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\%; \textit{p} < 0.001) and lumbar spine (68.9\% versus 37.9\%; \textit{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 extra-pulmonary co-morbidities, posing additional problems in the management of COPD [2]. There is a grow-
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 50% of patients with COPD [4–9], and osteopenia in 55% 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 [13]. 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 [FEV1]).
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%) by stage-IV (35.1%) and stage-II (9.5%). In the COPD 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 (43.2% versus 56.1%; $p < 0.05$) (Table 3). With lumbar spinal densitometry normal bone mineral density (5.4% versus 18.2%; $p < 0.05$) and osteoporosis found significantly more in the COPD group than in the controls (8.1% versus 27.3%; $p < 0.05$).

### Table 2

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>COPD ($n = 74$)</th>
<th>Control ($n = 66$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (% predicted)</td>
<td>33.93 ± 12.67</td>
<td>93.12 ± 11.63</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>52.49 ± 13.87</td>
<td>88.32 ± 11.88</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>46.83 ± 9.24</td>
<td>81.65 ± 5.99</td>
<td>$p &lt; 0.001$</td>
</tr>
</tbody>
</table>

$^*$Unpaired t-test was applied to analyse the data. Data were presented as mean ± standard deviation.
no use of steroids was not associated with osteoporosis (Table 4). In an Indian uncontrolled study among 102 COPD patients, after using logistic regression analyses BMI did not correlate with osteoporosis (Table 4). In an Indian uncontrolled study among 102 COPD patients, after using logistic regression analyses BMI did not correlate with osteoporosis (Table 4).

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD (n = 74)</th>
<th>Control (n = 66)</th>
<th>Statistical values</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Femoralneck</td>
<td>−2.31 ± 0.92</td>
<td>−1.65 ± 0.93</td>
<td>t = −4.187</td>
<td>*p &lt; 0.001</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>−3.01 ± 1.26</td>
<td>−1.92 ± 1.13</td>
<td>t = −5.352</td>
<td>*p &lt; 0.001</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoralneck</td>
<td>36 (48.6)</td>
<td>11 (16.7)</td>
<td>Z = 4.308</td>
<td>†p &lt; 0.001</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>51 (68.9%)</td>
<td>25 (37.9)</td>
<td>Z = 3.856</td>
<td>†p &lt; 0.01</td>
</tr>
<tr>
<td>Osteopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoralneck</td>
<td>32 (43.2)</td>
<td>37 (56.1)</td>
<td>Z = −1.537</td>
<td>†p &gt; 0.05</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>19 (25.7)</td>
<td>29 (43.9)</td>
<td>Z = −2.291</td>
<td>†p &lt; 0.05</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Femoralneck</td>
<td>6 (8.1)</td>
<td>18 (27.3)</td>
<td>Z = −3.031</td>
<td>†p &lt; 0.05</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>4 (5.4)</td>
<td>12 (18.2)</td>
<td>Z = −2.358</td>
<td>†p &lt; 0.05</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41–50 years</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>51–60 years</td>
<td>4.67 (0.67–32.38)</td>
<td>0.83 (0.26–4.30)</td>
</tr>
<tr>
<td>61–70 years</td>
<td>5.19 (1.20–22.88)</td>
<td>1.02 (0.22–5.56)</td>
</tr>
<tr>
<td>71–80 years</td>
<td>5.40 (1.26–23.17)</td>
<td>0.15 (0.02–1.36)</td>
</tr>
<tr>
<td>Smoking-pack years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20 pack/year</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>21–40 pack/year</td>
<td>4.25 (0.82–22.13)</td>
<td>0.634 (0.19–2.06)</td>
</tr>
<tr>
<td>41–60 pack/year</td>
<td>2.74 (0.68–11.05)</td>
<td>0.54 (0.13–2.18)</td>
</tr>
<tr>
<td>61–80 pack/year</td>
<td>1.71 (0.37–7.85)</td>
<td>0.312 (0.05–2.02)</td>
</tr>
<tr>
<td>BMI in Kg/M²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5 Kg/M²</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>18.5–22.9 Kg/M²</td>
<td>2.12 (0.96–4.69)</td>
<td>0.85 (0.34–2.13)</td>
</tr>
<tr>
<td>23.0–24.9 Kg/M²</td>
<td>1.04 (0.30–3.65)</td>
<td>0.41 (0.15–8.95)</td>
</tr>
<tr>
<td>25.0–29.9 Kg/M²</td>
<td>4.09 (0.83–20.03)</td>
<td>0.72 (0.09–5.85)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>4.737 (2.146–10.45)</td>
<td>4.549 (1.793–11.537)</td>
</tr>
</tbody>
</table>

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

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 ($p = 0.68$).

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 = 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 the 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 vertebrae. 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 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.

**Acknowledgments**

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**Conflict of interest**

The authors have no conflict of interest to report.

**References**


