. Our findings showing the clinical difference of emphysematous phenotype from other groups in agreement with previous studies and support the importance of this phenotype.

In the present study, severity of osteoporosis according to femoral neck *T*-score increased in emphysematous phenotype. In other words, reduction of FEV1 in patients was related with low levels of bone mineral density. The etiology of osteoporosis and osteopenia in COPD is complicated and may subscibe to its physio-pathogenesis. Also systemic inflammation can play an important role in detecting a progressive BMD decreasing[17]. Also systemic inflammation is especially related to the activation of osteoclastogenesis by way of osteoprotegerin/receptor activator of nuclear factor. kB (RANK)/ RANK ligand (RANKL) system[17].

Moreover, some novel in vitro and in vivo experimental researchs have noticed that the noradrenergic activation in beta-2receptors ready on osteoblasts cause to production of RANKL with increased osteoclastogenesis and diminished bone mineral density[18]. Although, two compre-

hensive studies have excluded an higher risk of decreasing in bone mineral density in patients who were treated with inhaled beta-2 agonists, suggesting that the seriousness of the underlying causes in pulmonary disease, rather than the use of beta-2 agonists, may play a role in the aetiology of fracture[19,20].

Also Watanabe et al. approached to this disease by pulmonary function tests ,found that FEV1/FVC was the predictor for existence of bone fracture in COPD, and also lower FVC, higher FEV1 was significantly associated with bone fractures and BMD decrease. Also they trust that these findings point out a potent relationship among COPD and osteoporosis. On the other hand, we were evaluated the osteporosis and osteopenia by the evaluation of phenotypes like a bit diferent angle of the same trigon, our findings are corelate with its results.

Graat-Verboom et al. researched and compared the society of COPD patients with osteoporosis to COPD patients without osteoporosis and found that decreasing in BMI and increasing in RV%TLC (residual volume as the rate of total lung capacity) results have increased the risks for osteoporosis.,also overweight and obese BMI values were found protective for osteoporosis. According to our results its outcomes correate with our outcomes partially however we were determined the different pulmonary parameters of FEV1, FVC, FEV1/FVC and approached to this disease by these phenotype outcomes.

In present stıudy , a significant relationship was found between BMI and osteoporosis in femoral neck based on *T*-score, such that a reduction in BMI was shown to be associated with increased severity of osteoporosis. As a result of this relationship BMD is directly associated with BMI and patients with higher BMI have higher BMD[23,24]. Nuti and his colleagues also found similar results and showed that BMD in COPD patients was low and correlated pulmonary disease severity[25].

At the same time Bon et al. detected that patients who have diagnosed solo radiographic emphysema with COPD is the strongest predictor and has highly significant relationship with low BMD in smoker society with various grades of airway obstruction and inflammation. This outcomes are compliance with ours[26].

The mechanism of the relationship between low BMI and osteoporosis is not fully understood in patients with COPD. It is probably due to the increase in inflammatory processes, the decrease in physical activity and using inhaled and oral corticosteroids. Therefore, osteoporosis is considered as a major problem in patients with COPD. It can cause multiple fractures, reduce pulmonary capacity and trigger the adverse effects of COPD in patients. Therefore identfying the commmon risk factors for COPD is essential[27-30].

In a research study applied by Vrieze et al., found that low BMD is oftenly existence in COPD. In addition to sophisticated stage of COPD, low BMI and low FFM (fat free mass) are the most important predictors and risk factors for the presence of low BMD. We were reached to similar decisions by assessing the subtypes of COPD, with a different point of view[31].

On the other hand Chubachı et al. approached genetically to this disease by the way of LRP5 A1330V (low-density lipoprotein receptor-related protein 5) polymorphism which was an independent risk factor for low BMD in emphysematous COPD patients, found that the genetic efficacy of LRP5 A1330V polymorphism in COPD patients is related to low BMD. These results are helped us to look by a new perspective[32].

Our results show that emphysematous phenotype had mostly lower T-scores than others; the osteoporosis prevalence rates were two-fold higher in emphysematous phenotype patients than others, even after adjusting for PFT,6MWT,MMRC,BODE, PTH, and DXA.

Different point of view by Silva DR et.al. assessed the prevalence of osteoporosis in COPD patients, found that significant positive relationship between femoral-neck T-score with pulmonary function test results, BMD and BMI, on the other hand found a significant opposite connection between femoral-neck T-score and BODE index.Whereas in our research femur, femur neck, lumbal BMD and T score of this parameters were studied with phenotypes of COPD. We have believe that both of these studies indirectly reached the similar results[33].

Another perspective, by Romme et al found that approaching to these kind of diseases clinically with 5 step (case finding, risk evaluation,differential diagnosis, therapy, follow -up), would help us to result and find a solution. This 5 step clinical approach has not yet validated, however this research will shed light on other studies[3].

The use of corticosteroids in these patients is also considered as another cause of low bone density (34, 35). This was examined in the present study as well, and a significant relationship was observed between the osteoporosis in femoral neck based on

T-score. In other words, by increasing the systemic corticosteroid use, an increased risk for osteoporosis was observed. In the TORCH study carried out by Ferguson et al., is similar with us and detected no significant effect on bone mineral density for inhaled corticosteroids[36].

Moreover Jaramillo et al. found in their cohort study of smoker population with or without COPD that, emphysematous phenotype of COPD is related with lower vBMD (volumetric bone mineral density) and lead to diminished bone density. As a result of this, they decided that smoking increase the risk for decreasing bone mineral density. However we did not approached to this disease by the way of smoking also our statistic outcomes are not significant in smoking[16].

In contrast, Nuti et al. showed that both severity of COPD and using inhaled glucocorticoid therapy increase the risk of vertebral fractures[25]. In a similar study of Dam et al. found that patients with COPD or asthma using inhaled corticosteroid had the lowest amount of BMD, and the risk of osteoporosis in their bones was two times more compared to those without COPD and asthma[37].

In present study, a significant relationship was found between BMI and osteoporosis in femoral neck based on *T*-score, such that a reduction in BMI was shown to be associated with increased severity of osteoporosis. However, no association was observed in *T*- score of femur and lumbal regions. Cifuentes et al. and Ozalevli et al., were found that lower BMI values were associated with higher osteoporosis rates among patients[38,39], its results are similar with us .

Another study by Yang et al. concluded that proximal femur fracture risk and osteoporosis in postmenopausal women who walked at least 4 hours per week was lower than walked 1 hour per week. When we compared the groups according to osteoporosis prevalence, the emphysematous group had the highest prevalence, consistent with the findings of Yang et al. due to shorter walking distance capacity[40].

On the other hand Bolton et al.reported that the different anthropometric sizes (BMI, %IBW (ideal body weight)) which show the patients nutritional situation is informative and when it is diminished it leads more risk for osteoporosis in COPD society[41].

Comparison of groups according to DXA measurements accurately predicted osteoporosis and osteopenia risks. The classification of our patients into groups according the GOLD stage showed osteoporosis findings similar to those of the TORCH study (Towards a Revolution in COPD Health), which included 6112 patients with COPD by Heijdra et al.[42].

Our findings indicate that COPD phenotype and BMI correlated with the prevalence of osteoporosis, consistent with previous findings in the literature. The TORCH study demonstrated a higher prevalence of osteoporosis and osteopenia at baseline in patients with spirometrically confirmed COPD.

As with the DXA measurements, which were related to the COPD phenotypes evaluated in this study, the parameters differed significantly between the two clinically identified COPD phenotypes. A significantly lower BMI and more destroyed pulmonary function were more common in the emphysematous group. The study of Cote et al. found similarly that the BODE index is a sensitive method to evaluate COPD phenotype and progression which evaluates the PFT,6MWT,mMRC parameters[43].

However present study have some limitations. Firstly, recall bias and incorrect diagnosis cannot be ruled out, but misdiagnosis of COPD was minimized by including only patients who had been diagnosed with COPD before the age of 40 years so the number of participants remained limited. Secondly,the use of inhaled corticosteroids (ICS) and systemic corticosteroids (SCS) as possible cause for decrease in BMD could not be confirmed. ICS remains controversial as a risk factor for osteoporosis, however SCS are clearly a risk factor, as the study was retrospective and individuals were surveyed using a questionnaire, the use of ICS and SCS could not be accurately evaluated. Although this may affect the results, the findings are important, as they confirm that decrease in BMD on emphysematous group more severe than others.

And lastly, we could not confirm the clinical outcomes (e.g.,fractures or death) of a severe decrease in BMD in emphysematous group patients; however, these patients may be assumed to have similar outcomes with chronic bronchitis group. Follow-up studies are needed to verify our results.

Conclusions

Differences in BMD were found among the phenotypes. Patients with emphysematous phenotype had lower T-scores than those with other phenotype. Osteopenia and osteoporosis prevalence rates were higher in emphysematous group patients

than other groups. Especially, emphysematous group patients had approximately two-fold higher risk of developing osteoporosis and low BMD than chronic bronchitis group patients. Further studies need to be performed and these results indicate that clinicians managing COPD patients should actively assess and manage decrease in BMD.

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