

Assessment of reduced mineral bone density in COPD

Mona S. El-Hoshy^a, Enas El-Sayed^a, Dalia A. Moaty El-Neely^b

Background Chronic obstructive pulmonary disease (COPD) is responsible for reduced bone mineral density (BMD).

Aim The aim of this study was to explore and assess the association of low BMD with systemic inflammation in patients with COPD.

Patients and methods A total of 10 healthy normal control individuals and 30 patients with clinically stable COPD (Global Initiative for Chronic Obstructive Lung Disease stages I–III) were included in the study and divided into four groups. All patients underwent chest radiography; computed tomographic scan of the chest; spirometry; dual-energy X-ray absorptiometry for measurement of BMD of the lumbar (L) spines, forearm, and femur; and blood sampling for measurement of C-reactive protein (CRP) and total and ionized serum calcium.

Statistical analysis Descriptive data are expressed as mean±SD. Pearson's correlation analysis was used for drawing correlations.

Results Osteoporosis in the spine was detected in 20% of both mild and moderate COPD cases and 100% of severe COPD cases, with statistical significant difference between patients with severe COPD and control group ($P=0.027$). Osteoporosis in the femur bone was shown in 30, 50, and 90% of mild, moderate, and severe COPD cases,

respectively, whereas 20% of moderate and 30% of severe COPD cases had osteoporosis in the forearm. T-scores of BMD were different among the four studied groups ($P=0.0001$). BMD correlated positively with BMI and forced expiratory volume at timed interval 1 s (%) predicted. CRP values differed significantly between the four studied groups ($P=0.0001$). CRP correlated negatively with forced expiratory volume at timed interval 1 s (%) predicted and BMD.

Conclusion CRP is seen in high levels with low BMD in severe COPD, indicating the association of low BMD with systemic inflammation in COPD.

Egypt J Bronchol 2017 11:111–119

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Egyptian Journal of Bronchology 2017 11:111–119

Keywords: BMI, bone mineral density, chronic obstructive pulmonary disease, osteoporosis

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Received 24 October 2016 **Accepted** 12 December 2016

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory pulmonary disease that is now recognized as a systemic disease being complicated by various comorbidities including osteoporosis [1–4]. Recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines reflect the importance of these comorbidities [5–8].

Osteopenia and osteoporosis are prevalent systemic comorbidities of COPD. Osteoporosis is defined by a bone mineral density (BMD) of 2.5 SD below the mean for young adults (T-score ≤ -2.5), as measured by bone densitometry. Osteopenia is considered as a 'preclinical' stage and is defined as a T-score of between -2.5 and -1 [9].

Many risk factors have been described for osteoporosis in COPD especially smoking and systemic inflammation [10]. Tobacco smoke lowers the pH of bone tissue, inducing systemic damage and resulting in bone salts resorption. It also acts indirectly by inducing an inflammatory response in the lungs [11,12].

Another explanation for the low BMD in COPD is physical inactivity. Little or no weight-bearing

exercise increases the risk of developing musculo-skeletal fragility and osteoporosis. As the number of vertebral fractures increases, total lung capacity is progressively compromised, potentiating the already present physical inactivity in those patients. Meanwhile, physical inactivity further increases the risk of vertebral fractures, which may also lead to kyphosis, the latter hinders inspiration and decreases lung function parameters [9% reduction in forced vital capacity (FVC) per fracture, and reduced forced expiratory volume at timed interval 1 s (FEV₁)]. In other words, COPD causes osteoporotic fractures, and these have significant effect on patients' pulmonary functions and daily life performance and possibly their prognosis. Thus, the two diseases will form a vicious cycle, causing significant burden on these patients [12].

Moreover, as osteoporotic fractures augment immobility in patients with COPD, thereby, they increase the risk of deep venous thrombosis and pulmonary embolism.

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Therefore, early detection, appropriate treatment, and timely prevention of osteoporosis should be an important objective in COPD management [13].

Aim

The aim of this study was to assess the association of low BMD with systemic inflammation in patients with COPD.

Patients and methods

The study included 40 participants who were chosen as follows: 10 healthy control individuals (group I) (who had never smoked with no known current lung or cardiovascular disease) and 30 patients with clinically stable COPD, defined as having no requirement for antibiotic or oral corticosteroid therapy and having no change in respiratory symptoms beyond normal day-to-day variation in the preceding month [5], and were current smokers. Patients were admitted to Alexandria University Hospital over a 1-year period between July 2015 and July 2016 in exacerbation with ranging degree of severity of airflow obstruction. Participants were categorized for analysis as 10 patients with mild COPD (group II), 10 patients with moderate COPD (group III), and 10 patients with severe COPD (group IV) using the GOLD staging system according to the results of spirometry [5]. The following patients were excluded from the study: elder age group above 80 years; those who were previously diagnosed with osteoporosis or systemic diseases affecting bone metabolism (e.g. metabolic bone disease as Paget's disease, parathyroid disorder or renal osteodystrophy); those who had received steroids for extended periods; and those with previous bone fractures, vehicle accidents or falls, or pathologic fractures.

Informed consent was obtained from all the participants before the study, and the study protocol was approved by the local Ethics Committee of Alexandria University.

Data were collected from control individuals and all patients using full medical history, including pack-year index formula=number of packs per day×number of years [14]. Dyspnea index score was estimated for both cases and control individuals using the Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness [15]. Full local and general clinical examinations were done for all participants who underwent testing to determine the distance walked in 6 min [16] and estimation of the BMI to calculate the BODE index

which gives a composite score (BMI, Obstruction, Dyspnea and Exercise) [17]. Plain chest radiography, computed tomography of chest, arterial blood gases, and spirometry [18–20] were also performed as recommended by the American Thoracic Society. The following values were evaluated: FEV₁, FVC, and the ratio of FEV₁-to-FVC (FEV₁/FVC). Laboratory investigations included routine measurements in addition to measurement of serum levels of C-reactive protein (CRP) and total and ionized serum calcium. Enzyme-linked immunosorbent assays were used to determine the serum levels of CRP (R&D Systems Inc., Minneapolis, Minnesota, USA) according to manufacturer's instructions [21].

Measurements of bone mineral density in vertebral bone

Bone mineral parameters were measured by using a dual-energy X-ray absorptiometry (DEXA, GE-Lunar Prodigy; GE Healthcare, Houston, Texas, USA) [22] at the lumbar spine (vertebrae L1–L4), forearm, and femur. Parameters were expressed in standard globally accepted terms: BMD (g/cm²). Individual bone density determinations for the study participants were compared with those of young normal control individuals of the same sex. This was done to standardize the BMD measurements to peak bone mass, which occurs at 30 years of age. The BMD is presented as absolute figures, and osteoporosis is defined by T-scores. The BMD measured is therefore correlated with the peak bone mass and is expressed as a T-score, which is the number of SDs below or above peak bone mass for the relevant sex. T-scores equal to or greater than -1.0 represent normal bone density. T-score values between -1.0 and -2.5 are definable for osteopenia, and T-scores below -2.5 are definable for osteoporosis [9].

Statistical analysis

Descriptive data are expressed as mean±SD. Statistical significance of differences between the four studied groups was tested with one-way analysis of variance. Pearson's correlation analysis was used to know relationship between a parameter of BMD and each variable. Statistical analysis was performed using SPSS-PC for Windows, version 17.0 (SPSS Inc., Chicago, Illinois, USA). To find out independent correlates of BMD, multiple linear regression analysis was used. Statistical significance was accepted at *P* value less than 0.05.

Results

Table 1 shows the results of the studied parameters in the four studied groups. The age ranged between 33 and 78 years and showed statistical significant

Table 1 Results of some parameters in the four studied groups

	Group I (control) (n=10)	Group II (mild COPD) (n=10)	Group III (moderate COPD) (n=10)	Group IV (severe COPD) (n=10)	P value
Age (years)	51.42±9.43	47.65±7.67	54.2±3.54	62.2±9.09	0.021*
Smoking index	5.88±8.61	17.8±11.2	33±9.276	37.67±25.8	0.0001*
BMI (kg/m ²)	26.22±2.23	27.34±2.169	26.3±4.72	23.04±5.86	0.004*
Grade of dyspnea according to MRC	1±0	2.6±0.894	2.43±0.62	3.02±0.51	0.0001*
6MWD (m)	99.48±7.9	74.8±6.87	61.12±13.65	43.5±5.97	0.0001*
FVC% predicted	108.89±12.6	101.89±3.44	96.32±14.67	86.54±3.78	0.0001*
FEV ₁ % predicted	88.09±4.30	81.18±0.96	67.43±7.45	42.87±5.32	0.0001*
FEV ₁ /FVC	91.34±7.35	61.39±2.15	59.23±6.98	55.36±3.26	0.0001*
BODE index	1.67±1.5	1.34±0.08	3.24±1.12	5.3±1.29	0.0001*
pH	7.42±0.01	7.41±0.01	7.36±0.01	7.35±0.01	0.0001*
PaO ₂	78.82±2.56	77.76±3.67	72.5±4.56	67.45±0.96	0.0001*
SaO ₂	96.85±0.78	94.32±1.12	92.53±0.07	88.98±1.45	0.0001*
PaCO ₂	32.57±1.34	39.89±1.09	39.97±1.14	59.57±2.98	0.0001*
Serum calcium (mg/dl)	8.06±0.73	7.89±0.93	7.26±0.59	5.30±0.95	0.0001*
Ionized calcium (mmol/l)	1.15±0.04	1.01±0.02	1.16±0.03	1.19±0.02	0.0001*
C-reactive protein	6.0±6.0	16.81±11.23	23.67±12.54	38.69±11.12	0.0001*

Data are presented as mean±SD. BMD, bone mineral density; BODE, BMI, Obstruction, Dyspnea and Exercise; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; 6MWD, 6-min walk distance; MRC, Modified Medical Research Council. **P*<0.05, significant.

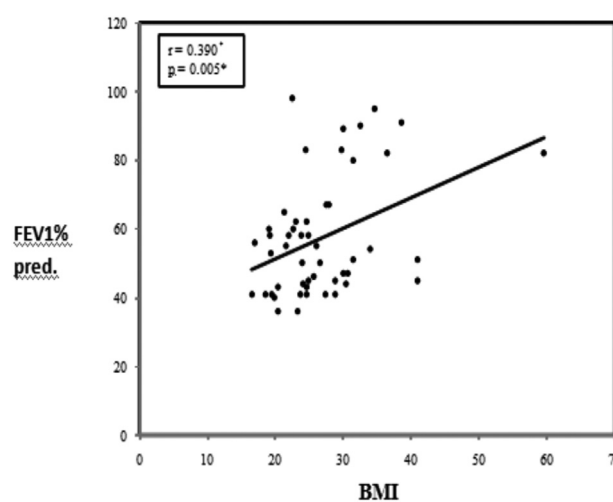
difference between studied groups (*P*=0.021). Overall, 100% of controls and patients were males. Smoking index was significantly higher in patients with moderate and severe COPD than controls (*P*=0.0001 and 0.0001, respectively).

Regarding evaluation of dyspnea, BMI values showed statistically significant difference between each of the groups II, III, and IV and control group. BMI decreased with increased severity of COPD. There was a statistical significant direct correlation between BMI and FEV₁% predicted (Fig. 1). Also, there was a statistical significant direct correlation between BMI and DEXA scan, that is, BMD.

Regarding spirometric data, FEV₁, FVC, and FEV₁/FVC showed a statistical significant difference between each of the groups II, III, and IV and control group. There was an inverse correlation between FEV₁% predicted and CRP and a statistical significant direct correlation between FEV₁% predicted and DEXA scan, that is, BMD.

Values of 6-min walk distance showed statistical significant differences between the four studied groups (*P*=0.0001), and a statistically significant direct correlation with FEV₁% predicted (Fig. 2).

Grade of dyspnea according to Modified Medical Research Council showed a statistical significant difference between the four studied groups and a statistically significant inverse correlation with

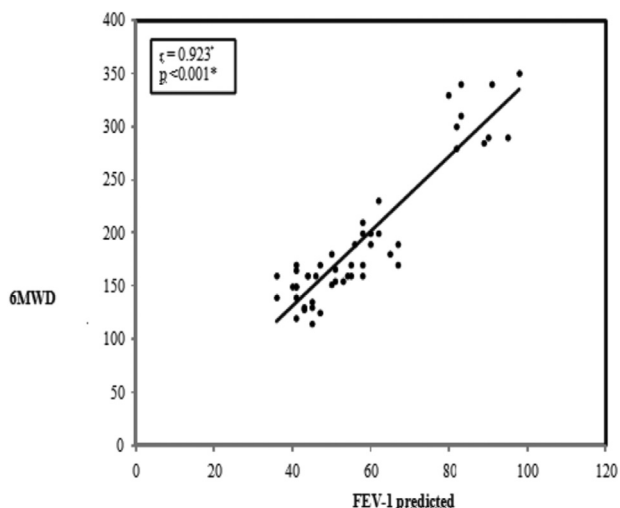
Figure 1

Correlation between BMI and FEV-1 predicted: forced expiratory volume in 1 sec.

FEV₁% predicted (Fig. 3). BODE index showed a statistical significant difference between the four studied groups, and a statistically significant inverse correlation with DEXA scan (Fig. 4) and ionized calcium, and a statistically significant direct correlation with CRP level.

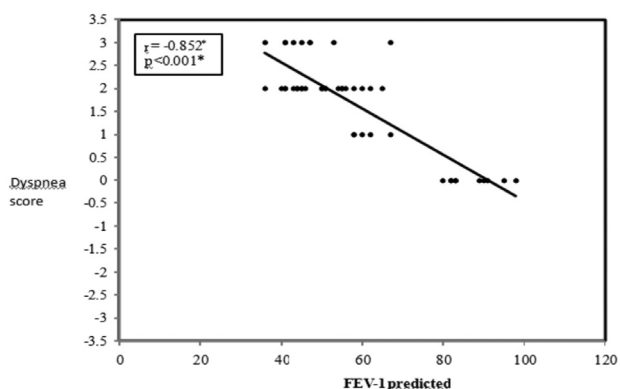
Values of pH, PaCO₂, PaO₂, SaO₂ showed statistically significant differences between the four studied groups (*P*=0.0001). There was a statistically significant direct correlation between FEV₁% predicted and PaO₂ and statistically significant inverse correlation between FEV₁% predicted and PaCO₂.

Figure 2



Correlation between 6MWD and FEV₁% predicted. FEV₁: forced expiratory volume in 1 s; 6MWD: 6-min walk distance.

Figure 3



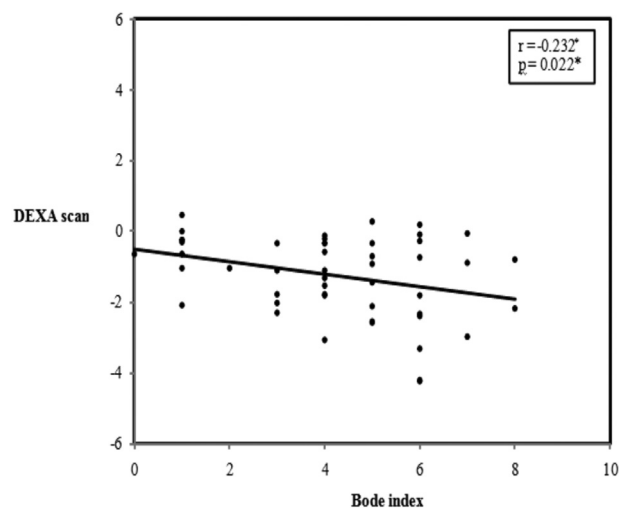
Correlation between FEV-1 predicted and dyspnea score.

Values of serum calcium presented in Table 1 revealed a statistical significant difference between each of severe and moderate groups as compared with the control group ($P=0.0001$ and 0.0001 , respectively). Also there was a statistical significant difference between the four studied groups regarding ionized calcium. Serum calcium correlated inversely with BODE index (Fig. 5), whereas serum and ionized calcium correlated positively with BMD.

CRP values (Table 1) showed a statistically significant difference between the four studied groups ($P=0.0001$). CRP correlated negatively with FEV₁% predicted (Fig. 6) and BMD and positively with BODE index (Fig. 7).

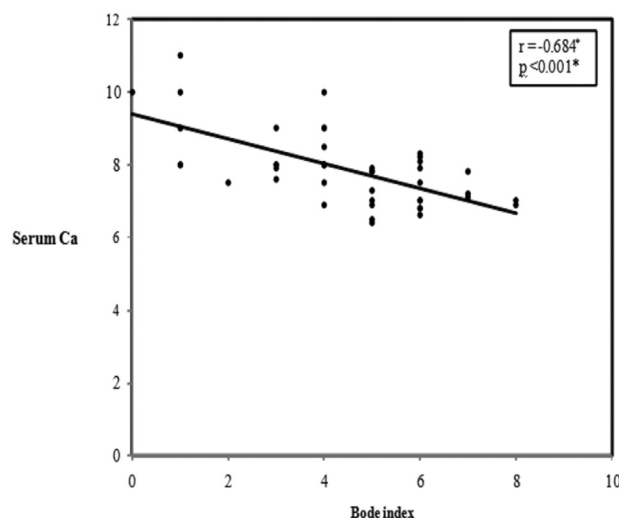
Table 2 shows a comparison between the different studied groups according to T-score of DEXA scan. There was a statistical significant difference

Figure 4



Correlation between bode index and DEXA scan.

Figure 5



Correlation between BODE index and Serum Ca.

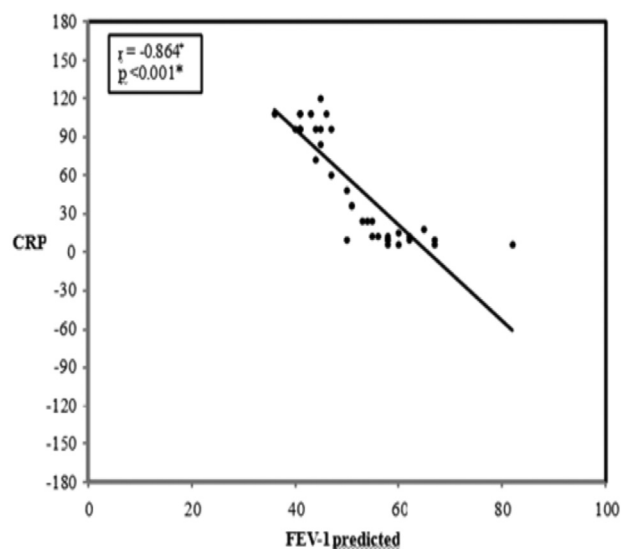
between T-scores of the four studied groups ($P=0.0001$).

Table 3 shows that 20% of mild and moderate COPD cases had osteoporosis in the spine, whereas 100% of severe COPD cases had osteoporosis in the spine, with statistically significant difference between patients with severe COPD and control group ($P=0.027$). The study revealed no statistically significant difference either between patients with mild or moderate COPD and control group regarding osteoporosis in the spine ($P=0.217$ and 0.091 , respectively).

Osteoporosis in the femur bone was shown in 30% of mild, in 50% of moderate, and in 90% of severe COPD cases. The study revealed a statistically significant

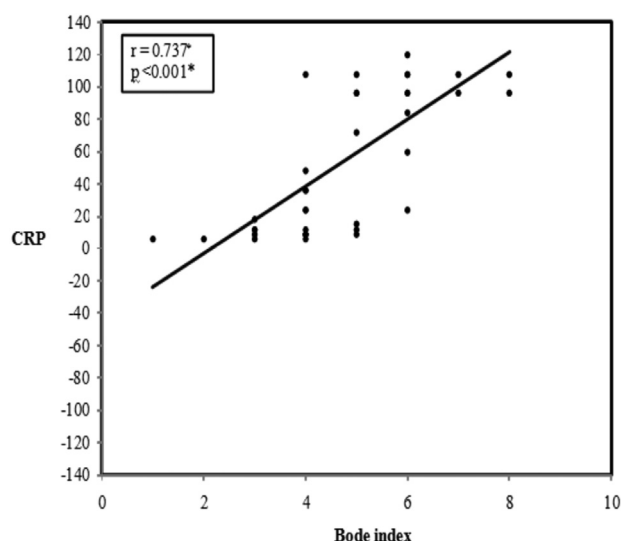
difference between patients with moderate COPD and control group ($P=0.048$) and between patients with severe COPD and control group regarding osteoporosis in the femur bone ($P=0.004$).

Figure 6



Correlation between FEV-1 predicted and CRP.

Figure 7



Correlation between bode index and CRP.

Table 3 also shows that none of mild cases, 20% of moderate, and 30% of severe COPD cases had osteoporosis in the forearm, with no statistically significant difference between patients with severe COPD and control group ($P=0.127$) or between patients with moderate COPD and control group regarding osteoporosis in the forearm ($P=0.221$).

BMD (DEXA scan) correlated positively with BMI (Fig. 8) and FEV₁% predicted (Fig. 9), indicating that BMI and degree of severity of COPD are predictive of BMD. There was a negative correlation between BMD (DEXA scan for spine, femur, or forearm) and CRP, indicating that BMD decreases with systemic inflammation. However, there was a positive correlation between BMD and serum total and ionized calcium.

Discussion

Up to date, cigarette smoking is the most important risk factor for long-term obstructive pulmonary disease [22]. In all those who smoke, smoking elicits airway inflammation, which becomes persistent in those who develop airflow obstruction, even after cessation of smoking [23]. This has created the concept that cigarette smoke evokes an abnormal inflammatory response that leads to the development in susceptible individuals of COPD with a vast spectrum, airway narrowing at one end and emphysema on the other, with most patients existing somewhere in the middle [24].

Smoking is also the most important risk factor for many comorbidities of COPD, including coronary heart disease, heart failure, and lung cancer. Some of these comorbidities are directly caused by COPD such as pulmonary artery disease and malnutrition, whereas others, such as systemic hypercoagulable state, osteoporosis, anxiety, depression, diabetes, sleep disturbance, and anemia, exist with COPD with no evident physiopathological relationship. Long-term systemic inflammation is the common ground between most of these extrapulmonary manifestations. These comorbidities make the management of COPD difficult. Consequently, they lead to increased

Table 2 Comparison between the different studied groups according to T-score of dual-energy X-ray absorptiometry scan

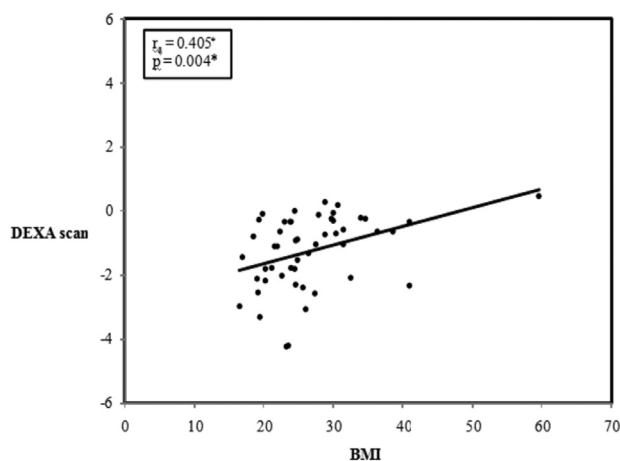
T-score	Control (n=10)	Mild (n=10)	Moderate (n=10)	Severe (n=10)
Mean±SD	-1.26±0.87	-1.59±1.40	-2.53±0.68	-3.46±1.27
P			0.0001*	
P ₁	-	0.030	0.000	0.000
P ₂	-	-	0.002	0.000
P ₃	-	-	-	0.569

P₁ is the level of significant difference between group I (mild) and the other studied groups. P₂ is the level of significant difference between group II (moderate) and the other studied groups. P₃ is the level of significant difference between group III (severe) and the other studied groups. *Statistically significant at $P \leq 0.05$.

Table 3 Comparison between the different studied groups regarding presence of osteopenia or osteoporosis

	Control (n=10) [n (%)]	Mild (n=10) [n (%)]	P value (mild vs. control)	Moderate (n=10) [n (%)]	P value (moderate vs. control)	Severe (n=10) [n (%)]	P value (severe vs. control)
Spine							
Normal	7 (70)	1 (10)	0.124	0 (0)	0.063	0 (0)	0.288
Osteopenic	3 (30)	7 (70)	0.346	8 (80)	0.114	0 (0)	0.354
Osteoporotic	0 (0)	2 (20)	0.217	2 (20)	0.091	10 (100)	0.027*
Femur							
Normal	10 (100)	3 (30)	0.675	3 (30)	0.354	0 (0)	0.319
Osteopenic	0 (0)	4 (40)	0.438	2 (20)	0.325	1 (10)	0.421
Osteoporotic	0 (0)	3 (30)	0.762	5 (50)	0.048*	9 (90)	0.004*
Forearm							
Normal	10 (100)	8 (80)	0.537	0 (0)	0.281	0 (0)	0.211
Osteopenic	0 (0)	2 (20)	0.243	8 (80)	0.326	7 (70)	0.402
Osteoporotic	0 (0)	0 (0)	0.311	2 (20)	0.221	3 (30)	0.127

*Statistically significant at $P \leq 0.05$.

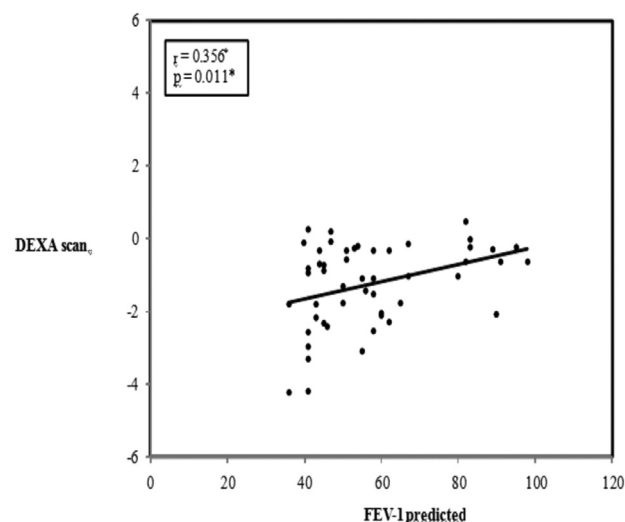
Figure 8

Correlation between BMI and DEXA scan.

hospitalizations and healthcare costs, as they potentiate the morbidity of COPD and can frequently cause death, independently of respiratory failure. Thus, there is always a need to evaluate these comorbidities to adequately treat them [10].

Osteoporosis is one of the systemic effects of smoking in COPD [1]. Bone disorders prevalence increases with age: it is estimated that 8–18% of females and 5–6% of males aging 50 years have osteoporosis. Thus, osteoporosis is to be expected in COPD, the latter being a disorder of the second half of life [25].

Ward and Klesges showed a dose-dependent, cumulative, independent effect of smoking on bone mass. They demonstrated significantly reduced bone mass in smokers particularly men and elderly as compared with nonsmokers at several major sites of osteoporosis-related fractures, including the hip, lumbar spine,

Figure 9

Correlation between FEV-1 predicted and DEXA scan.

and forearm, but the effect was most pronounced at the hip [26]. Smoking induces osteoporosis by several potential mechanisms including effects on collagen metabolism and bone angiogenesis, altered metabolism of calcitropic hormone; dysregulation in the production, metabolism, and binding of estradiol; and altered metabolism of adrenal cortical hormone [27].

In the present study, all patients (100%) with severe COPD were osteoporotic in the spine whereas osteoporosis was detected in 20% of moderate and mild COPD cases. There was a statistically significant difference between the T-score of BMD of the four studied groups ($P=0.0001$) at the spine and femur but not at the forearm. BMDs at the lumbar spine, femur, and forearm were lower in patients with severe COPD

than in patients with mild and moderate COPD and also than in controls. This indicates that osteoporosis and a low BMD increases with a higher GOLD stage (increased severity of COPD according to GOLD staging).

Dam *et al.* [28] stated that men with COPD or asthma had lower total hip, femoral neck, and spine BMD compared with healthy controls. Duckers and colleagues demonstrated that hip BMD was lower in patients with COPD; however, lumbar spine measurements were not different. This finding may reflect physical deconditioning or different bone compositions [29].

Liu and colleagues reported that patients with COPD have an increased prevalence of osteoporosis compared with healthy people. The mean age of their patients was 70 years [30]. Vrieze *et al.* [31] reported a rise in the prevalence from 28.6% in GOLD stage II to 75.0% in GOLD stage IV. Other studies reported variable prevalence of osteoporosis in patients with COPD: 50, 49, and 60%, respectively. However, the mean age of their patients was 72, 70, and 71 years, respectively [32–34].

BMI values in the present study showed a statistical significant difference among the studied groups with a significant direct correlation between BMI and FEV₁% predicted suggesting a relationship between low BMI and increased severity of COPD. The present study showed that BMD correlated positively with BMI and FEV₁% predicted, so the degree of osteoporosis increased with increase in severity of COPD.

Sim and colleagues reported that BMI is the most important factor related to BMD. In the general population, low BMI has also been identified as a risk factor for osteoporosis. Increased systemic inflammation in COPD and/or other proteolytic mechanisms could be the link between low BMI and low BMD in COPD [24,35–40]. Another explanation for more osteoporosis in patients with lower BMI could be that patients with COPD have been shown to be physically inactive compared with healthy participants [41]. Hence, these patients have relatively low mechanical loading on their bones with consequent decreased bone formation and low BMD [42].

In the present study as well as others [31,39], FEV₁ was related to BMD. This is different from the study of Ohara *et al.* [40] who showed that the extent of emphysema and BMI were predictive of BMD rather than FEV₁. Also, in individuals without COPD, significant correlations between FEV₁ and BMD have been found [43,44].

CRP, one of the acute-phase reactants synthesized by hepatocytes in systemic inflammation, has been found in patients with COPD of the present study in increased amounts. CRP values showed a statistical significant difference between the four studied groups ($P=0.0001$). There was a statistical significant direct correlation between CRP and BODE index and an inverse correlation between CRP and FEV₁% predicted which indicates the increase of CRP with increase of the severity of the disease. CRP correlated inversely with 6-min walk test indicating that 6-min walk distance decreased with increased markers of inflammation in patients with COPD.

Urboniene *et al.* [45] found that in patients with COPD, CRP level correlated with FEV₁, FEV₁/FVC, and pack-years index, and this supports the hypothesis that systemic inflammation plays a role in the pathogenesis of COPD. Fogarty *et al.* [46] in a cross-sectional analysis of data from 1991 and 2000 found that serum CRP levels were inversely related to FEV₁ and FVC. Rasmussen *et al.* [47] found that CRP levels were higher in patients with COPD than in controls, and the level of CRP increased with decline in FEV₁.

Conclusion

This study shows that a low BMD is frequently present in COPD. Advanced COPD and low BMI are risk factors for the presence of low BMD. Abnormal BMD is seen in 100% of patients with severe COPD. Low BMI and FEV₁ are the most important predictors of low BMD in patients with COPD. Since CRP is seen in high levels with low BMD in severe COPD, it is also concluded that systemic inflammation in COPD is closely associated with the low BMD encountered in those patients.

Future studies are needed to determine the best way to identify high-risk patients and whether early treatments such as lifestyle interventions or medications are able to reverse the osteoporotic process.

Acknowledgements

Authors' contribution: Mona El-Hoshy: application of the concept, design and definition of intellectual content, literature search, performing clinical studies, data acquisition and analysis, manuscript preparation, editing and reviewal; Enas M. El-Sayed: application of the concept, design and definition of intellectual content, literature search, performing clinical studies, data acquisition and analysis; Dalia A. El Moaty El-Neely: data analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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