A Comparison of Bone Mineral Density in Elderly Female Patients With COPD and Bronchial Asthma*

Hideki Katsura, MD; and Kozui Kida, MD, FCCP

**Background:** A recent study has shown that osteoporosis and vertebral fractures are quite common in patients with advanced COPD and showed a significant relationship to the mortality of these patients. These results suggested that management of osteoporosis in advanced COPD is an important intervention. But whether patients with COPD who had never received chronic systemic corticosteroids have a high incidence of osteoporosis and whether these patients require treatment strategies to decrease osteoprotic fracture is not yet known. Furthermore, it is unclear whether there are differences in terms of the degree of osteoporosis between patients with COPD and patients with bronchial asthma.

**Objectives:** To compare the degree of osteoporosis and bone metabolism markers between elderly women with COPD and those with bronchial asthma who had never received chronic systemic corticosteroids, and to determine the factors influencing bone metabolism in these patients.

**Design:** Cross-sectional medical survey.

**Patients:** A total of 44 elderly female patients with COPD (n = 20) or bronchial asthma (n = 24) who had not received chronic systemic corticosteroids were enrolled (mean ± SEM age, 74.6 ± 1.0 years).

**Measurements:** Total body and lumbar bone mineral density (BMD) were measured by dual-energy x-ray absorptiometry, and the data were compared between the two groups. In addition, the association between bone mass and clinical variables was determined.

**Results:** When lumbar BMD was expressed as a Z score, the Z scores of patients with COPD were significantly lower than those of patients with bronchial asthma (p < 0.01). The prevalence of osteoporosis was also significantly higher in patients with COPD (50% vs 21%, p < 0.05). In patients with COPD, body mass index was positively correlated with BMD in the lumbar spine (r = 0.55, p = 0.02) and total body (r = 0.49, p = 0.03). Other clinical, biochemical, and anthropometric variables were not correlated with BMD.

**Conclusions:** In elderly female patients, osteoporosis is more common in cases of COPD than in bronchial asthma, even if these patients had not received long-term systemic corticosteroids. The explanation for the higher prevalence of osteoporosis in COPD is still not known, but preventive strategies to decrease osteoporotic fractures should be added to the management of elderly patients with COPD.

KEY WORDS: body mass index; bone mineral density; bronchial asthma; COPD; elderly female

ABBREVIATIONS: ADL = activities of daily living; BDL = basic activities of daily living; BPD = beclomethazone dipropionate; BMD = bone mineral density; BMI = body mass index; IADL = instrumental activities of daily living; PTH = parathyroid hormone; 6MWD = 6-min walk distance; TNF = tumor necrosis factor

It has been well recognized that osteoporosis and bone fractures are common diseases that impact on activities of daily living (ADL) and quality of life in many elderly patients, especially women. Studies have shown that osteoporosis is quite common in patients with end-stage pulmonary diseases such as cystic fibrosis and in patients with COPD who are candidates for lung transplantation. Such studies also have demonstrated an association between chronic systemic corticosteroid use and lower bone mineral density (BMD) in patients with these lung...
diseases. The study by McEvoy et al showed that vertebral fractures are common in elderly male patients with COPD and the degree of these fractures is greatest in those receiving continuous systemic corticosteroids. A study by Kado and coworkers reported that in elderly women with vertebral fractures, mortality is increased compared with that among those without vertebral fractures. They also reported that vertebral fractures were related to the risk of subsequent pulmonary death, such as COPD and pneumonia. These findings suggest that uncontrolled body pain due to osteoporosis may promote acute exacerbations of COPD. These results suggested that existing vertebral fractures and osteoporosis are serious problems in patients with pulmonary diseases such as COPD, and management of osteoporosis in advanced COPD is an important intervention. However, whether patients with COPD who had never received chronic systemic corticosteroids also have a high incidence of osteoporosis remains controversial, and whether these patients require treatment strategies to decrease osteoporotic fracture is not known.

In the elderly population, COPD and bronchial asthma show a similar clinical manifestation, but whether there are differences in the degree of osteoporosis between these two diseases is not known. The present study compared the degree of osteoporosis and bone metabolism markers between elderly women with COPD and bronchial asthma who had never received chronic systemic corticosteroids, and the factors influencing bone metabolism in these patients were determined.

**Materials and Methods**

**Subjects**

Forty-four elderly female Japanese patients with COPD (n = 20) and bronchial asthma (n = 24) regularly followed up at the outpatient clinic of Tokyo Metropolitan Geriatric Medical Center were recruited for this study. The criteria for diagnoses of COPD and bronchial asthma were based on the standards of the American Thoracic Society. None of the patients had a history of chronic systemic corticosteroid use, defined as any oral steroids received continuously for > 1 week during the previous 10 years. All patients were postmenopausal. Patients were excluded if they had a coexisting medical disorder that might affect bone metabolism. Patients were also excluded if they had received medications known to affect bone metabolism apart from inhaled corticosteroids. The study was approved by the Tokyo Metropolitan Geriatric Medical Center ethics committee, and all patients gave written informed consent.

**Measurements**

FEV1 and FVC were measured using a pulmonary function instrument with computer processing (CHESTAC; Chest; Tokyo, Japan), and FEV1 was expressed as a percentage of predicted. Peripheral blood was collected in the morning under fasting conditions, and the plasma concentrations of calcium, phosphate, total protein, albumin, BUN, creatinine, alkaline phosphatase, and urinary concentration of calcium, phosphate and creatinine were measured in the hospital laboratory by routine assays using a Toshiba autoanalyzer (Toshiba; Tokyo, Japan). Measurement of bone metabolism markers were described elsewhere. Briefly, serum levels of 25-hydroxyvitamin D were measured by a competitive protein binding assay (Mitsubishi Kagaku Bio Clinical Laboratories; Tokyo, Japan). Serum levels of intact parathyroid hormone (PTH) were measured by an immunoradiometric assay (Allegro Intact PTH; Nichols Institute; San Juan Capistrano, CA), and serum levels of osteocalcin were measured by enzyme-linked immunosorbent assay (Kokusai Sylvania; Kobe, Japan). Total urinary deoxypyridinoline was measured in morning voided urine samples with Pyrilinks and Pyrilinks-D assay kit (Metry Biosystems; San Diego, CA). Bone mineral content (grams) and BMD (grams per centimeter squared) were measured with dual-energy x-ray absorptiometry using a Lunar DPX densitometer (Lunar Radiation; Madison, WI). Regions of interest that were assessed included total body and lumbar spine (L2–4). Lumbar BMD was also expressed as a Z score and T score. The Z score is a SD from the young adult mean of BMD, and the T score is a SD from peak bone mass. All scans were performed and analyzed by one operator. Osteoporosis was diagnosed according to the criteria of the committee of the Japanese Society for Bone and Mineral Research for development of diagnostic criteria for osteoporosis; lumbar BMD < 70% of the young adult mean of BMD represents osteoporosis.

**Study Design**

Historical information was obtained from all patients on current and past exposure to systemic and inhaled glucocorticoids, tobacco exposure, pharmacologic regimens, and general possible risk factors for osteoporosis such as menopausal status and family history. These data were obtained by self-administered questionnaire. Spirometric testing, 6-min walk distance (6MWD), BMD analysis, bone metabolism marker measurements, and thoracic and lumbar radiography were performed. ADL was assessed by the basic ADL score (BADL) by Barthel index and instrumental ADL score (IADL) described elsewhere. The total cumulative dose of inhaled steroid, beclomethasone dipropionate (BDP), was verified from the patient’s medical diary and expressed as the cumulative dose.

**Statistical Analysis**

All data were expressed as mean ± SEM. An unpaired Student t test and χ2 test were used to compare differences between patients with bronchial asthma and patients with COPD. Relationships between the variables were assessed with Pearson correlation coefficients.

**Results**

Patient characteristics, anthropometric variables, and details of inhaled corticosteroid use are shown in Table 1. All patients with COPD were ex-smokers; however, none of the patients with bronchial asthma had a smoking habit. Compared to patients with
bronchial asthma, the patients with COPD were relatively lean and the body mass index (BMI) was significantly smaller (p < 0.04). FEV1 expressed as percentage of predicted value was significantly lower in patients with COPD (p < 0.01), but ADL assessed by BADL and IADL scores did not differ between the two groups. All patients in the bronchial asthma group and 75% of the patients in COPD group were prescribed inhaled corticosteroids. None of the patients in either group received estrogen-replacement therapy. On comparison between the two groups, the durations and total accumulation dose of inhaled corticosteroid in patients with bronchial asthma were significantly higher than those in patients with COPD (p < 0.01 and p < 0.001, respectively).

The BMD of the total body and lumbar area of the spine were all significantly lower in patients with COPD compared to that of those with bronchial asthma (p < 0.03 and p < 0.04, respectively) [Table 2]. When lumbar BMD is < 70% of the young normal mean of BMD, a diagnosis of osteoporosis is made according to the criteria in Japan.10 According to these criteria, 50% of patients with COPD and 21% of patients with bronchial asthma received a diagnosis of osteoporosis. The prevalence of osteoporosis among patients with COPD was significantly higher than that among patients with bronchial asthma (p < 0.05). Because BMD is known to be affected by age, lumbar BMD was expressed by the Z score (Table 2, Fig 1). The Z score is the score representing the SD from the weight-adjusted average BMD of each age.9 The Z score of the patients with COPD was significantly lower than that of patients with bronchial asthma (p < 0.01). Spinal radiographs were performed in patients with COPD and in patients with bronchial asthma. The prevalence rate of more than one vertebral fracture was 40% in patients with COPD and 15% in patients with bronchial asthma, and the prevalence of vertebral fractures was significantly higher in patients with COPD (p < 0.05). When comparing the Z score, the total amount of tobacco use, and the total amount of inhaled corticosteroid between COPD patients with and without vertebral fractures, the Z score was signifi-

### Table 1—Patient Characteristics, Anthropometric Variables, and Details of Inhaled Steroid Use of the Study Group*

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD (n = 20)</th>
<th>Bronchial Asthma (n = 24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>72.3 ± 1.3</td>
<td>76.6 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history, No.</td>
<td>20</td>
<td>0</td>
<td>0.34</td>
</tr>
<tr>
<td>Pack-yr</td>
<td>26.1 ± 4.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FEV1, L</td>
<td>0.94 ± 0.08</td>
<td>1.17 ± 0.08</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>49.9 ± 3.8</td>
<td>66.5 ± 3.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>362.6 ± 18.6</td>
<td>359.9 ± 14.8</td>
<td>NS</td>
</tr>
<tr>
<td>IADL</td>
<td>29.7 ± 0.5</td>
<td>29.9 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>BADL</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>148.6 ± 1.5</td>
<td>147.1 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>48.7 ± 2.0</td>
<td>53.5 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>22.0 ± 0.8</td>
<td>24.6 ± 0.9</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Patients receiving inhaled steroids, No. (%)</td>
<td>15 (75)</td>
<td>20 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of inhaled steroid use, mo</td>
<td>20.1 ± 5.4</td>
<td>39.5 ± 6.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Total amount of inhaled steroid use, mg</td>
<td>288.3 ± 78.9</td>
<td>743.2 ± 178.9</td>
<td>&lt; 0.04</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM unless otherwise indicated. NS = not significant.

### Table 2—Bone Densitometry Data*

<table>
<thead>
<tr>
<th>Bone Data</th>
<th>COPD (n = 20)</th>
<th>Bronchial Asthma (n = 24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body BMD, g/cm²</td>
<td>0.89 ± 0.02</td>
<td>0.98 ± 0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Spine BMD</td>
<td>g/cm²</td>
<td>0.80 ± 0.04</td>
<td>1.01 ± 0.04</td>
</tr>
<tr>
<td>Z score</td>
<td>−0.33 ± 0.27</td>
<td>1.08 ± 0.34</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>T score</td>
<td>−2.54 ± 0.32</td>
<td>−1.01 ± 0.35</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM.

Figure 1. Comparison of BMD of the lumbar spine by Z score. The Z score represents a SD from the weight-adjusted average BMD of each age based on the data of Japanese women. BMD of patients with COPD expressed by Z score was significantly lower than that of patients with bronchial asthma.
corticosteroids, amount of tobacco use, FEV1, inhaled corticosteroids influence BMD, such as total amount of inhaled corticosteroids between COPD patients with and without vertebral fractures (data not shown). Table 3 shows the concentrations of serum and urinary bone metabolism markers. Compared to those of patients with bronchial asthma, serum osteocalcin appeared lower and urinary deoxypyridinoline appeared higher in patients with COPD, but none of the variables demonstrated significant differences.

Correlation coefficients were calculated between the BMD of patients with COPD and a number of lifestyle, anthropometric, and biochemical variables. The BMI of patients with COPD was positively correlated with total body BMD (r = 0.49, p = 0.03; Fig 2) and BMD of the lumbar spine (r = 0.55, p = 0.02; Fig 2). None of the other factors that may influence BMD, such as total amount of inhaled corticosteroids, amount of tobacco use, FEV1, FEV1, percent predicted, ADL assessed by IADL, and 6MWD, showed any correlation with BMD.

**DISCUSSION**

In this study, we compared the degree of BMD and bone turnover markers between elderly women with COPD and elderly women with bronchial asthma who had not received chronic systemic corticosteroids, and determined the factors that influence bone metabolism in these patients. This study has clearly shown that even in elderly women with COPD who have not received chronic systemic corticosteroids, total body and lumbar BMD was much lower than that in asthmatic patients. The prevalence of osteoporosis in patients with COPD was 50%, and this was significantly higher than that of bronchial asthma. It has been reported that osteoporosis was diagnosed in 24% of postmenopausal women in Japan, and the prevalence of osteoporosis in women with COPD was almost two-fold higher than that in the general population.

The reports on lung transplantation related to osteoporosis demonstrated an increased incidence of lower BMD in lung transplantation candidates with end-stage pulmonary disease. Shane and colleagues reported that osteoporosis was detected at the lumbar spine in 30% and at the femoral neck in 49% of lung transplantation candidates, especially in COPD and cystic fibrosis patients. They also reported that the glucocorticoid-treatment group tended to have a lower BMD. Aris et al also reported that the BMD of patients with COPD was severely depressed before lung transplantation. They reported that in 45% of patients with COPD, BMD was below the fracture threshold. They also reported that the best predictors of BMD were BMI and cumulative steroid dose. These results suggest that osteoporosis appears to be widespread in patients with end-stage COPD and that BMD was influenced by the use of corticosteroids. However, it is not known whether the presence of COPD itself is a risk factor for osteoporosis. Riancho and coworkers reported that vertebral deformity in COPD patients without long-term corticosteroid treatment did not differ from that of an age-matched control group. However, a study by McEvoy et al reported that COPD itself showed a correlation with the prevalence of vertebral fractures in elderly male patients with COPD who had never received corticosteroids. Thus, they speculated that COPD itself may promote the development of osteoporosis. A study by Iqbal et al also reported that male patients with chronic pulmonary disease, including those with COPD and bronchial asthma, who had not received systemic corticosteroids had almost a four-times-higher prevalence of osteoporosis compared with the control group. Our results showed that the prevalence of osteoporosis in postmenopausal women with COPD was much higher than that in those with bronchial asthma, and our results support the hypothesis proposed by McEvoy et al and Iqbal et al that the presence of COPD itself is a risk factor for osteoporosis.

It is known that in elderly women with deterioration of ADL, habitual smoking and drinking, use of drugs such as systemic corticosteroids, and malnutrition are risk factors for osteoporosis. In this study,

<table>
<thead>
<tr>
<th>Bone Metabolism Markers</th>
<th>Normal Range</th>
<th>COPD (n = 20)</th>
<th>Bronchial Asthma (n = 24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25-hydroxyvitamin D, ng/mL</td>
<td>9.0 to 33.9</td>
<td>19.0 ± 1.0</td>
<td>19.1 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum intact PTH, pg/mL</td>
<td>14 to 66</td>
<td>40.1 ± 3.8</td>
<td>35.3 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Serum osteocalcin, ng/mL</td>
<td>3.1 to 12.7</td>
<td>7.0 ± 1.1</td>
<td>7.4 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary deoxypyridinoline, μM/mM × Cr</td>
<td>2.8 to 7.6</td>
<td>6.5 ± 0.5</td>
<td>6.0 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. Cr = creatinine; see Table 1 for expansion of other abbreviation.
the BMI of patients with COPD positively correlated with total body and lumbar BMD, but did not correlate with the total amount of inhaled steroids, amount of tobacco use, FEV₁, FEV₁ percent predicted, or IADL score. Body weight has previously been shown to be closely related to BMD in both men and women.¹⁴,¹⁵ It is well recognized that patients with chronic lung disease such as COPD sometimes show a malnourished status, so-called pulmonary cachexia.¹⁶ Our results suggest that weight loss or malnutritional states may be involved in the pathogenesis of low BMD in patients with COPD. A similar relationship between malnutrition and low BMD was reported in adult patients with cystic fibrosis.¹⁷,¹⁸

The reason a malnourished state in patients with COPD is associated with decreased BMD is not known. Some studies have speculated that COPD is a disease not only involving the lungs but also causing systematic inflammatory response and proinflammatory cytokines such as tumor necrosis factor (TNF)-α may cause peripheral muscle dysfunction and malnutrition.¹⁹ Studies have shown that serum TNF-α level and the lipopolysaccharide-stimulated TNF-α production by peripheral blood monocytes was significantly higher in patients with COPD who are losing weight, compared with that in weight-stable patients with COPD and normal subjects.²⁰,²¹ TNF-α is also known as a potent inhibitor of bone collagen synthesis and a stimulator of osteoclastic bone resorption,²² suggesting that systemic inflammatory response and increased production of TNF-α causes weight loss as well as bone loss in patients with COPD. However, inflammatory cytokines other than TNF-α are also known to affect BMD,²² and further study is needed to clarify this point. Also, a recent study by Takabatake and coworkers²³ showed that chronic hypoxemia is related to TNF-α production in patients with COPD. However, the relationship between chronic hypoxemia and osteoporosis is not known.

In this study, the only factor that correlated with BMD of patients with COPD was low BMI. However, the Z score (a SD from the weight-adjusted average BMD of each age- and gender-matched mean BMD)⁹ was lower in patients with COPD compared with that in patients with asthma, even though the Z score was adjusted by age and body weight. This result suggests that other factors that influence the BMD of patients with COPD other than low body weight, such as use of inhaled glucocorticoids and smoking, should be considered.

Herrala et al²⁴ retrospectively examined the BMD of postmenopausal female asthmatics receiving BDP, 1,000 μg/d for 1 year, and showed that there was no effect on bone density in the lumbar spine or proximal femur as measured by dual-energy x-ray absorptiometry. However, the Lung Health Study showed that 3 years of usage of inhaled triamcinolone significantly lowered the BMD of patients with COPD.²⁵ Our results showed that even when using a significantly higher dose of BDP, the BMD of asthmatic patients was much higher than that of patients with COPD, and the total cumulative dose of BDP did not correlate with the BMD of patients with COPD. It is not known whether the BMD of patients with COPD is more affected by inhaled corticosteroids compared with that of patients with bronchial asthma. Further prospective study is needed to clarify this point.

Studies link smoking to low bone density in women by a variety of factors attributable to smoking, such as early menopause, thinness, reduced circulating estrogens, and decreased calcium absorp-

![Figure 2. Total BMD (left panel) and lumbar BMD (right panel) of patients with COPD plotted against BMI. Total and lumbar BMD were significantly correlated with BMI.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21985/)
These results suggest a relationship between smoking and low BMD in patients with COPD. In this study, there was no significant correlation between the amount of smoking and BMD in patients with COPD. One explanation is an inaccurate estimation of smoking history on self-report. A study by Law and Hackshaw showed that smoking has greater effects on BMD in elderly women if smoking is continued after menopause. Another explanation is that because all of the patients with COPD in this study were ex-smokers, smoking cessation made the detection of correlation between low BMD and smoking more difficult.

Whether the presence of bronchial asthma itself is a risk factor for osteoporosis has not been extensively studied. The study by Laatikainen and coworkers showed that BMD of perimenopausal asthmatics with no history of corticosteroid use did not differ from those of nonasthmatics. They concluded that asthma itself is not a risk factor for osteoporosis. According to the reference value for lumbar spine BMD in Japanese women, the lumbar BMD from 75 to 79 years of age is expected to be $0.840 \pm 0.189$ g/cm$^2$. Compared with the reference value, the patients with bronchial asthma in this study showed significantly higher BMD. In our study population, all asthmatic patients were receiving inhaled corticosteroids, but even after taking the use of inhaled corticosteroids into account, our result suggested that the presence of bronchial asthma itself is not a risk factor for osteoporosis in postmenopausal women.

Kado and coworkers reported that in elderly women with more than five vertebral fractures, mortality is increased almost 2.3 times compared with that of those without vertebral fractures. They also reported that vertebral fractures were related to the risk of subsequent pulmonary death such as COPD and pneumonia. Because of a high prevalence of osteoporosis in elderly patients with COPD, it is very important to pay attention to osteoporosis in the management of COPD.

The limitations of our study must be noted. The main problem is that we did not include a healthy control group. One may assume that we could not compare the degree of osteoporosis between COPD and bronchial asthma without a control group. In order to address this point, we expressed BMD as a Z score derived from the reference value for age- and body weight-matched normal Japanese women. Second, only patients not receiving long-term systemic corticosteroid therapy were enrolled and therefore more severe cases may have been excluded, which might have obscured the relationship between BMD and clinical factors. Finally, our study population consisted only of women. Further study is needed to examine BMD in male patients to generalize our hypothesis.

In conclusion, the results of our study demonstrate that compared with the incidence among elderly female asthmatic patients, osteoporosis is common among elderly female patients with COPD even if these patients have not received systemic corticosteroids. The explanation for higher prevalence of osteoporosis in COPD is still not known, but preventive strategies to decrease osteoporotic fractures should be added to the management of elderly patients with COPD.

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