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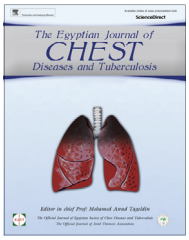

ORIGINAL ARTICLE

Assessment of osteoporosis in patients with chronic obstructive pulmonary disease

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KEYWORDS

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Abstract *Background:* COPD is a widely distributed disease with high morbimortality, associated with important pathologies, among which is osteoporosis. However, osteoporosis is often undiagnosed in these patients.

Objectives: To evaluate the prevalence of osteoporosis among COPD patients and to determine its relation to demographic data and disease severity.

Subjects and methods: This study was conducted on 30 male patients with severe to very severe COPD, in addition to 30 age and sex matched lifelong nonsmoker healthy volunteers. Spirometric indices, serum Ca, phosphorous, ALP, albumin, and PTH were measured. BMD was measured by broadband heel ultrasound method.

Results: Corrected Ca was significantly decreased, PTH was significantly increased and ALP showed non-significant increase in the COPD group. As regards BMD; BUA, Z-score and T-score were significantly decreased while RRF was significantly increased in the COPD group. In addition 56.6% of COPD patients had low BMD. Both COPD group either with normal BMD or with low BMD were matched as regards all demographic data. VC%, FVC% and FEV_1%, BUA, T-score,

Abbreviations: COPD, chronic obstructive pulmonary disease; S. index, smoking index; cor. Ca, corrected calcium; ph, phosphorous; ALP, alkaline phosphates; PTH, parathormone hormone; VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory flow in first second; BMI, body mass index; BMD, bone mineral density; DXA, dual energy absorptiometry; BUA, broadband ultrasonic attenuation; RRF, relative risk of fracture.

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and Z-score were significantly decreased while PTH and RRF were significantly increased in the COPD group with low BMD. Z-score was negatively correlated with FEV_1 and PTH while BUA was positively correlated with ALP and negatively correlated with FEV1/FVC.

Conclusion: Low BMD is prevalent among men with COPD (*GOLD stage III–IV*) than age matched males. The degree of the loss of BMD has been found to be proportionate to the COPD severity. COPD patients with low BMD have threefold increase in fracture risk.

Introduction

COPD is considered to be a chronic non specific inflammation, which occurs in the airways, lung parenchyma and pulmonary vessels. This can cause the activation of inflammatory cells and the release of various inflammatory mediators [1]. It is considered as a syndrome of chronic wasting, and associated with a chronic inflammatory response [2].

Osteoporosis is a systemic skeletal disease characterized by a low bone mass and/or microarchitectural deterioration of bone tissue leading to increased bone fragility and increased fracture risk [3]. Osteoporosis is often disabling in COPD patients, and may be equally disabling as COPD itself. However, osteoporosis is often undiagnosed in these patients, and may impair respiratory function even further, if the patient experiences vertebral compressions and loss of height. Increased awareness is therefore essential in order to diagnose and treat bone loss to reduce the risk of fractures [4].

Aim of the work

The majority of COPD patients in clinical practice are men of older age with many under-diagnosed additional risk factors for osteoporosis. Therefore this study is carried out to evaluate the prevalence of low BMD (osteopenia or osteoporosis) among patients with COPD and to determine its relation to sociodemographic data and to disease severity.

Subjects and method

This case control study included 60 individuals. All patients and healthy controls were males to avoid effect of sex hormones on BMD. Written informed consent was obtained from all participants before study inclusion, and the study was approved by the institutional ethical review board of Al-Azhar University, Faculty of Medicine for Girls. They were divided into 2 groups:

- COPD group: Included 30 COPD patients with symptoms of chronic airflow limitation and fulfilled lung function criteria as set out by the GOLD 2011 [1]. Most of them were using medications to treat COPD, including β2-agonists (salbutamol and formetrol), theophyline and inhaled corticosteroids (budesonide), none of them was using oral steroids during the time of the study.
- Control group: Included 30 healthy life long non smoker, sex and age-matched volunteers, who have no symptoms or signs of any chest disease or other chronic diseases and normal spirometry. Screening of control subjects for study inclusion involved a medical history, clinical examination, serum investigation, electrocardiogram, and spirometry.

Subjects known to have bronchial asthma, interstitial lung diseases, renal, hepatic, cardiac, metabolic, and endocrinal disorders that could affect serum calcium or BMD were excluded from the study. Moreover, patients known to have a known cause for osteoporosis or those receiving systemic corticosteroids were excluded from the study.

All subjects were underwent the following

Detailed history taking, complete clinical examination with special emphasis on musculoskeletal system. Fasting, postprandial blood sugar, liver and renal function tests were done. Measurements of serum calcium (Ca), phosphorus (ph), albumin, alkaline phosphatase (ALP) and serum parathormone hormone (PHT) were done to differentiate between different types of bone pathology (osteoporosis, osteopenia, osteopetrosis, osteomalacia, osteitis fibrosa cystica and Paget disease of bone), moreover, serum Ca and serum albumin were used to calculate corrected Ca (cor. Ca) to avoid the effect of hypoalbuminaemia on serum Ca.

Spirometry was performed using Spirosift spirometry 5000 FUKUDa DENSHI. The following indices were recorded (VC, FVC, FEV_1, $FEF_{25–75}$ and FEV_1/FVC ratio). The highest values of FEV_1 and FVC from at least three technically accepted measurements were used for analysis [1].

We use broadband heel ultrasound attenuation bone densitometry to measure BMI. The BMD of the left heel bone was measured. The system incorporates two ultrasound transducers positioned opposite to each other, touching the lateral aspects of the heel that is being placed in between the transducers. The densitometer measures the broadband ultrasonic attenuation (BUA) in dB/MHz of an ultrasound beam that passes through the calcaneus. It makes an estimation of BMD and the T-score from this data by the system software. The T-score quantifies the difference between the patient's BMD and the mean value for healthy young adults from the reference group. According to WHO, the normal value for T-score is within 1 SD of the mean value for young adults (−1 to +1). Osteopenia is considered when T-score is between −1 and −2.5. Osteoporosis is considered to be present when the value for BMD is less than −2.5 SD below the mean for young adults [5].

However, the International Society for Clinical Densitometry states that, for premenopausal women, Z-scores (*comparison with age group rather than peak bone mass*) rather than T-scores should be used, and the diagnosis of osteoporosis in

such women also should not be made on the basis of densitometric criteria alone [6]. So in this study we diagnose low BMD on the bases of both T-score and Z-score.

Statistical presentation and analysis of the study data were conducted, using SPSS V17. $p > 0.05$ is considered non-significant, $p < 0.05$ is considered significant while $p \leqslant 0.01$ is considered highly significant.

Results

Table 1 shows that Corrected Ca was significantly decreased (p 0.05), while PTH was significantly increased ($p < 0.01$) and ALP was non-significantly increased in the COPD group (p 0.052). BUA, Z-score and T-score were significantly decreased ($p < 0.01$) while RRF was significantly increased in the COPD group than control group.

Table 2 shows that Z-score was negatively correlated with FEV_1, RRF and PTH and positively correlated with BUA and T-score. T-score was positively correlated with BUA and negatively correlated with RRF. BUA was negatively correlated with RRF. On the other hand RRF was not correlated with sociodemographic data, spirometric-indices, and bone profile ($p > 0.05$).

COPD group is divided into two subgroups: COPD with low BMD 17 patients (56.6%) and COPD with normal BMD 13 patients (43.4%). Both groups were matched as regards all sociodemographic data. VC%, FVC% and FEV_1%, BUA, T-score and Z-score were significantly decreased while PTH and RRF were significantly increased in the COPD group with low BMD than the COPD group with normal BMD ($p < 0.01$) (Table 3).

Table 1 Comparison of all variables between COPD group and control group.

Item	COPD (No. 30) Mean ± SD	Control (No. 30) Mean ± SD	t	p
Demographic-data				
Age	60.9 ± 5.4	59.6 ± 5.6	2.25	0.06
BMI	26.5 ± 5.5	25.9 ± 2.5	2.28	0.052
D.D	12.9 ± 9.3	–	–	–
S. index	914.0 ± 745.5	–	–	–
Spirometric-indices%				
VC%	34.8 ± 12.6	84.0 ± 8.8	17.4	< 0.01
FEV_1/FVC	61.7 ± 9.1	84.8 ± 6.3	16.3	< 0.01
FEV_1	24.2 ± 10.6	106.9 ± 23.4	17.5	< 0.01
FVC	27.7 ± 12.3	99.0 ± 20.3	11.4	< 0.01
$FEF_{25–75}$	19.5 ± 14.0	80.6 ± 7.8	20.7	< 0.01
Bone profile				
Cor.Ca	9.0 ± 0.8	9.5 ± 0.6	0.28	0.02
Ph	3.8 ± 0.4	4.0 ± 0.39	1.65	0.11
ALP	196.0 ± 66.4	167.0 ± 43.2	2	0.052
PTH	89.6 ± 50.1	53.7 ± 11.8	3.8	< 0.01
BMD				
BUA	57.3 ± 7.3	65.1 ± 4.7	4.9	< 0.01
Z score	−1.4 ± 1.1	0.28 ± 0.9	6.3	< 0.01
T score	−2.3 ± 1.1	−0.8 ± 0.9	5.45	< 0.01
RRF	7.0 ± 8.0	2.1 ± 1.23	3.33	< 0.01

Discussion

COPD and osteoporosis are strongly associated because of common risk factors such as age, smoking, and inactivity. In addition, COPD-related systemic inflammation, vitamin D deficiency, and the use of systemic corticosteroids enhance ongoing bone destruction [7].

In this study BMD was assessed by broadband heel ultrasound attenuation bone densitometer because it is readily available and easy to perform, but this method is not considered a gold standard as dual energy absorptiometry (DXA), however, it has a comparable accuracy to DXA [8].

In this study COPD patients and control subjects were age, sex and BMI matched (Table 1), all subjects in this study were male to avoid the effects of sex hormones in BMD. The incidence of osteoporosis is higher in women than in men, and it could be expected that women with COPD would be even more susceptible to develop osteoporosis than women with normal lung function [4]. Moreover, the most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; oestrogen deficiency following menopause or oophorectomy is correlated with a rapid reduction in BMD, while in men, a decrease in testosterone levels has a comparable (but less pronounced) effect [9].

This study demonstrated that corrected serum Ca, ph, ALP and PTH for COPD group and control group were in normal ranges, however the corrected serum Ca was significantly decreased, ALP was non-significantly increased, while PTH was significantly increased in the COPD group than the control group (Table 1). These findings of bone profile indicate that all COPD patients and control subjects in this study did not have any bone pathology other than osteoporosis or osteopenia.

The current study showed Z-score (−1.46 ± 1.15) for COPD and (0.28 ± 0.97) for control group, and T-score (−2.36 ± 1.17) for COPD and (−0.80 ± 0.96) for control group. In addition, the 2 indices were significantly lower in the COPD group than the control group ($p < 0.001$). Moreover, both T-score and Z-score for the COPD group were in osteopenic range. On the other hand RRF was significantly higher in the COPD group than the control group (7.06 ± 8.00 and (2.14 ± 1.23 respectively) ($p < 0.01$) (Table 1). This finding means that COPD patients had threefold increased risk of fracture than healthy subjects of same age and sex. Jørgensen et al. [4] reported that the mean ± SD of T-score at lumbar spine was −1.54 ± 7 1.27 while that at femoral neck −1.49 ± 7 1.63.

In the current study Z-score was negatively correlated with FEV_1%, RRF and PTH, while it positively correlated with BUA and T-score ($p < 0.01$). T-score was positively correlated with BUA and negatively correlated with RRF. Lastly BUA was negatively correlated with RRF (Table 3).

Correlation of BMD with BMI had been reported in several studies [10–15]. Moreover age, and PTH level were significant independent correlates for osteoporosis [10,11]. Jorgensen and Schwartz [16] reported that the BMD was strongly correlated with reduced FFV_1%. Scanlon et al. [17] have found age > 56 years and female sex to be independent correlates of osteoporosis in COPD. Different results were reported by WHO [5] that PTH is negatively associated with BMD.

Table 2 Correlation between BMD-Indices and different variables among COPD group.

Item	Z-score		T-score		BUA		RRF	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	−0.07	0.72	−0.26	0.16	−0.35	0.06	0.25	0.18
Smoking index	−0.10	0.60	−0.19	0.31	−0.14	0.45	0.21	0.28
COPD duration	−0.23	0.23	−0.25	0.19	−0.26	0.17	0.17	0.38
BMI	−0.20	0.29	0.01	0.94	0.12	0.52	−0.01	0.94
VC%	−0.29	0.13	−0.23	0.23	−0.18	0.36	0.21	0.27
$FEV_1/FVC\%$	0.09	0.66	0.05	0.78	0.08	0.69	0.11	0.56
$FEV_1\%$	−0.39	0.03*	−0.33	0.07	−0.23	0.22	0.33	0.08
FVC%	−0.35	0.06	0.26	0.17	−0.19	0.33	0.16	0.39
$FEF_{25-75\%}$	−0.28	0.14	0.27	0.16	−0.18	0.34	0.30	0.11
Corrected Ca	0.22	0.25	0.15	0.43	0.12	0.53	−0.07	0.70
Serum ph	−0.16	0.39	−0.06	0.75	−0.10	0.61	−0.04	0.85
ALP	−0.31	0.10	−0.26	0.17	−0.26	0.16	0.16	0.39
PTH	−0.35	0.04*	−0.16	0.39	0.12	0.54	−0.05	0.80
BUA	0.76	< 0.01*	0.94	< 0.01*	–	–	–	–
T-score	0.83	< 0.01*	–	–	–	–	–	–
RRF	−0.73	< 0.01*	−0.86	< 0.01*	−0.84	< 0.01	–	–

* *p* value is significant.

Table 3 Comparison of all variables between patients with normal and lowBMD among COPD group.

Item	COPD with low BMD (No. 17) Mean ± SD	COPD with normal BMD (No. 13) Mean ± SD	*t*	*p*
Sociodemographic data				
Age	61.4 ± 6.3	60.3 ± 4.3	0.51	0.61
BMI	27.1 ± 6.6	25.7 ± 4.0	0.71	0.48
D.D	14.2 ± 10.5	11.3 ± 7.7	0.85	0.40
S. index	902. 4 ± 859.8	929.2 ± 597.7	0.1	0.92
Spirometric-indices%				
VC	29.2 ± 10.5	39.1 ± 12.8	2.30	0.03*
FVC	21.9 ± 8.7	32.1 ± 13.1	2.43	0.02*
FEV_1	19.9 ± 7.8	27.5 ± 11.5	2.10	0.05
FEV_1/FVC	63.7 ± 8.4	60.3 ± 9.6	1.01	0.32
FEF_{25-75}	16.5 ± 10.1	21.9 ± 16.3	1.05	0.30
Bone profile				
Cor. Ca	8.95 ± 0.8	9.2 ± 0.9	0.89	0.38
ALP	208.5069.8 ±	179.8 ± 60.5	1.18	0.25
PTH	105.71 ± 48.2	68.54 ± 46.1	2.13	0.04
BMD				
BUA	53.3 ± 6.7	62.5 ± 4.2	4.30	0.01*
T-score	−3.0 ± 0.9	−1.4 ± 0.7	4.84	0.00*
Z-score	−1.4 ± 1.1	0.28 ± 0.9	6.3	0.01*
RRF	10.07 ± 9.6	3.1 ± 1.3	2.9	0.00*

* *p* value is significant.

On the basis of both T-score (WHO) and Z-score we further classify COPD patients into 2 groups; COPD with normal BMD and COPD with low BMD. Our results showed low BMD (osteopenia or osteoporosis) in approximately 56.66% (17/30) of the COPD group. None of these patients suffered from any symptoms related to fracture or any history of previous fractures. Thus, a large number of COPD patients have established osteopenia or osteoporosis and they do not receive any treatment.

Parthasarathi et al. [8] found that 73% of COPD patients (GOLD- IV) had low BMD and 27% had normal BMD. This slightly higher prevalence of low BMD reported by them may be attributed to the fact that their patients were male and female (35:2 ratio) while our study was conducted only on male subjects and also their patients were more older (65.32 ± 9.58 years) than those in the current study. Similar high prevalence of osteoporosis among COPD patients was reported by Graat-Verboom et al. [11]as they concluded that among clinically stable COPD patients, 51% had radiologic evidence of osteoporosis. Moreover, combining the results of local DXA with spinal X-rays augmented the proportion of COPD patients with osteoporosis compared with both

methods separately. Also Jorgensen and Schwartz [16] reported higher prevalence of low BMD among COPD as they found reduction of BMD in about 50% of COPD patients. TORCH Study Group [18], (*Towards a Revolution in COPD Health*) over half of the COPD patients recruited (out of the 6000 patients) had osteoporosis or osteopenia as determined by DXA. Jørgensen et al. [4] reported that 40.74% COPD patients were diagnosed as having osteoporosis, 29.62% were osteopenic and 29.62% had normal BMD. Combining history of fracture, X-rays and DXA, they found that 44.8% of COPD patients were osteoporotic, 22.4% were osteopenic and 25.9% had normal BMD.

Different prevalence of osteoporosis in COPD patients had been reported by different investigators [19–23]. This may be attributed to different study population characteristics (*age, sex, smoking index, GOLD stages*), different BMD diagnostic methods. It may also attributed to variable genetic susceptibility to osteoporosis or different resident areas (*sunny vs. foggy areas*).

Shepherd et al. [24] reported that the prevalence of low BMD in COPD patients varies between 9–69% and 27–67%, respectively, depending on the diagnostic methods used, the population studied, and the severity of the underlying respiratory disease. In COPD patients, the prevalence of osteoporosis is assumed to be two- to fivefold higher than that in age-matched subjects without airflow obstruction. In a recently developed screening tool for males at risk for osteoporosis, the presence of COPD is one of the parameters increasing this risk almost fourfold times.

In this study COPD patients with low BMD had more age, BMI and disease duration than those with normal BMD, however this difference was non-significant ($p > 0.05$). No difference in smoking index could be detected between COPD patients with normal BMD and those patients with low BMD in (Table 3). This does not indicate that smoking is not a risk factor of osteoporosis, but it might suggest that, in addition to a genetic component, osteoporosis is strongly affected by environmental factors that might outweigh the effects of smoking on the bones. This result confirmed that reported by Jørgensen et al. [4] as they concluded that there is no differences in tobacco pack years could be detected between the osteoporotic and non-osteoporotic COPD patients.

In this study the COPD group with low BMD also demonstrated significant decrease in VC%, FVC% and FEV_1% than those with normal BMD ($p < 0.05$) (Table 3). Different results were reported by Jørgensen et al. [4] that no statistically significant differences in the pulmonary function were detected between osteoporotic, osteopenic, and normal BMD COPD patients. Parthasarathi et al. [8] revealed that the disease severity FEV_1% was equal in magnitude between both groups (p 0.09).

The current study showed that T-score and Z-score were decreased significantly in COPD with low BMD than those with normal BMD (0.000), however, T-score was in osteoporotic range while Z-score was in osteopenic range (-3.04 ± 0.99 and -1.4 ± 1.1 respectively), which means that T-score is more sensitive for assessment of BMD than Z-score as recommended by WHO 2007. Similar result was reported by Parthasarathi et al. [8] as they found that the mean ± SD of T-scores was (-2.10 ± 0.57) for COPD with low BMD and (0.51 ± 0.27) for those with normal BMD with significant difference between both groups ($p < 0.001$).

Moreover, RRF was significantly increased in the COPD group with low BMD than those with normal BMD (10.07 ± 9.6 and 3.1 ± 1.3 respectively) ($p < 0.01$) (Table 3) which means that COPD patients with low BMD had more than threefold increase in fracture risk than COPD patients with normal BMD. This fracture would increase cost of COPD management, hospitalization, morbidity and mortality. Jørgensen et al. [4] reported that there is a clear tendency towards increased fracture risk in COPD as the percentage of individuals with fracture increases from 6.3% in the group with normal BMD, 18.8% in the osteopenic group to 31.8% in the osteoporotic group.

Finally, this study has some limitations that need to be mentioned. *Firstly:* All the patients were in GOLD III/IV stage and we have not noted the BMD of the early COPD patients. Hence, the actual prevalence of osteoporosis/osteopenia in overall COPD population cannot be detected from our observation. *Secondly* with a small number of COPD patients, it is not possible to make any comparison between the osteopenic and osteoporotic patients.

Conclusions

- The present study showed a high prevalence of low BMD (56.6%) among men with COPD (GOLD stage III–IV) than age and sex matched healthy individuals and the degree of the loss of BMD has been found to be proportionate to the severity of the disease.
- COPD patients with low BMD have threefold increase in fracture risk than COPD patients with normal BMD.

Recommendation

- Despite the limitations of this study there is no doubt that low BMD is a major problem in COPD patients, and patients with severe COPD should have performed diagnostic X-ray/DXA in order to diagnose osteoporosis.
- Assessment of low BMD in COPD is important from a clinical point of view as appropriate intervention may lessen the morbidity of the COPD patients.
- Osteopenic patients should be followed closely in order to start anti-osteoporotic treatment as soon as necessary before fractures occur. Further, if the patient is continuously treated with glucocorticoids, treatment should be initiated already in osteopenic patients according to international recommendations.
- Chest physicians should be aware of the high prevalence of osteoporosis in patients with COPD, especially in elder COPD patients with and/or an increased PTH level.

Conflicts of interest

None declared.

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