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Association of COPD with osteoporosis in male smokers: A case control study in a tertiary medical college hospital in Bangladesh

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Abstract.
OBJECTIVES: Chronic obstructive pulmonary disease (COPD) may increase the risk of osteoporosis and resulting fractures can contribute to disability and mortality of patients. We intended to evaluate the frequency of osteoporosis in male smokers with and without COPD and study whether any correlation existed between osteoporosis and COPD.
MATERIALS AND METHODS: This case-control study was carried out in the Department of Medicine, Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, Bangladesh between July 2013 and June 2015. Seventy four male smokers with COPD and 66 age-matched male smokers without COPD were enrolled. All individuals underwent Bone Mass Densitometry (BMD) by Dual-Energy X-Ray Absorptiometry (DEXA).
RESULTS: COPD and non-COPD groups did not differ regarding age and smoking pack-years. Osteoporosis at femoral neck (48.6% versus 16.7%; $p < 0.001$) and lumbar spine (68.9% versus 37.9%; $p < 0.01$) was significantly higher in COPD compared to controls. Osteopenia did not differ significantly. Patients with COPD were 4.5 times more likely to develop osteoporosis than controls after adjusting age, smoking-pack years and BMI (adjusted OR = 4.5; 95% CI = 1.8–11.5).
CONCLUSIONS: Osteoporosis is more frequent in male smokers with COPD compared to smokers without COPD. COPD is a risk factor of osteoporosis independent of age, smoking and BMI.

Keywords: Osteoporosis, male smokers, COPD, developing country, bangladesh

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as a preventable and treatable disease that is primarily characterized by progressive airflow limitation. This airflow limitation is not fully reversible and is associated with an abnormal inflammatory response of the lung to noxious particles or gases, most often cigarette smoke [1].

In addition to progressive loss of lung function, there is an increasing awareness of the development of extrapulmonary co-morbidities, posing additional problems in the management of COPD [2]. There is a grow-

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Table 1
Baseline characteristics of the two groups of patients: Smokers with COPD and control smokers without COPD

Variables	COPD ($n = 74$)	Control ($n = 66$)	p value
Age			
41–50 years	6 (8.1)	3 (4.5)	$^{*}p > 0.05$
51–60 years	25 (33.8)	33 (50.0)	
61–70 years	37 (50.0)	26 (39.4)	
71–80 years	6 (8.1)	4 (6.1)	
Mean ± SD	62.57 ± 8.02	60.65 ± 7.12	$^{\dagger}p = 0.139$
Smoking (pack-years)	37.50 ± 16.77	33.39 ± 13.82	$^{\dagger}p = 0.118$
BMI (Kg/M^2)	18.22 ± 2.58	21.33 ± 4.43	$^{\dagger}p < 0.001$

*Chi-square (Yates' corrected) test and †unpaired t-test were applied to analyse the data. Figure in the parenthesis indicates the corresponding percentage

ing evidence that osteoporosis is one of the systemic effects associated with COPD [3]. A low bone mineral density (BMD), leading to osteoporosis is common in COPD, studies reporting osteoporosis in 24 to 60% of patients with COPD [4–9], and osteopenia in 35% to 72% [10] Osteoporosis and its related fractures are common in patients with COPD and may have significant impact on quality of life and even respiratory function [11].

Several studies showed that the prevalence of osteoporosis is two-to five-fold higher in COPD than in age-matched subjects without airflow obstruction [6,7]. Graat-Verboom et al. [12] found an overall prevalence of osteoporosis of 31.7% in COPD versus 5.8% in healthy subjects, $p < 0.001$). Naghshin et al. [13] found that the frequency of osteoporosis in male smokers with COPD is much higher than in male smoker controls. Indeed, COPD patients are 12.5 times more likely to develop osteoporosis. Furthermore, in a screening tool for males at risk for osteoporosis, the presence of COPD is one of the parameters increasing this risk almost four times [14]. COPD patients have a higher prevalence of osteoporosis than healthy elderly subjects [15]. However, Karadag et al. [16] and Sim et al. [17] did not find a significant difference in prevalence of osteoporosis between COPD patients and healthy subjects.

This problem has not yet been studied in Bangladesh, a developing country with a high percentage (31.1%) of male smokers [18], and COPD (13.5%) [19]. Moreover, in osteoporosis, subsequent vertebral fractures or hip fractures may further compromise lung function and quality of life and increase the mortality of COPD [20,21]. Hence, this study is undertaken to compare the frequency and association of osteoporosis between male smokers with and without COPD in a developing country, Bangladesh. Knowledge of exact data would make it possible to improve the quality of life in this risk group, by appropriate preventive strategies that could avoid or reduce the consequences of osteoporosis.

2. Materials and methods

2.1. Study participants

This case-control study was carried out in the Department of Medicine, Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, Bangladesh between July, 2013 and June, 2015. All data were collected prospectively using pre-fabricated data sheets.

All male smokers with at least 10 pack years aged over 40 years and diagnosed as cases of COPD fulfilling the selection criteria were enrolled. Controls were volunteers selected from accompanying persons of the patients or other patients or hospital staff members, who were age matched male smokers without COPD/chronic respiratory diseases (e.g. interstitial lung diseases). Exclusion criteria for patients and controls were: bronchial asthma, chronic heart failure, liver cirrhosis, thyroid dysfunction and rheumatologic disorders, malignancies, chronic renal disease, as well as patients taking systemic corticosteroids for more than 3 months during the last year, bisphosphonates, ergocalciferol, levothyroxin, lithium, calcium and/or vitamin D preparations.

Considering an anticipated effect size of 20% and a number of predictors of 4 with 5% significance level and 80% power, the minimum sample size was 65. In this study 74 COPD patients and 66 non-COPD subjects were enrolled.

2.2. Diagnosis of COPD and osteoporosis

To diagnose COPD, all subjects underwent spirometry (Forced expiratory volume in 1 second [FEV_1],

Table 2
Lung function measured by spirometry in the two groups

Spirometry	COPD ($n = 74$)	Control ($n = 66$)	P value
FEV_1 (% predicted)	33.93 ± 12.67	93.12 ± 11.63	$^*p < 0.001$
FVC (% predicted)	52.49 ± 13.87	88.32 ± 11.88	$^*p < 0.001$
FEV_1/FVC (%)	46.83 ± 9.24	81.65 ± 5.99	$^*p < 0.001$

*Unpaired t-test was applied to analyse the data. Data were presented as mean ± standard deviation.

Forced Vital Capacity [FVC], and FEV1/FVC ratio) using RMS Helios 702 spirometer (Recorders and Medicare systems private limited, MEDSPIROR, India). The diagnosis of COPD was made based on clinical history (cough and sputum on most days for at least 3 consecutive months for at least 2 successive years along with breathlessness with history of exposure to risk factors especially tobacco smoking) and confirmed by pulmonary function testing. Staging of COPD was done as per GOLD criteria: stage-I, $FEV_1/FVC < 0.70$, $FEV_1 \geqslant 80\%$ predicted; stage-II, $FEV_1/FVC < 0.70$, FEV_1 50–79% predicted; stage-III, $FEV_1/FVC < 0.70$, FEV_1 30–49% predicted and stage-IV, $FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted if respiratory failure present [22]. Spirometry was also performed in controls. and all the observations were compared with those of the COPD patients (Table 2).

To measure osteoporosis, bone mineral density of the cases and controls was determined using whole body densitometer, DEXA (Dual Energy X-Ray Absorptiometry) scan (GE Healthcare Lunar prodigy advance, scanner serial no. PA + 302343, software version ± ENCORE 2008 version 12.2, Germany). BMD, bone mineral content (BMC), and area were measured at the femoral neck and at the lumbar spine (vertebrae L1–L4) [23]. All parameters were expressed in standard globally accepted terms: BMD (g/cm^2), BMC (g), and area (cm^2). A patient's BMD was given a T-score, which was derived by comparing it to an average score for a healthy 30-year-old male [8,9]. The differences between the "normal young" score and the patient's score were referred to as standard deviation (SD). T-score values below-2.5 SD were defined as osteoporosis, between-1.0 and-2.5 SD as osteopenia and-1 SD as normal bone density [9]. Osteoporosis score was measured both in cases and controls and compared.

Data regarding the use of corticosteroids orally and as inhalers are collected from history taking and previous clinical records.

2.3. Statistical analyses

The statistical analyses were performed using SPSS (Statistical Package for Social Science) version 21 for Windows. Descriptive statistics and frequency distributions were generated for the data. A chi-square test was used to show a relationship between categorical variables and a unpaired t-test was used to show a relationship between numerical variables. Statistical significance was set at $p < 0.05$ for all tests.

2.4. Ethical disclosure

Approval of the study protocol was obtained from the Institutional Ethical Committee of Sylhet M.A.G Osmani Medical College, Sylhet, Bangladesh and informed written consent was obtained from the patients or attendants (where appropriate) after full explanation of the details of the disease process and purpose of the study.

3. Results

The mean age of the COPD group was 62.57 ± 8.02 years and of controls 60.65 ± 7.12 years; ($p = 0.139$ NS). The mean smoking pack-years also did not differ significantly ($p = 0.118$ NS) (Table 1). In this study, FEV_1 (% predicted), FVC (% predicted) and FEV_1/FVC (%) were significantly lower in the COPD group than that of the control group ($p < 0.001$ each) (Table 2). GOLD stage-III was the most frequent stage of COPD and constituted 55.4% of the cases, followed by stage-IV (35.1%) and stage-II (9.5%). In the COPD group oral corticosteroids were used by 9 (12.2%) patients, inhaled steroids by 47 (63.5%) and 18 (24.3%) patients did not use steroids.

Using femoral neck densitometry normal bone mineral density was found significantly fewer in the COPD group than in the controls (8.1% versus 27.3%; $p < 0.05$). Osteoporosis was found significantly more in the COPD group than in the controls (48.6% versus 16.7%; $p < 0.001$); whereas osteopenia did not differ significantly between the COPD and control groups (43.2% versus 56.1%; $p > 0.05$) (Table 3).

With lumber spinal densitometry normal bone mineral density (5.4% versus 18.2%; $p < 0.05$) and os-

Table 3
Comparison of bone density and osteoporosis in smokers with COPD and smoking controls

Variables	COPD ($n = 74$)	Control ($n = 66$)	Statistical values	p value
T score				
Femoralneck	-2.31 ± 0.92	-1.65 ± 0.93	$t = -4.187$	$^{*}p < 0.001$
Lumbarspine	-3.01 ± 1.26	-1.92 ± 1.13	$t = -5.352$	$^{*}p < 0.001$
Osteoporosis				
Femoralneck	36 (48.6)	11 (16.7)	$Z = 4.308$	$^{\dagger}p < 0.001$
Lumbarspine	51 (68.9%)	25 (37.9)	$Z = 3.856$	$^{\dagger}p < 0.01$
Osteopenia				
Femoralneck	32 (43.2)	37 (56.1)	$Z = -1.537$	$^{\dagger}p > 0.05$
Lumbarspine	19 (25.7)	29 (43.9)	$Z = -2.291$	$^{\dagger}p < 0.05$
Normal				
Femoralneck	6 (8.1)	18 (27.3)	$Z = -3.031$	$^{\dagger}p < 0.05$
Lumbarspine	4 (5.4)	12 (18.2)	$Z = -2.358$	$^{\dagger}p < 0.05$

*Unpaired t-test and †Z test for proportion were applied to analyse the data.

Table 4
Risk factors of osteoporosis in patients with COPD by multiple logistic regression analyses

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Age		
41–50 years	Reference	Reference
51–60 years	4.67 (0.67–32.38)	0.83 (0.26–4.30)
61–70 years	5.19 (1.20–22.38)	1.102 (0.22–5.56)
71–80 years	5.40 (1.26–23.17)	0.15 (0.02–1.36)
Smoking-pack years		
$\leqslant$ 20 pack/year	Reference	Reference
21–40 pack/year	4.25 (0.82–22.13)	0.634 (0.19–2.06)
41–60 pack/year	2.74 (0.68–11.05)	0.54 (0.13–2.18)
61–80 pack/year	1.71 (0.37–7.85)	0.312 (0.05–2.02)
BMI in kg/M^2		
$<$ 18.5 Kg/M^2	Reference	Reference
18.5–22.9 Kg/M^2	2.12 (0.96–4.69)	0.85 (0.14–5.05)
23.0–24.9 Kg/M^2	1.04 (0.30–3.65)	0.15 (0.15–8.95)
25.0–29.9 Kg/M^2	4.09 (0.83–20.03)	0.73 (0.09–5.85)
COPD		
No	Reference	Reference
Yes	4.737 (2.146–10.455)	4.549 (1.793–11.537)

COPD: Chronic obstructive pulmonary disease; OR = Odds ratio, CI = Confident Interval.

Table 5
Association between osteoporosis and steroid use in COPD patients ($n = 74$). Crude OR and adjusted OR for age, smoking pack years and BMI

Steroiduse	Crude OR (95% CI)	Adjusted OR (95% CI)
Oral	1.96 (0.39–9.93)	1.77 (0.29–10.71)
Inhalation	1.95 (0.64–5.89)	1.74 (0.51–5.91)
No use of oral or inhalational steroids	Reference	Reference

OR = Odds ratio, CI = Confident interval.

teopenia (25.7% versus 43.9%; $p < 0.05$) was found significantly fewer in the COPD group than in controls; while osteoporosis was found significantly more in the COPD group than in controls (68.9% versus 37.9%; $p < 0.01$) (Table 3).

Multivariate analysis showed that the presence of COPD significantly correlates with osteoporosis (adjusted OR = 4.55; 95% CI = 1.79–11.54), but age, smoking-pack years and BMI did not correlate with osteoporosis (Table 4).

Use of oral corticosteroids (adjusted OR = 1.77; 95% CI = 0.29–10.71) and inhalation steroids (adjusted OR = 1.74; 95% CI = 0.51–5.91) compared to no use of steroids was not associated with osteoporosis in patients with COPD when adjusted for age, smoking pack year and BMI (Table 5).

4. Discussion

Osteoporosis is a major problem in men with chronic ailments. In men with COPD, osteoporosis may be particularly disabling because vertebral fractures reduce vital capacity, which further compromises ventilation [24]. Evidence suggests that the prevalence of osteoporosis in patients with COPD is high and potentially important [25,26]. When studying the relationship between osteoporosis and COPD, one has to realize that the two diseases have a number of risk factors in common including: smoking, older age, long-term treatment with corticosteroids, and low body mass index.

In the current study the mean BMI was significantly lower in the COPD group than in the smoking controls ($p < 0.001$) (Table 1), but with multivariate multiple logistic regression analyses BMI did not correlate with osteoporosis (Table 4). In an Indian uncontrolled study among 102 COPD patients, after using multivariate logistic regression analysis, BMI was not found to be a significant risk factor for osteoporosis

in COPD patients [26]. A significantly lower BMI in the COPD group than controls was reported in several studies [17,26–28].

In the present study T-scores of the femoral neck were significantly lower in COPD patients than in controls ($p < 0.001$). These results were in agreement with other studies [13,17]. In contrast, Karadag et al. [16] found T-scores of the femoral neck were significantly lower in COPD patients but difference was not significant ($p = 0.9$).

This study revealed that osteoporosis in the femoral neck was in 36 (48.6%) COPD compared to 11 (16.7%) in controls ($p < 0.001$). Several studies were comparable with our findings [17,30–32]. Karadag et al. [16] disagreed with this finding, as they reported that the frequency of osteoporosis was higher in COPD but that the difference was not significant ($p = 0.68$). They performed their study in COPD patients who were clinically stable and perfectly treated; this choice may have influenced their findings. Graat-Verboom et al. [33] assessed risk factors for developing osteoporosis in clinically stable COPD outpatients at baseline and after 3 years. The prevalence of osteoporosis in COPD patients increased from 47% to 61% in 3 years mostly due to an increase of vertebral fractures. Lower baseline T-scores at the trochanter independently increased the risk for the development of osteoporosis.

In our study significantly more osteoporosis was found in the lumbar spine and femoral neck in the smoking COPD group than in smoking controls ($p < 0.01$). This result was comparable with a study by Naghshin et al. [13].

In our study we showed by multivariate analysis that the presence of COPD significantly correlates with osteoporosis (adjusted OR = 4.50; 95% CI = 1.79–11.54), but age, smoking pack years and BMI did not predict osteoporosis. This result was supported by the study by Naghshin et al. [13], who stated that the risk of osteoporosis in patients with COPD was almost 12.5 fold compared to control group (OR: 12.46, CI 95% = 3.9–39.85). In Korea osteoporosis was found in 191 (17.7%) of 1,081 COPD patients. In multivariate analyses, older age (odds ratio [OR] = 1.10, $P < 0.001$) was a risk factor for osteoporosis. Patients with male sex (OR = 0.06, $P < 0.001$), high house income (OR = 0.75, $P = 0.045$), and high BMI (OR = 0.74, $P < 0.001$) were less likely to have osteoporosis. In addition, osteoporosis was associated with poor HRQOL ($\beta = -0.21$, $P = 0.023$) [34].

In the current study use of oral corticosteroids compared to no use of steroids was not associated with osteoporosis in patients with COPD when adjusted for age, smoking pack year and BMI (adjusted OR = 1.77; 95% CI = 0.29–10.71). Inhalation steroids compared to no use of steroids was also not associated with osteoporosis in patients with COPD (adjusted OR = 1.74; 95% CI = 0.51–5.91). Some studies showed that one of the most obvious causes of osteoporosis in COPD patients is treatment with glucocorticoids, both as systemic therapy and as inhaled glucocorticoids [1,9,15,35,36], whereas others reported little or no effect of glucocorticoids on osteoporosis [23,37]. So glucocorticoid use does not fully account for the low bone mineral density (BMD) and high prevalence of osteoporosis in COPD patients [12]. Furthermore the classic explanation of osteoporosis in COPD as a result of accelerated decline in bone mineral density among users of inhaled corticosteroids is not supported by clinical trials [35,36,38,39]. Moreover in a randomized controlled trial, Mathioudakis et al. [40] have shown that long-term use of low-dose inhaled corticosteroids protects the COPD patients from developing osteoporosis. This is secondary to the decrease of inflammation in the lungs, which further decreases the systemic spill-over. The long-term treatment with inhaled corticosteroids had also no effect on fracture risk in patients with COPD [41], and at conventional doses [35]. One year of inhaled corticosteroid treatment was shown to exert no effects on bone mineral density [42], while a treatment of 3 years with inhaled triamcinolone was found to reduce bone mineral density [43]. In this study use of oral steroid in COPD patients was less than 3 months and this may explain differences with some of the above mentioned studies.

In an Indian controlled study among 30 COPD patients, the risk of osteoporosis and osteopenia was found to increase with the increase of COPD severity [44]. This fits in with our finding that COPD is an independent risk factor for osteoporosis.

Our study has some limitations. First, this was a single-centre study. A second limitation is that we did not include X-Ray studies of the vertebra. Third, we did not assess the physical activity of COPD and control subjects as this might have influenced osteoporosis; none of our patients or controls were bed-ridden. Fourth, we did not record the life time cumulative doses of inhaled or systemic corticosteroids.

The strength of the study is the fact that it is the first study in Bangladesh and one of the first large controlled studies in a developing country in Asia studying the frequency of osteoporosis in smokers with and without COPD.

5. Conclusions

The frequency of osteoporosis is higher in male smokers with COPD compared to those without COPD. Thus COPD appears to be a risk factor for osteoporosis independent of smoking. During rehabilitation of COPD patients back problems due to osteoporotic deformation of the spine and or fractures should be a point of special attentions Physicians should be aware of this complication and BMD should be measured in every male smoker with COPD; prevention of osteoporosis should be part of the medical care for COPD patients.

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Conflict of interest

The authors have no conflict of interest to report.

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