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FeNO, systemic inflammation and other risk factors for osteoporosis in COPD

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ABSTRACT

Aim: The bone is one of the tissues that is adversely affected as a result of inflammation in COPD. The aim of this study is to examine the relationship between airway inflammation, systemic inflammation and osteoporosis in COPD.

Material and Method: A cross-sectional study was performed, including 50 patients with stable COPD. FeNO as a marker of airway inflammation; hs-CRP, WBC and fibrinogen as systemic inflammation markers; arterial blood gas, BMI and FEV_1 were measured. To identify osteoporosis, DEXA was performed.

Results: The prevalence of osteoporosis was 26%. Osteoporosis was associated with WBC and hs-CRP (OR: 1.80, 95% CI, 1.26-2.57 and OR: 2.32, 95% CI, 1.28-4.20, respectively). It was observed that the risk increased as FEV_1 and BMI decreased (OR: 0.94, 95% CI, 0.89-0.98 and OR: 0.75, 95% CI, 0.61-0.91, respectively). There was no relationship between osteoporosis and FeNO and fibrinogen (OR: 1.05, 95% CI, 0.99-1.12 and OR: 1.04, 95% CI 0.98-1.09, respectively). Arterial blood gases (PaO_2 and $PaCO_2$) were not effective on osteoporosis (OR: 1.01, 95% CI, 0.95-1.05 and OR: 1.04, 95% CI, 0.90-1.19, respectively). The cut-off values of hs-CRP and WBC for osteoporosis risk were 15.9 mg/L and 11.6 $\times 10^9$/L, respectively.

Conclusions: Osteoporosis was associated with low BMI, airway stenosis and high levels of hs-CRP and WBC.

Keywords: COPD, inflammation, osteoporosis, FeNO, arterial blood gas

This study was produced from my pulmonary disease specialization thesis [Kronik obstruktif akciğer hastalığında lokal ve sistemik inflamasyon belirteçleri ile kemik mineral dansitesi arasındaki ilişki (in English; the relationship between local and systemic markers of inflammation and bone mineral density in chronic obstructive pulmonary disease)]. It was presented as a poster at the Turkish Thoracic Society's 17th Annual Congress (poster number P291).

INTRODUCTION

Osteoporosis is one of the systemic consequences of chronic obstructive pulmonary disease (COPD), which is often underdiagnosed and affects the prognosis. Inflammation may contribute to the initiation or worsening of comorbidities such as osteoporosis (1). However, the development of low-grade systemic inflammation in COPD is not as well understood as in other chronic diseases. Systemic inflammation is an important factor in the formation and progression of the decrease in bone mineral density. Several studies have shown changes in various circulating inflammatory cells, including neutrophils and lymphocytes, in COPD (2). White blood cells (WBC) are one of the most studied inflammatory markers in COPD (3). Fibrinogen is a soluble acute-phase plasma glycoprotein and is synthesized primarily in the liver. During coagulation, it is converted to fibrin by thrombin. It has been associated with the presence, exacerbations and mortality of COPD. Fibrinogen can be used as a biomarker for comorbidities in COPD. It may be useful in identifying individuals at higher risk of mortality, whether due to respiratory complications or inflammatory co-morbidities, within the COPD population (4). High-sensitivity C-reactive protein (Hs-CRP) is a sensitive marker of low-grade systemic inflammation (5). Hs-CRP has been associated with various prognostic factors in COPD (6). This parameter may be worth considering both in estimating the likelihood of extrapulmonary comorbidities such as osteoporosis and in determining the presence and severity of inflammation in COPD (7).

Studies attempting to explain the relationship between airway inflammation and a decrease in bone mineral density are limited. Fractional exhaled nitric oxide (FeNO) measurements can be useful for determining

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the level of airway inflammation in the clinical setting. Endogenous nitric oxide (NO) is a gaseous signaling molecule and is released from inflammatory cells in the airways and alveoli. It plays an important role in regulating airway and vascular function. In COPD patients, FeNO levels have been shown to increase in exacerbations (8). It appears to reduce levels in current smokers and those with severe diseases (9).

The aim of this study is to investigate the effect of airway inflammation and systemic inflammation on bone mineral density (BMD) in COPD. Another aim of this study is to examine other factors such as hypoxemia that may affect the bones in COPD. At the same time, we assessed which biomarkers can be used to identify individuals at risk of osteoporosis. Selection of patients for BMD scanning may allow early diagnosis and treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 17.12.2012, Decision No: 12/14-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Desing and Population

A total of 50 patients with COPD were recruited for the study. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Patients with unstable COPD, history of smoking for the last four weeks; other metabolic, neoplastic and inflammatory diseases; any infection in the last two months; using inhaled steroids and those who received systemic steroid therapy in the last four weeks were excluded from the study. After informing the patients and signing the consent form, FeNO measurements were performed first. Blood collection for systemic inflammation biomarkers was performed after body mass index (BMI) measurements. An arterial blood gas was taken on the same day that an appointment was made for dual energy X-ray absorptiometry (DEXA). Two groups of participants were formed. Those with osteoporosis formed one group, while those with osteopenia and normal BMD formed the non-osteoporotic group. The pulmonary function test was performed concurrently with the DEXA.Written informed consent was obtained from all participants.

FeNO Measurement

In all groups, FeNO was measured with a NioxMino® analyzer (Aerocrine AG, Solna, Sweden) device at a speed of 50 ml/sec for 10 seconds and a constant flow rate of 10 cmH_2O, according to recommendations of American Thoracic Society/European Respiratory Society (ATS/ERS) Committee. The results of FeNO were represented as parts per billion (ppb).

Blood Inflammatory Biomarkers

For hs-CRP, venous blood samples were taken in two separate tubes without anticoagulation while the patients were in a sitting position. Hs-CRP samples were centrifuged at +4 degrees at 2000×g for 5 minutes with a cooled centrifuge in accordance with the cold chain, and then their serums were separated. Separated sera were transferred to Eppendorf tubes for the study and stored at -80 degrees until the working day. DiaSource® hs-CRP enzyme immunoassay was used. Fibrinogen was studied in a citrate tube using the SF-8100 series coagulation device of Succeeder® (Changping Science Zone, Beijing, China). The results of hs-CRP and fibrinogen were represented as mg/L. The upper limit of normal (ULN) were 15.23 mg/L and 40 mg/L, respectively. Hemogram was studied in an EDTA tube with Beckmancoulter® (Lakeview Parkway, Indianapolis, USA) in the LH780 series complete blood count device (autoanalyzer). The results of WBC were represented as $\times 10^9$/L and the ULN was 12 $\times 10^9$/L.

Arterial Blood Gases

While the patients were breathing room air, 2 ml of arterial blood was taken into heparinized syringes and blood gas analyses were performed. The Rapiblab 1265 series blood gas measurement device by Siemens® (Henkestrasse, Erlangen, Germany) was studied. The results were represented as mmHg.

Bone Mineral Density Measurement

The Hologic® Discovery QDR (Shelly Seaman Inc., Danbury, USA) series DEXA device was used to measure BMD. The T-score expresses how many standard deviations (SD) the BMD measurements are below or above from the mean of BMD measurements in young adults of the same gender. BMD was classified according to WHO guidelines. The T-score values above -1.0SD were normal, between -1.0 and -2.5SD were osteopenia, and below -2.5SD were osteoporosis. The diagnosis was determined by the lowest T-score at the lumbar or femoral neck.

Statistical Analysis

The SPSS for Windows 23.0 program was used to analyze all of the patients' data. The descriptive statistical methods (mean and standard deviation) and quantitative data comparison to compare parameters that did not show normal distribution between groups were calculated by the Mann Whitney-U test. The Spearman correlation test was used for continuous data. Univariate logistic regression analyses were performed to assess the impact of airway inflammation, systemic inflammation and other factors on the likelihood of having osteoporosis. The effect of confounders was examined using multivariate logistic regression analysis. Results were evaluated at 95% confidence interval and significance level of $p < 0.05$.

The area under the receiver operating characteristic curve (AUC-ROC) was used to measure the ability to distinguish between the osteoporosis group and the non-osteoporosis group. The AUC-ROC is a useful metric for summarizing a diagnostic model's discriminative power, and it can vary from 0.5 (no discrimination) to 1.0 (complete discrimination) (perfect discrimination). A value of 0.7-0.8 is considered reasonable discrimination and a value of greater than 0.8 indicates good discrimination (10).

RESULTS

There were 50 COPD patients participating in the study and 10 (20%) were women. The mean age was 62.98 years, the mean duration of diagnosis was 6.87 years, the mean of smoking pack-years was 39.84, and the mean BMI was 26.29 m²/kg. The mean of FeNO, an airway inflammation marker, was 21.20 (ppd), and the means of fibrinogen, WBC and hs-CRP which are systemic inflammation biomarkers were 31.72 (mg/L), 8.23 (x109/L) and 13.93 (mg/L), respectively. The femur-T score average was -1.85 SD and the lumbar-T score average was -1.12 SD. The mean forced expiratory volume in 1 second (FEV_1) was 43.94, the mean partial oxygen pressure (PaO_2) was 62.75 (mmHg) and the mean partial carbon dioxide pressure ($PaCO_2$) was 42.34 (mmHg). The prevalence of osteoporosis was 26% (n=13) and the prevalence of osteopenia was 58% (n=29). The remaining 8 (16%) participants had normal BMD. Participant demographic information and inflammation biomarkers are presented in **Table 1**.

Table 1. Demographics of COPD patients (n=50)

	Mean (sd)	Min-max
Age	62.98 (9.31)	44-88
Gender F/M, n (%)	10/40 (20/80)	
Body mass index (m²/kg)	26.29 (4.77)	17-41
Diagnosis year of COPD	6.87 (4.44)	1-20
Smoking (pack-years)	39.84 (19.58)	20-120
FEV_1 (%)	43.94 (19.22)	16-83
PaO_2 (mmHg)	62.75 (12.66)	38-91
$PaCO_2$ (mmHg)	42.34 (4.55)	35-51
FeNO (ppd)	21.20 (10.29)	5-47
Fibrinogen (mg/L)	31.72 (11.82)	13.00-74.30
WBC (×10⁹/L)	8.23 (3.05)	2.80-18.00
Hs-CRP (mg/L)	13.93 (1.01)	12.76-16.55
Osteoporosis, n (%)	13 (26)	
Osteopenia, n (%)	29 (58)	
Normal bone mineral density, n (%)	8 (16)	
Femur T-score (SD)	-1.85 (1.08)	(-0.10)-(-4.48)
Lumbar T-score (SD)	-1.12 (1.11)	(0.89)-(-3.43)

T-score less than or equal to -1 at either the hip or lumbar spine. FEV_1 (Forced expiratory volume in 1 second), PaO_2 (Partial oxygen pressure), $PaCO_2$ (Partial carbon dioxide pressure), FeNO (Fractional exhaled nitric oxide), WBC (White blood cells), Hs-CRP (High-sensitivity C-reactive protein)

While the osteoporosis group is compared with the non-osteoporosis group, there was no difference between age (p=0.14), year of diagnosis of COPD (p=0.57) and the pack-years of smoking (p=0.61). In the osteoporosis group, BMI and FEV_1 were significantly lower (p=0.004, p=0.003; respectively.) than the non-osteoporosis group. There was only one woman who had osteoporosis. There was no significant difference in PaO_2 values between the two groups (p=0.87). In addition, the PCO_2 values were similar (p=0.64). WBC and hs-CRP were significantly higher in those with osteoporosis (p=0.001, p=0.006; respectively.) but there was no significant difference between fibrinogen levels (p=0.10). FeNO values were higher in the osteoporosis group, but there was no statistical difference (p=0.12). The comparison of osteoporosis and non-osteoporosis groups is presented in **Table 2**.

Table 2. Comparison of osteoporosis and non-osteoporosis group

	Normal BMD and Osteopenia group (non-osteoporosis) (n=37)	Osteoporosis group (n=13)	p
Age	61.76 (8.98)	66.46 (9.70)	0.14
Gender F/M	9/28	1/12	
Body mass index	27.51 (27.51)	22.80 (4.53)	0.004*
Diagnosis year of COPD	6.64 (4.41)	7.50 (4.65)	0.57
Smoking (pack-years)	38.92 (18.92)	42.46 (21.95)	0.61
FEV_1 (%)	48.24 (19.09)	31.69 (14.20)	0.003*
PaO_2 (mmHg)	62.57 (12.67)	63.23 (13.14)	0.87
$PaCO_2$ (mmHg)	42.14 (4.23)	42.92 (5.46)	0.64
FeNO (ppd)	19.68 (9.41)	25.54 (11.80)	0.12
Fibrinogen (mg/L)	30.11 (9.33)	36.28 (16.71)	0.10
WBC (x10⁹/L)	7.17 (2.06)	11.25 (3.45)	0.001*
Hs-CRP (mg/L)	13.69 (0.85)	14.60 (1.27)	0.006*

mean (sd), *p-value <0.05 significant, FEV_1 (Forced expiratory volume in 1 second), PaO_2 (Partial oxygen pressure), $PaCO_2$ (Partial carbon dioxide pressure), FeNO (Fractional exhaled nitric oxide), WBC (White blood cells), Hs-CRP (High-sensitivity C-reactive protein)

The association between the presence of osteoporosis with inflammation markers and other variables was examined using univariable logistic regression. Osteoporosis was not associated with age (OR: 1.06, 95% CI, 0.98-1.14; p=0.12). Although it was observed that being male increased the risk 3.85 times, it was not statistically significant (95% CI, 0.43-33.91; p=0.22). Lower BMI levels were associated with increased osteoporosis risk (OR: 0.75, 95% CI, 0.61-0.91; p=0.005). It was observed that the risk increased as FEV_1 decreased (OR: 0.94, 95% CI, 0.89-0.98; p=0.015). It was found that the presence of osteoporosis did not change with PaO_2 levels (OR: 1.01, 95% CI, 0.95-1.05; p=0.57). It was observed that the risk of osteoporosis did not increase with the year of diagnosis of COPD (OR: 1.04, 95% CI, 0.90-1.20; p=0.58). The risk was not affected by the smoking burden (OR: 1.01, 95% CI, 0.97-1.04; p=0.57).

Airway inflammation was not associated with the presence of osteoporosis (OR: 1.05, 95% CI, 0.99-1.12; p=0.85). Similarly, fibrinogen, which is one of the systemic inflammation markers, was not associated with the presence of osteoporosis (OR: 1.04, 95% CI, 0.98-1.09; p=0.12). WBC and hs-CRP were associated with the possibility of osteoporosis (OR: 1.80, 95% CI, 1.26-2.57; p=0.001 and OR: 2.32, 95% CI, 1.28-4.20; p=0.005). The risk of osteoporosis is shown in **Table 3**.

Table 3. The risk of osteoporosis in COPD

	OR (95% CI)	p
Age	1.06 (0.98-1.14)	0.12
Gender (male)	3.85 (0.43-33.91)	0.22
Body mass index	0.75 (0.61-0.91)	0.005*
Diagnosis year of COPD	1.04 (0.90-1.20)	0.55
Smoking (pack-years)	1.01 (0.97-1.04)	0.57
FEV_1 (%)	0.94 (0.89-0.98)	0.015*
PaO_2 (mmHg)	1.01 (0.95-1.05)	0.87
$PaCO_2$ (mmHg)	1.04 (0.90-1.19)	0.58
FeNO (ppd)	1.05 (0.99-1.12)	0.85
Fibrinogen (mg/L)	1.04 (0.98-1.09)	0.12
WBC ($\times 10^9$/L)	1.80 (1.26-2.57)	0.001*
Hs-CRP (mg/L)	2.32 (1.28-4.20)	0.005*

*p-value <0.05 significant, OR>1 implies the probability of osteoporosis, FEV_1 (Forced expiratory volume in 1 second), PaO_2 (Partial oxygen pressure), $PaCO_2$ (Partial carbon dioxide pressure), FeNO (Fractional exhaled nitric oxide), WBC (White blood cells), Hs-CRP (High-sensitivity C-reactive protein)

Multivariate logistic regression analyses were performed based on the risk factors that either reached significance in univariate analyses or that have been established as having a potential impact on osteoporosis. Considering that age and gender have an effect on bone mineral density, the effects of WBC and hs-CRP were examined by adjusting. While the effect of WBC was almost the same (OR: 1.83, 95% CI, 1.22-2.75), a slight decrease was observed in hs-CRP (OR: 2.54, 95% CI, 1.20-5.37). In a model that was adjusted with age, gender, FEV_1 and BMI, both WBC and hs-CRP significantly increased the likelihood of having osteoporosis (OR: 2.26, 95% CI, 1.19-4.30 and OR: 3.36, 95% CI, 1.22-9.22). The results are presented on an oddsplotty in **Figure 1**.

Using the AUC-ROC, predicted probabilities were calculated for the risk of osteoporosis by two systemic inflammation biomarkers that are significant in logistic models (WBC and hs-CRP). The AUC-ROC of the WBC was 0.84 (95% CI, 0.70-0.97) and the cut-off value was 11.6 $\times 10^9$/L (sensitivity 69% and specificity 89%). The AUC-ROC of the hs-CRP was 0.72 (95% CI, 0.53-0.89) and the cut-off value was 15.9 mg/L (sensitivity 69% and specificity 81%). The ROC curves and results are presented in **Figure 2**.

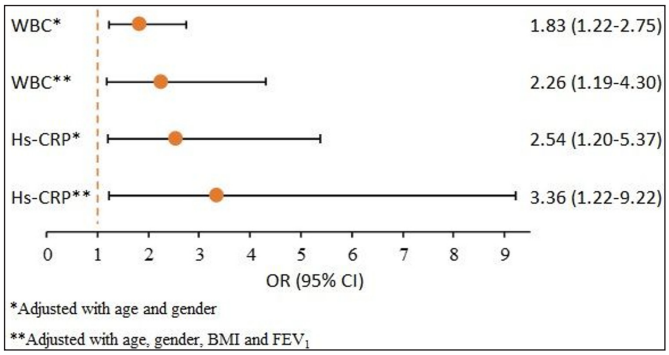

Figure 1. Multivariate logistic regression analysis for the risk of osteoporosis an oddsplotty

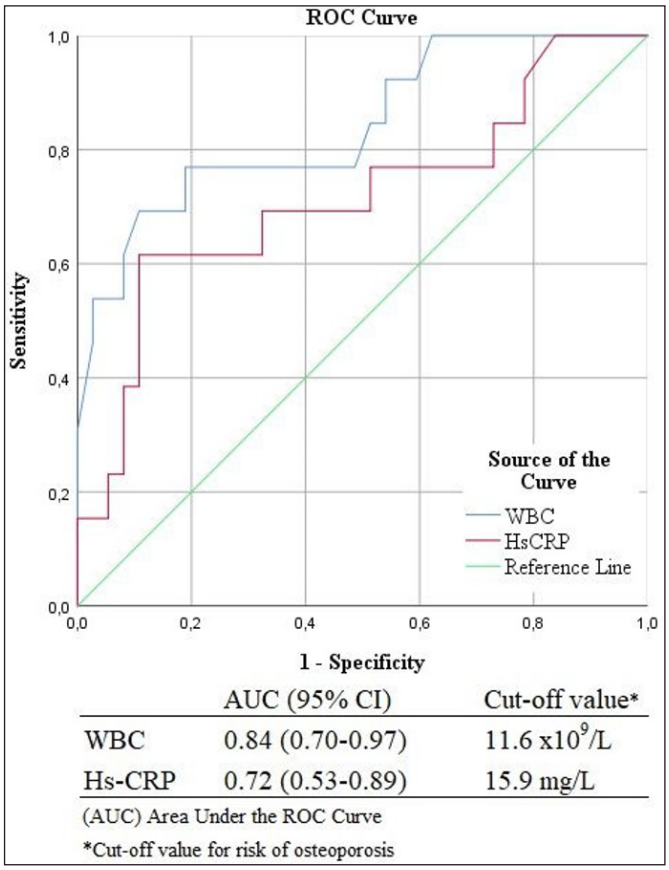

Figure 2. ROC Analysis for the risk of osteoporosis

DISCUSSION

Osteoporosis is a comorbidity with significant sequelae such as vertebral and hip fractures. The disability, which builds on patients who already have shortness of breath and respiratory failure, has extremely negative effects on their quality of life both in the short term and in the long term. At the same time, there is a serious financial loss when considering the treatment of fractures, inpatient stays and loss of workforce. The mechanism of osteoporosis in COPD is complex and multifactorial (11). This study examined the relationship of osteoporosis in COPD with both airway and systemic inflammation. We also examined other factors that may be influential. We found that systemic inflammation, WBC and hs-CRP were strongly associated with osteoporosis (OR: 1.80,

95% CI, 1.26-2.57 and OR: 2.32, 95% CI, 1.28-4.20). We assessed that participants with a lower BMI are more likely to develop osteoporosis (OR: 0.75, 95% CI, 0.61-0.91) and found that the risk of osteoporosis increases with the severity of airway limitation (OR: 0.94, 95% CI 0.89-0.98). In the results of our study, it is known that although the risk of osteoporosis in COPD does not appear to be statistically significant in terms of age and gender, it is more common in the female gender and the risk increases with advancing age in the general population. Considering this situation, when we used age and gender as confounding factors, we observed that the effect of systemic inflammation continued (OR: 1.83, 95% CI, 1.22-2.75 and OR: 2.54, 95% CI, 1.20-5.37). The prevalence of osteoporosis in COPD has been reported to be between 36% and 60%, and osteopenia between 35% and 72% (12). In the present study, the prevalence of osteoporosis in COPD was slightly lower than other data (26%), and the prevalence of osteopenia was 46%. There was a statistically nonsignificant trend toward osteoporosis in males compared with females (OR: 3.85, 95% CI, 0.43-33.91). The reason for this tendency, which is in contrast to other studies (13,14) and the general population, may be that there was only one woman in the osteoporosis group. Our study is a prospective cross-sectional study and better results may be obtained in a larger study population.

FeNO has been shown to be associated with respiratory comorbidities in inflammatory and autoimmune diseases, especially psoriasis (15). Inflammation pathogenesis has also been considered in most comorbidities of COPD. Studies examining the relationship between FeNO and the comorbidities of COPD are rare. FeNO measurements may be useful clinically in COPD patients to determine the level of airway inflammation both at baseline and during therapy in relation to comorbidities such as pulmonary arterial hypertension (PAH) and cardiovascular diseases. The presence of decreased FeNO levels in patients with PAH or atherosclerosis suggests that serial monitoring of FeNO may be beneficial in these comorbidities. Decompensated heart failure was associated with higher FeNO levels (16). In our study, when the groups were compared, there was no statistical difference between FeNO levels and it was seen that FeNO did not affect the risk of osteoporosis (OR: 1.05, 95% CI, 0.99-1.12). However, the FeNO level was higher in the osteoporosis group. The pathophysiological changes found in the lungs in COPD are associated with an inflammatory response. This results in progressive airflow limitation, air trapping, and parenchymal tissue destruction (11). In a study conducted on patients with COPD, the relationship between osteoporosis and emphysema was examined (13). While emphysema was associated with a decrease in BMD, a common inflammatory response was thought to affect both the lungs and bones. Our findings support that systemic findings such as osteoporosis can be preserved in patients where inflammation can remain localized in the airway. We think that airway inflammation does not have a direct effect on osteoporosis. Better analysis of the effect of airway inflammation on systemic inflammation will give more insight into this issue.

There are specific and non-specific causes of the decrease in BMD in COPD. Systemic inflammation is a specific etiopathogenic factor (11). This effect of systemic inflammation on bones has also been shown in various rheumatic and endocrinological diseases (17,18). At the same time, its association with other comorbidities such as atherosclerosis, anemia and PAH in COPD can be attributed to systemic inflammation (19,20). In a study conducted on 102 stable male Thai COPD patients, hs-CRP was used as a systemic inflammation marker (21). Similar to our study, hs-CRP and BMI were found to be associated with osteoporosis. Patients with osteoporosis were compared with normal age matched participants and no difference was found between age, cigarette pack years and FEV_1. The cut-off value for hs-CRP was 2.3 mg/L and the mean value of hs-CRP was 5.9 mg/L. Our cut-off value for hs-CRP was 15.9 mg/L and it was above the upper limit value (15.2 mg/L). The reason for the different results is that the kits used for measurement and the patient populations were different. Another study of male COPD patients in Taiwan revealed that parameters such as increased hs-CRP and decreased body mass index are independent risk factors for the development of osteoporosis, similar to the current study, implying that increased systemic inflammation and possibly decreased muscle mass play important roles in bone loss (22). In a cohort study of 2164 patients with COPD followed for 3 years, high fibrinogen, IL-6 and IL-8 levels were associated with heart disease. Fibrinogen has not been found to be associated with osteoporosis (23). A study of 1634 COPD patients examined the correlation of computer tomography (CT) measured bone attenuation with clinical parameters and inflammatory biomarkers. While CT measured bone attenuation correlated positively with FEV_1, BMI and CRP after adjusting for age, sex and pack-years of smoking, it didn't correlate with fibrinogen and WBC (24). In our study, we also examined the effect of arterial blood gases on osteoporosis. Similar to a previous study (25), we found that PaO_2 and $PaCO_2$ had no effect on BMD (OR: 1.01, 95% CI, 0.95-1.05 and OR: 1.04, 95% CI, 0.90-1.19).

One of the limitations of this study is that it is based on a small group of patients with the characteristics specified in the study population. Although FeNO is a marker of airway inflammation, inflammation in the lung parenchyma may be different. The relationship

between lung inflammation and systemic inflammation was not sufficiently investigated. Factors that may affect osteoporosis, such as vitamin D intake and physical activity, were not adequately questioned. Another limitation is that this study did not include other systemic inflammation markers such as IL-6 or IL-8. Our study was cross-sectional, and measurements were made only once. The situation might be different in a cohort design with repeated measurements.

CONCLUSION

Despite the increasing recognition of the prevalence of osteoporosis in COPD, the underlying pathophysiology and cause are still not fully understood. FeNO was not associated with osteoporosis. Our findings suggest that some biomarkers of systemic inflammation were related to osteoporosis in COPD independent of some predetermined risk factors. According to our findings, patients with high hs-CRP and WBC values may be suitable for osteoporosis scanning. Early treatment of these patients will result in better care and lower morbidity rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 17.12.2012, Decision No: 12/14-02).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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