RISK OF OSTEOPOROSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The study was conducted on 2 groups including patients group and control subjects group at the outpatient clinic of Ibn Sina teaching hospital in Mousl during the period between 1/1/2010 and 1/5/2011. The first group consists of 53 patients with chronic obstructive pulmonary disease (COPD), and the second group consists of 53 apparently healthy subjects matched for age and gender who denied respiratory symptoms were kept as control group. The aim of this study was to assess whether there is an increase in the risk of osteoporosis in patients with COPD compared to that in healthy age-matched control subjects, and the correlation of osteoporosis to various degrees of disease severity. All the study groups were subjected to assessment of medical and drug history, measurement of weight and height to derive body mass index, pulmonary function testing, biochemical tests, and dual-energy X-ray absorptiometry. The data obtained from the study revealed that patients with COPD have a significantly increased risk of osteoporosis as compared to that in healthy age-matched control subjects, 22(41.5%) versus 11(20.7%), respectively. The risk of osteoporosis was significantly different after stratification for Global Initiative for Chronic Obstructive Lung Disease-stage. Most patients with osteoporosis did not receive pharmacological treatment. Age, body mass index, menopausal duration and forced expiratory volume in 1 second (FEV1) % predicted were significant independent correlates for osteoporosis.

INTRODUCTION

Although chronic obstructive pulmonary disease (COPD) is a nonspecific term referring to a set of conditions that develop progressively as a result of a number of different disease processes, it is most commonly referred to chronic bronchitis and emphysema and a subset of patients with asthma (GOLD Committee, 2006). These conditions can be present with or without significant physical impairment. Despite being a very common disease and the fourth leading cause of death in the United States (Benson and Marano, 1998), COPD is often a silent and unrecognized disease, particularly in its early phases (Mannino et al., 2000). COPD is an increasing problem in both the Western and developing world. It causes significant morbidity and disability, and excess mortality is expected to become the third most common cause of death worldwide by 2020 (Mannino et al., 2000). Osteoporosis is the most common metabolic bone disease and represents an increasingly serious problem, particularly as the population ages. Elderly white women are the most affected group by osteoporosis. However, osteoporosis is commonly seen in both sexes, all races and all age groups (Naghshin et al., 2004). Osteoporosis can result in devastating psychosocial, physical, and economic consequences.

Despite its great importance, osteoporosis often remains overlooked and undertreated, mainly because it is a clinically silent disease until it manifests in the form of a pathologic fracture (Kado et al., 1999). It is important to define causes and risk factors of osteoporosis. Some of these causes are determined, including female sex, advanced age, hormonal disturbances, alcohol, smoking, genetic factors, and low calcium intake (Wasnich, 1996). There are other conditions that have been suggested to be risk factors for osteoporosis, although their definitive role has not been proven. Among these, chronic obstructive pulmonary disease (COPD) is one of the most common debilitating diseases that have been linked to the development of osteoporosis (Szymanski et al., 2002; Sinet al., 2003; Katsura and Kida, 2002). Osteoporosis often remains undiagnosed, as the focus during the last few decades has been on the level of lung function and ability of oxygenation, but not on the bone loss. Osteoporosis, however, may be equally as disabling as COPD, and may impair respiratory function further if the patient experiences vertebral compressions and loss of height (Leech et al., 1990; Biskobing, 2002). Although primarily a pulmonary disease, COPD has important systemic features (Jorgensen and Schwarz, 2008), like skeletal muscle atrophy and weakness (Wouters, 2004), arterial stiffness (Sabit et al., 2007) and osteoporosis. Indeed, COPD patients have been found to have an increased prevalence of osteoporosis as compared to healthy subjects (Graat-Verboom et al., 2009).
One of the most obvious causes of osteoporosis in COPD patients is the treatment with glucocorticoids, as systemic therapy or inhaled glucocorticoids (Kanis et al., 2004; McEvoy et al., 1998). Furthermore, Johnell et al., (2002) showed that treatment with inhaled corticosteroid did not increase the risk of osteoporosis in patients with COPD. It is expected that women with COPD would be more susceptible to develop osteoporosis than women with normal lung function. Furthermore, the incidence of osteoporosis is higher in women than in men in presence of COPD. It is well-established that women are more prone to develop COPD even if they on an average basis do not smoke as much as men. This is partially because they are less resistant to the harmful side effects of smoking than men, but also that women live longer, and live to an older age with their lung disease (Prescott et al., 1997). The pathophysiology underlying the development of osteoporosis in COPD patients is largely unknown, but during the last few years a number of studies have shed light on the possible mechanisms involved. Patients with COPD appear to be under a state of continuous systemic inflammation, (Jorgensen and Schwarz, 2008) and this inflammatory state seems to be associated with the production of a number of chemoattractants and inflammatory markers as well as markers of destruction, including members of the matrix metalloproteinase (MMP) enzyme family (Jorgensen and Schwarz, 2008). These biomarkers also appear to be predictive of the lung capacity measured by forced expiratory volume in 1 s (FEV1), (Jorgensen and Schwarz, 2008), suggesting that more serious inflammation results in more severe lung disease. Osteoporosis is found in a proportion of patients with COPD and confirms the view that long-term epidemiological studies which would take into account various stages of the disease are required in order to identify the patients who have a high risk to develop osteoporosis (Biskobing, 2002).

**Aim of the Study**

**The aim of this study was to assess:**

- The risk of osteoporosis in chronic obstructive pulmonary disease compared to that in healthy age-matched control subjects, and study this risk in various degrees of disease severity.
- The correlations of age, body mass index and forced expiratory volume in 1 second (FEV1) % predicted with the osteoporosis.

**MATERIAL AND METHODS**

The study had approved from regional committee of Mosul health administration and conducted at the outpatient clinic of Ibn Sina teaching hospital in Mosul during the period between 1/11/2010 and 1/5/2011. It is a clinical case controlled study. Fifty three Known cases of chronic obstructive pulmonary disease followed at the respiratory outpatient clinic by their physicians in Ibn Sina teaching hospital in Mosul participated in the study are included in the study.

**Inclusion criteria included**

- Age ranges between 50 - 83 years.
- Abnormal findings of pulmonary function tests, demonstrating nonreversible airway obstruction based on ATS criteria (< 200 ml and 12% improvement in FEV1 OR FVC after inhalation of salbutamol) (American Thoracic Society, 1991) and known to have COPD.

**Exclusion criteria included**

- Respiratory symptoms rather than COPD.
- Reversible airway obstruction after bronchodilator therapy.
- Diabetic patients.
- Rheumatic diseases.

**Controls:** Fifty three apparently healthy individuals matched for age and sex with the patients were kept as control group. They denied respiratory symptoms like dyspnoea or chronic sputum production, or diagnosed respiratory diseases.

**Data collection**

The main source of data was obtained directly from all the studied subjects during interviews with them. The study was designed as a case controlled study, based on historical data on concomitant medication combined with clinical data and a questionnaire obtained at the study visit at the outpatient clinic. Basic demographic and clinical data were collected during the study using a questionnaire concerning: age, gender, body weight in (kg), height in (m), previous bone fractures, present and previous medication, tobacco consumption (pack-years), daily exercise, daily diet and characteristic symptoms of both COPD and osteoporosis (Appendices No.1, 2, 3, 4).

**Instruments and materials**

- Weight and height scale (seca; made in Germany).
- Computerized spirometer (Discom-14; made in Tokyo-Japan).
- Dual-energy X-ray absorptiometry (DEXA) (Hologic; made in China).
- Three kits for serum calcium, phosphorus and alkaline phosphatase (Biolabo; made in France).
- Disposable syringes.
- Plastic tubes.
- Micropipettes.
- Centrifuge (Kukusan; made in Japan).
- Sputum production, or diagnosed respiratory diseases.
- Stethoscope.
- Spectrophotometer (C-cil; made in France).
- Nebulizer (Atomizer; made in France).

Figures (3-1) and (3-2) show the way of measurement of bone mineral density using DEXA scanner.
MATERIALS AND METHODS

All the study groups were subjected to the following clinical assessment: Weight was measured with barefoot and light clothes by weighting scale with fixed tape for height measurement. Body mass index was calculated according to the following equation: \( \text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \). Low BMI was defined as 18.5 kg/m\(^2\) or less, based on WHO criteria. A person's smoking intensity is measured in pack-years. "One pack-year" means that a person has smoked approximately 1 pack (20 cigarettes) per day for 1 year; smoking 1/2 pack a day for 1 year is equivalent to 1/2 pack-year; and smoking 2 packs a day for 1 year is equivalent to 2 pack-years. The forced expiratory volume in 1 second (FEV\(_1\)) was measured with the computerized spirometer in the respiratory outpatient clinic of Ibn Sina teaching hospital in Mosul. This computerized spirometer is reliable (r=0.84 to 0.96) and valid, according to the American Thoracic Society standards (Gardner and Hankinson, 1988). The FEV\(_1\)% pred. was used to determine the level (severity) of COPD using the global initiative of obstructive lung disease (GOLD) (Pauwels et al., 2001). The GOLD classifies patients into different stages based on FEV\(_1\)% predicted. Accordingly, patients with normal FEV\(_1\)% predicted were classified as GOLD 0, patients with an FEV\(_1\) \(\geq\) 80% predicted were classified as GOLD I, patients with an FEV\(_1\) between 50% and 80% of predicted as GOLD II, patients with an FEV\(_1\) between 30% and 50% as GOLD III and finally, patients with an FEV\(_1\) < 30% as GOLD IV. Table (3-1) shows the classification of COPD in GOLD stages. From Pauwels et al., 2001. Dual-energy X-ray absorptiometry (DEXA) method is considered to be the gold standard to measure bone mineral density (BMD) (Mautalen, 2001; Sadat-Ali et al., 2004). So in this study, the BMD was measured by DEXA method of both lumbar spine and hip to diagnose osteoporosis based on the lowest T-score of the measured locations and conducted in the DEXA unit of Ibn Sina teaching hospital in Mosul. According to the WHO criteria for diagnosis of osteoporosis in concern to T-score for BMD, we categorize the patients and control subjects to osteoporosis, osteopenia, or normal bone mass. The lowest T-score at either region determined the diagnosis. Thus, if the T-score at either region was below -2.5, the individual was diagnosed as having osteoporosis. If the lowest T-score at either region was between -2.5 and -1.0 the subject was diagnosed with osteopenia. If both hip and lumbar spine T-score was above -1.0 the study subject was grouped as having normal bone mass. The type of dual-energy X-ray absorptiometry was Hologic. For more accurate way to reflect the day-to-day variance is to establish the baseline phantom value would be to scan the phantom once a day for 15 to 25 consecutive days and then averaging these scans. After baseline value established subsequent BMD results should not vary by more than 1.5% of the established baseline. If any single measurement is more than 1.5% from the baseline, the phantom measurement should be repeated. If the second measurement is more than 1.5% from baseline, the equipment service representative should be contacted for a more detailed system evaluation. Basic laboratory parameters were analyzed in order to exclude patients with other causes of osteoporosis. The following parameters were determined: ESR (m.m./H), S. alkaline phosphatase (u/L), S. calcium(mmol/L), S. phosphorus (mmol/L).
**Statistical analysis:** All variables were presented as means ± standard deviation (SD) and compared with analysis of variance, paired samples T-test. Some of data were calculated manually as strict number and percentage in relation to the same sample. Variables correlation by paired samples correlation was performed to know the direction and degree of affection of each variable. Univariate and multivariate multinomial logistic regression analyses (enter procedure) were performed to investigate determinants of osteopenia and osteoporosis based on DEXA findings. All study subjects were analyzed. Univariate analyses with osteoporosis, osteopenia and normal BMD as dependent variable were used to test for the potentially confounding effect of biomedical and demographic factors. If significant at \( p<0.05 \), the variables were included into the multivariate analyses. A \( p \)-value <0.05 was used to indicate statistical significance. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 17.0.

**RESULTS**

Table (4-1) shows the number and percentage of male and female in each group included in the study. There was no statistically significant difference between the patients and healthy control groups (\( P \)-value= 0.497).

Table (4-2) shows ages in both groups included in the study. There was no statistically significant difference between the patients and the healthy control groups (\( P \)-value= 0.940). Table (4-3) shows the number and percentage of the three degrees of bone mineral density (BMD) in both patients and healthy control group included in our study. Twenty two (41.5%) patients were shown to have osteoporosis by BMD, while 25(47.2%) were osteopenic and 6(11.3%) had normal bone mass. Again, 11(20.7%) control subjects were diagnosed as having osteoporosis by BMD, while 33(62.3%) were osteopenic and 9(17%) had normal bone density. Table (4-4) shows the number and percentage of the patients with COPD in different Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) stages in patients with Chronic Obstructive Pulmonary Disease (COPD) in relation to the BMD. There was positive correlation between the severity of osteoporosis and GOLD stages (severity) of the COPD (\( r=0.658 \)). Table (4-5) shows the baselines characteristics of patients for the different Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages with its correlations to different variables including sex, age, body mass index and FEV1 (% predicted). According to the Global Initiative for Chronic Obstructive Lung Disease criteria (GOLD, 2006), there were 7, 20 and 26 patients, respectively, with stage 0, I and II disease.

### Table 3-1. Classification of Chronic Obstructive Pulmonary Disease by Severity

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>Severity</th>
<th>GOLD Criteria for COPD Severity</th>
<th>FEV1/FVC</th>
<th>FEV, % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>At Risk</td>
<td>Chronic cough, sputum production</td>
<td>≥70%(0.07)</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>Mild</td>
<td>With or without chronic cough or sputum production</td>
<td>&lt;70%(0.07)</td>
<td>≥80%</td>
</tr>
<tr>
<td>II</td>
<td>Moderate</td>
<td>With or without chronic cough or sputum production</td>
<td>&lt;70%(0.07)</td>
<td>50–79.9%</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>With or without chronic cough or sputum production</td>
<td>&lt;70%(0.07)</td>
<td>30–49.9%</td>
</tr>
<tr>
<td>IV</td>
<td>Very severe</td>
<td>With or without chronic cough or sputum production</td>
<td>&lt;70%(0.07)</td>
<td>&lt;30%</td>
</tr>
</tbody>
</table>

### Table 4-1. The number and percentage of male and female in the patients and the control groups

<table>
<thead>
<tr>
<th>Sex</th>
<th>Patients group (n=53)</th>
<th>Control group (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32(60.4%)</td>
<td>29(54.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>21(39.6%)</td>
<td>24(45.3%)</td>
</tr>
</tbody>
</table>

### Table 4-2. The age in the patients and the control groups. Data expressed as Mean±SD

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Patients</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>59.72±7.78</td>
<td>59.59±9.31</td>
</tr>
</tbody>
</table>

### Table 4-3. The number and percentage of the three categories of bone mineral density in patients and control groups

<table>
<thead>
<tr>
<th>T-score / BMD</th>
<th>Patients (n=53)</th>
<th>Control (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Normal (≥-1)</td>
<td>6</td>
<td>11.3</td>
</tr>
<tr>
<td>Osteopenia (-1 &lt; &gt; -2.5)</td>
<td>25</td>
<td>47.2</td>
</tr>
<tr>
<td>Osteoporosis (≥-2.5)</td>
<td>22</td>
<td>41.5</td>
</tr>
</tbody>
</table>

### Table 4-4. The number and percentage of the patients with COPD in different GOLD stages in relation to the BMD

<table>
<thead>
<tr>
<th>T-score</th>
<th>GOLD* stage 0/ n=7</th>
<th>GOLD stage I/ n=20</th>
<th>GOLD stage II/ n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: (≥-1) (n = 6)</td>
<td>2(28.6%)</td>
<td>3(15%)</td>
<td>1(3.8%)</td>
</tr>
<tr>
<td>Osteopenia: (-1 &lt; &gt; -2.5) (n =25)</td>
<td>3(42.9%)</td>
<td>10(50%)</td>
<td>12(46.2%)</td>
</tr>
<tr>
<td>Osteoporosis: (≥-2.5) (n = 22)</td>
<td>2(28.6%)</td>
<td>7(35%)</td>
<td>13(50%)</td>
</tr>
</tbody>
</table>

### Table 4-5. The sex, age and BMI in different GOLD stages in patients with COPD. Data expressed as Mean±SD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>GOLD Stages</th>
<th>GOLD Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>stage 0/ n=7</td>
<td>stage I/ n=20</td>
<td>stage II/ n=26</td>
</tr>
<tr>
<td>Male/female</td>
<td>32/21</td>
<td>3/4</td>
<td>11/9</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>59.7±7.8</td>
<td>58.9±9.3</td>
<td>59.4±8.5</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.9±6</td>
<td>30.4±7.4</td>
<td>26.4±5.9</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>82.2±21.3</td>
<td>107.5±12.7</td>
<td>90.7±23.3</td>
</tr>
</tbody>
</table>

*FEV1 = forced expiratory volume in 1 second
There was a statistically significant difference in the listed characteristics for the different GOLD stages (P-value=0.001). The correlation between COPD severity and age and BMI was positive (r=0.061, r=0.091, respectively) in contrast to sex and FEV1 (% predicted) was negative (r=-0.219, r=-0.699, respectively). Table (4-6) shows the body mass index in normal, osteopenia and osteoporosis in both groups included in the study. There was no statistically significant difference between the patients and healthy control group (P-value=0.322). Table (4-7) shows the number and percentage of the patients and the control group who had body mass index less than 20 kg/m² in the normal, osteopenia and osteoporosis.

Table 4-6. The body mass index (BMI) in normal, osteopenia and osteoporosis in the patients with COPD and the control subject. Data expressed as Mean±SD

<table>
<thead>
<tr>
<th>T-score</th>
<th>BMI (kg/m²)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: ≥1</td>
<td>28.2±5.95</td>
<td>30±4.01</td>
</tr>
<tr>
<td>Osteopenia (-1&lt;&gt;-2.5)</td>
<td>25.42±5.65</td>
<td>27.66±6.66</td>
</tr>
<tr>
<td>Osteoporosis (-2.5)</td>
<td>23.61±3.76</td>
<td>24.03±5.72</td>
</tr>
</tbody>
</table>

Table 4-7. The number and percentage of the patients with COPD and the control group with body mass index less than 20 kg/m² in the normal, osteopenia and osteoporosis

<table>
<thead>
<tr>
<th>T-score / BMD*</th>
<th>BMI &lt; 20 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Normal: ≥1</td>
<td>0</td>
</tr>
<tr>
<td>Osteopenia: (-1&lt;&gt;-2.5)</td>
<td>1</td>
</tr>
<tr>
<td>Osteoporosis: (-2.5)</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4-8. Comparison of the fragility fractures between COPD patients and control group in number and percentage

<table>
<thead>
<tr>
<th>Fragility fractures</th>
<th>Patients No=53</th>
<th>Control No=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fracture</td>
<td>2(3.8%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>3(5.7%)</td>
<td>1(1.9%)</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>4(7.6%)</td>
<td>1(1.9%)</td>
</tr>
<tr>
<td>Chest fracture</td>
<td>2(3.8%)</td>
<td>1(1.9%)</td>
</tr>
<tr>
<td>Total number</td>
<td>11(20.9%)</td>
<td>3(5.7%)</td>
</tr>
</tbody>
</table>

Table 4-9. The number and percentage of the three categories of bone mineral density in women and men in COPD patients

<table>
<thead>
<tr>
<th>T-score</th>
<th>Total number</th>
<th>Women (n=21)</th>
<th>Men (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: ≥1</td>
<td>6(11.3%)</td>
<td>3(14.3%)</td>
<td>3(9.4%)</td>
</tr>
<tr>
<td>Osteopenia (-1&lt;&gt;-2.5)</td>
<td>25(47.2%)</td>
<td>10(47.6%)</td>
<td>15(46.9%)</td>
</tr>
<tr>
<td>Osteoporosis (-2.5)</td>
<td>22(41.5%)</td>
<td>8(38.1%)</td>
<td>14(43.7%)</td>
</tr>
</tbody>
</table>

Table (4-8) shows the number and percentage of each fragility fracture in both COPD patients and control subjects. There was increased percentage of fragility fracture in COPD patients (20.8%) in comparison to the control group (5.7%). In patients, 2 of them had vertebral fracture, 3 had hip fracture, 4 had wrist fracture and lastly 2 patients had chest fracture. In the other hand, the control group have developed only one fracture in each of hip, wrist and chest. Table (4-9) shows the number and percentage of normal, osteopenia, osteoporosis and patients with COPD regarding bone mineral density whether are males or females 3(9.4%), 15(46.9%), 14(43.7%) versus 3(14.3%), 10(47.6%), 8(38.1%), respectively. The number of osteoporosis in men patients was 14 while in women patients was 8.

Table (4-10) shows the correlation between the three bone density groups with age, BMI and FEV1% predicted in patients with COPD. There was a positive correlation between the bone mineral density and age (r=0.495), while the BMI and FEV1% predicted were negatively correlated with the bone mineral density (r=-0.383, r=-0.437, respectively). As shown, the BMI and FEV1% predicted of the patients had decreased with decreasing the (T-score) bone mineral density (BMD) that means the more decreased BMI the more severe osteoporosis.

Table 4-10. Correlation between the three bone density groups with different variables in patients with COPD. Data expressed as Mean±SD

<table>
<thead>
<tr>
<th>T-score / BMD</th>
<th>Age (yrs)</th>
<th>BMI kg/m²</th>
<th>FEV1% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (≥1)</td>
<td>55.8±6.9</td>
<td>28.2±6</td>
<td>77.9±14.4</td>
</tr>
<tr>
<td>Osteopenia (-1&lt;&gt;-2.5)</td>
<td>58.4±8</td>
<td>25.4±5.7</td>
<td>88.3±20.2</td>
</tr>
<tr>
<td>Osteoporosis (-2.5)</td>
<td>62.3±7.3</td>
<td>23.6±3.8</td>
<td>76.4±22.8</td>
</tr>
</tbody>
</table>

Figure 4-1 shows that the percentage of a low BMD increases with a higher Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) stage. The percentage of T-scores between -1 and -2.5 was (42.9%) in GOLD stage 0, (10.5%) in GOLD stage I and (12.46%) in GOLD stage II. Percentage of T-scores less than or equal to -2.5 was (28.6%) in GOLD stage 0, (735%) in GOLD stage I and (1350%) in GOLD stage II. There was a significant difference in bone mineral density between GOLD stage 1 and GOLD stage 2 in patients with COPD (P-value=0.001).

Figure 4-2. FEV1% predicted in different bone mineral densities
Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction with breathing-related symptoms such as chronic cough, exertional dyspnea, expectoration, and wheeze (Rennard, 1998). These symptoms may occur in conjunction with airway hyperresponsiveness and may be partially reversible. Although COPD is a nonspecific term referring to a set of conditions that develop progressively as a result of a number of different disease processes, it most commonly refers to chronic bronchitis and emphysema and a subset of patients with asthma (Ionescu and Schoon, 2003). COPD is a progressive disease of adulthood and older age.

While the initial treatment is focused on relieving the symptoms due to the impairment of the lung function, a variety of systemic effects become obvious as the disease progresses (Gross, 2001; Wouters et al., 2002; Ionescu and Schoon, 2003; Schols et al., 1996; DiFrancia et al., 1994).

**Global Initiative on Obstructive Lung Disease Criteria for chronic obstructive pulmonary disease:** Several different definitions have existed for COPD (American Thoracic Society, 1995; Mannino, 2001). The recently published and widely accepted definition from Global Initiative on Obstructive Lung Disease (GOLD) defines COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (Pauwels et al., 2001). Airflow limitation is the slowing of expiratory airflow as measured by spirometry, with a persistently low forced expiratory volume in 1 second (FEV1) and a low FEV1/forced vital capacity (FVC) ratio despite treatment (Mannino, 2001). The GOLD definition for airflow limitation is an FEV1/FVC ratio of less than 70% (Pauwels et al., 2001; WHO, 2001). Airflow limitation reversibility can occur spontaneously, in response to an inhaled bronchodilator, or in response to oral or inhaled corticosteroids (Mannino, 2001; Pauwels et al., 2001; WHO, 2001; Dirksen et al., 1991). The GOLD definition of COPD classifies reversibility as an FEV1 increase of 200 mL and 12% improvement above baseline FEV1 following administration of either inhaled corticosteroids or bronchodilators (GOLD Committee, 2006). The term partial reversibility describes patients who in fact have “reversibility” in response to administration of either corticosteroids or a bronchodilator, yet their best FEV1 and FEV1/FVC ratio classifies them as having airflow limitation.Severity of COPD has typically been determined using the degree of lung function impairment, although the wisdom of this approach has been questioned recently, with the suggestion that other signs and symptoms, such as arterial blood gases values, body mass index, timed walking distance, and the sensation of dyspnea, be included in this determination (Mannino, 2001; Bestall et al., 1999). The GOLD criteria classify COPD into 4 stages based primarily on lung function impairment (table 3-1): Stage I (FEV1 ≥ 80% predicted), Stage II (FEV1 50%–79% of predicted), Stage IIB (FEV1 30%–49% of predicted) and Stage III (FEV1 < 30% of predicted) (Pauwels et al., 2001; WHO, 2001). Additionally, GOLD lists a stage 0 level of disease, which describes persons who have normal lung function yet report respiratory symptoms such as chronic cough or sputum production.

**Osteoporosis:** Osteoporosis is a systemic skeletal disease characterized by microarchitectural reduction of bone tissue leading to a low bone mass, increased bone fragility and thereby increased fracture risk (Ionescu and Schoon, 2003). The preclinical state of osteoporosis is called osteopenia. Osteoporosis is commonly found in postmenopausal females and elderly subjects, or as a consequence of chronic disease or medical treatment (Naghshin et al., 2004).

**Pathophysiology:** Osteoporosis results from a combination of genetic and environmental factors that affect both peak bone mass and the rate of bone loss. These factors include medications, diet, race, sex, lifestyle, and physical activity. Osteoporosis may be either primary or secondary. Primary osteoporosis is subdivided into types 1 and 2. Secondary
To be an independent risk factor for osteoporosis in both men and women (Biskobing, 2002; Daniell, 1976; Sparrow et al., 1982), Biskobing (2002) reported that lumbar spine BMD was 12% lower in smokers who had smoked 20 pack-years compared to nonsmokers. There is a significantly greater rate of bone loss in smokers (Sparrow et al., 1982; Krall and Dawson-Hughes et al., 1991; Biskobing, 2002). Heavy smokers have been shown to have lower bone mineral content at the distal radius and lower BMD at the lumbar spine, while there was no difference between light smokers and nonsmokers. These findings were associated with addition of increased fractures in smokers who start this habit early in their life have a deficit in the peak bone mass (Biskobing, 2002). Both vertebral fractures and hip fractures are increased in smokers (Biskobing, 2002; Juliet, 2007; Cooper et al., 1988). The risk of vertebral fractures among long term smokers was increased 2.3-fold (Biskobing, 2002), while the risk for hip fractures was increased 1.7-fold among smokers (Lorentzon et al., 2007). The pathophysiologic mechanism for the lower bone mass and increased fracture risk in smokers is unclear. Estrogen levels have suggested that are lower in female smokers compared to nonsmokers (Seeman, 1996). Furthermore, there is evidence of decreased calcium absorption in the GI tract in smokers compared to nonsmokers (Krall and Dawson-Hughes et al., 1991). In addition to the effect of smoking on the deficit of peak bone mass, the level of regular exercise was the single most important determinant of peak bone mass (BMD at femoral neck was up to 10% greater in those who exercised regularly). Again, increased calcium intake contributed by a 4.7% increase in BMD at the femoral neck only in females (Ionescu and Schoon, 2003). Increased alcohol intake is an independent risk factor for osteoporosis (Biskobing, 2002). It is found in those who had >1.5 drinks per day (mean 95.5 g alcohol per week) than in those who did not drink (0.062 g·cm⁻³) (Lorentzon et al., 2007). The risk for vertebral fractures due to osteoporosis was greater for males who drank (relative risk 2.4, p=0.02) than for those who did not and it was 1.007 greater per ounce-year of drinking (p=0.02) (Juliet, 2007). The combination of tobacco and alcohol use markedly increases the risk for osteoporosis. Alcohol use has been shown to be independently related to bone loss in a dose-dependent manner (i.e., greater rates of bone loss are seen in those persons who consume higher amounts of alcohol). It is demonstrated that the highest rate of bone loss seen in those patients with high alcohol and tobacco use. Vertebral fracture risk is markedly increased in those who both smoke and drink alcohol, and magnifies the aging related risk. In non-obese smokers and drinkers aged 60 to 69 years, the relative risk for vertebral fracture was 3, and in those aged 70 years, the relative risk increased to 20.2 (Biskobing, 2002).

**Risk factors**

*Race:* Whites (especially of northern European descent) and Asian persons are at an increased risk for osteoporosis (National Osteoporosis Foundation, 2008).

*Sex:* Overall, osteoporosis has a female-to-male ratio of 4:1 (National Osteoporosis Foundation, 2008). Eighty percent of hip fractures occur in women (Smith and Wordsworth, 2005).

*Age:* The frequency of postmenopausal osteoporosis is highest in women aged 50-70 years. Senile osteoporosis is most common in persons aged 70 years or older. Secondary osteoporosis can occur in persons of any age. Ninety percent of hip fractures occur in persons aged 50 years or older (Smith and Wordsworth, 2005).

*Family history:* Family history of osteoporosis, particularly maternal history of fractures (Keen, 2007).

*Reproductive factors:* Reproductive factors, especially regarding early menopause and estrogen replacement therapy, in addition to the first years of menopause are associated with accelerated bone loss. The lack of gonadal hormones is thought to up regulate osteoclast progenitor cells (Smith and Wordsworth, 2005).

*Smoking and other lifestyle factors:* Smoking has been shown to be an independent risk factor for osteoporosis in both men and women (Biskobing, 2002; Daniell, 1976; Sparrow et al., 1982). Biskobing, (2002) reported that lumbar spine BMD was 12% lower in smokers who had smoked 20 pack-years compared to nonsmokers. There is a significantly greater rate of bone loss in smokers (Sparrow et al., 1982; Krall and Dawson-Hughes et al., 1991; Biskobing, 2002). Heavy smokers have been shown to have lower bone mineral content at the distal radius and lower BMD at the lumbar spine, while there was no difference between light smokers and nonsmokers. These findings were associated with addition of increased fractures in smokers who start this habit early in their life have a deficit in the peak bone mass (Biskobing, 2002). Both vertebral fractures and hip fractures are increased in smokers (Biskobing, 2002; Juliet, 2007; Cooper et al., 1988). The risk of vertebral fractures among long term smokers was increased 2.3-fold (Biskobing, 2002), while the risk for hip fractures was increased 1.7-fold among smokers (Lorentzon et al., 2007). The pathophysiologic mechanism for the lower bone mass and increased fracture risk in smokers is unclear. Estrogen levels have suggested that are lower in female smokers compared to nonsmokers (Seeman, 1996). Furthermore, there is evidence of decreased calcium absorption in the GI tract in smokers compared to nonsmokers (Krall and Dawson-Hughes et al., 1991). In addition to the effect of smoking on the deficit of peak bone mass, the level of regular exercise was the single most important determinant of peak bone mass (BMD at femoral neck was up to 10% greater in those who exercised regularly). Again, increased calcium intake contributed by a 4.7% increase in BMD at the femoral neck only in females (Ionescu and Schoon, 2003). Increased alcohol intake is an independent risk factor for osteoporosis (Biskobing, 2002). It is found in those who had >1.5 drinks per day (mean 95.5 g alcohol per week) than in those who did not drink (0.062 g·cm⁻³) (Lorentzon et al., 2007). The risk for vertebral fractures due to osteoporosis was greater for males who drank (relative risk 2.4, p=0.02) than for those who did not and it was 1.007 greater per ounce-year of drinking (p=0.02) (Juliet, 2007). The combination of tobacco and alcohol use markedly increases the risk for osteoporosis. Alcohol use has been shown to be independently related to bone loss in a dose-dependent manner (i.e., greater rates of bone loss are seen in those persons who consume higher amounts of alcohol). It is demonstrated that the lowest rate of bone loss seen in those patients with high alcohol and tobacco use. Vertebral fracture risk is markedly increased in those who both smoke and drink alcohol, and magnifies the aging related risk. In non-obese smokers and drinkers aged 60 to 69 years, the relative risk for vertebral fracture was 3, and in those aged 70 years, the relative risk increased to 20.2 (Biskobing, 2002).

**Vitamin D deficiency:** Vitamin D regulates the absorption of calcium, parathyroid hormone secretion and bone resorption. Vitamin D is essential for the absorption and assimilation of calcium. Vitamin D also has direct effects on bone remodeling and either direct or indirect effects on muscle strength and balance (Hausssler and McCain, 1992). Accordingly, vitamin D deficiency may lead to decreased mineralization of bone and contribute to decreased BMD (Raisz, 1988; Reid, 1996).

**Immobility and Reduced peripheral skeletal muscle mass and strength:** Normal weight-bearing activity has been shown to be required for maintenance of bone mass. Complete immobilization such as in paralysis or in experimental settings has been shown to accelerate bone turnover, resulting in decreased BMD (Kiralli, 1996; Gambert et al., 1995). The
force generated by the skeletal muscles during voluntary contractions has an important role in the postnatal development of the bone. The muscle strength increases with growth in childhood and declines in adulthood. It is usually followed by age-related changes in the bone mass (Frost, 1997). The physiological process of ageing is accompanied by a decline in the skeletal muscle mass, referred to as sarcopenia, where the progressive reduction of the diameter of the muscles and of the number of muscle fibres is associated with a decline in the muscle strength (Evans, 1995; Sandler, 1989). Both the muscle mass and strength are related to BMD (Sandler, 1989; Henderson et al., 1998). In the elderly sarcopenia and the muscle weakness are associated with increased rates of falls and hip fractures (Frost, 1999; Scheibel, 1985). The close relationship between the skeletal muscle strength and the bone mass is supported by the beneficial effects of resistance training on BMD (Layne and Nelson, 1999). The greater the stress on a bone area, the greater the bone mass, therefore the mechanical stress applied to the bone during training increases the BMD (Aniansson et al., 1984). The decreased activity and muscle strength may increase their risk for falls and fractures since several studies (Cummings et al., 1995; Cooper et al., 1988) have demonstrated an inverse correlation between hip fracture risk and activity level. Decreased activities such as standing, walking, stair climbing, and housework, as well as decreased grip strength and ability to rise from a chair, have been shown to be associated with a significantly increased risk for hip fracture in postmenopausal women (Cummings et al., 1995; Cooper et al., 1988).

**Body mass index and changes in body composition:** Bone mass is directly correlated with Body mass index (BMI) (Ionescu and Schoon, 2003; Heaney, 1998). Both men and women with high BMIs have higher BMD. This is thought to be partially due to the effect of the greater weight-bearing load on the bone. In addition, estrogen levels tend to be higher in obese people due to the increased aromatization of testosterone to estrogen in adipose tissue (Cauley et al., 1996). The resulting higher estradiol levels may help to explain the higher BMD in obese persons, since estradiol levels in both men and women correlate with BMD (Khosla et al., 1998; Greendale et al., 1997). Malnutrition, as well, may contribute to the low BMD associated with low BMI, as demonstrated in a recent study of otherwise healthy subjects (Biskobing, 2002). Bone mass is related to fat free mass (FFM) in males (Mostert et al., 2000), while in females some investigators reported a relationship between fat mass (FM) and bone density (Edelstein and Barrett-Connor, 1993; Ionescu and Schoon, 2003) and others between both FM and FFM and bone density (Ionescu and Schoon, 2003; Compton et al., 1992). The relationship between FM and/or FFM and bone mass suggests that the load of soft tissues is important in the preservation of bone mass. In underweight elderly the bone mineral content was reduced compared to age-matched subjects with a normal BMI (Ionescu and Schoon, 2003; Biskobing, 2002).

**Causes of secondary osteoporosis (Kelman and Lane, 2005)**

- Endocrine disorders - Hyperparathyroidism, hypogonadism, hyperthyroidism, diabetes mellitus, Cushing disease, prolactinoma, acromegaly, adrenal insufficiency.
- Gastrointestinal/nutritional conditions - Inflammatory bowel disease, celiac disease, malnutrition, history of gastric bypass surgery, chronic liver disease, anorexia nervosa, vitamin D or calcium deficiency.
- Renal disease - Chronic kidney disease, idiopathic hypercalcemia.
- Rheumatologic diseases - Rheumatoid arthritis, anklyosing spondylitis, systemic lupus erythematosus.
- Hematologic disease - Multiple myeloma, thalassemia, leukemia, lymphoma, hemophilia, sickle cell disease, systemic mastocytosis.
- Genetic disorders - Cystic fibrosis, osteogenesis imperfecta, homocystinuria, Ehlers-Danlos syndrome, Marfan syndrome, hemochromatosis, hypophosphatasia.
- Other - Porphyria, sarcoid, immobilization, pregnancy/lactation, COPD, parenteral nutrition, HIV/AIDS.

**Medications known to cause or accelerate bone loss** (Raisz, 2005; Van Staa et al., 2002):

- Corticosteroids - Prednisone (5 mg/d for 3 mo)
- Anticonvulsants - Phenytoin, barbiturates, carbamazepine (These agents are associated with treatment-induced vitamin D deficiency).
- Heparin (long-term).
- Chemotherapeutic/transplant drugs - Cyclosporine, tacrolimus, platinum compounds, cyclophosphamide, ifosfamide, methotrexate.
- Hormonal/endocrine therapies - Gonadotropin-releasing hormone (GnRH) agonists, luteinizing hormone-releasing hormone (LHRH) analogs, denopromedroxyprogesterone, excessive thyroid supplementation.
- Lithium.
- Aromatase inhibitors - Exemestane, anastroazole.

**Osteoporosis Secondary to the Chronic Obstructive Pulmonary Disease:** Osteoporosis has been recognized as one of the systemic effects of COPD and debate continues on the precise mechanisms involved and on the options for treatment (Biskobing, 2002; McEvoy et al., 1998; Praet et al., 1992). The etiology of osteoporosis in COPD is probably complex and various factors may contribute to its pathogenesis. Some of these are consequences of the chronic inflammatory lung disease and lung damage (reduced physical activity due to dyspnoea, reduced skeletal muscle mass and changes in body composition, systemic inflammation), of the therapy used during the disease (corticosteroid treatment), and of the natural changes due to ageing (hypogonadism, reduced muscle mass, inactivity). Environmental factors and habits from earlier in life also contribute to the pathogenesis of osteoporosis (Ionescu and Schoon, 2003). Large epidemiological trials aimed to assess the incidence and prevalence of osteoporosis within populations of patients with COPD at various stages of disease severity are lacking. Information about the frequency of osteoporosis associated with COPD is available mainly from assessments before lung transplantation in patients with severe disease and from studies on the use of corticosteroid treatments in COPD (Ionescu and Schoon, 2003). The incidences of osteopenia and osteoporosis (the T score is between -1 and -2.5 and ≤ -2.5, respectively) are increased with advancing Global Initiative on Obstructive Lung Disease (GOLD) stage (Vrieze et al., 2007). Furthermore, low BMD was correlated with low fat free mass (FFM) in GOLD IV patients and FFM could thus...
be used as a determinant of bone loss in this population. These findings were supported by a case-control study, (Kjensli et al., 2007), in which patients with COPD were found to have lower bone mass than controls, and decreasing BMD was found with increasing GOLD stage. In another hand, 68% of COPD patients had either low bone mass (osteopenia or osteoporosis) or a previously undiagnosed vertebral fracture, with 25% of the included patients having a vertebral fracture (Jorgensen et al., 2007). Patients with cystic fibrosis (CF) referred for lung transplantation had greater frequency of osteoporosis (75%) than the COPD patients in the group studied by the same authors, while only 15% of those with other pulmonary disease had osteoporosis. Not surprisingly, of the 12 fractures that occurred in 45 patients after transplantation, six were found in patients with COPD and the rest in those with CF. A similar finding was reported in another group of 28 patients with COPD awaiting lung transplantation who had significantly lower BMD at the femoral neck site, which was only matched by patients with CF but not by those with other severe lung disease in the pre-transplantation group (Shane et al., 1996). The same authors reported a 29% prevalence of vertebral fractures in the pre-transplantation patients with COPD. With long-term oral corticosteroid treatment, a low BMD was found at the radial and vertebral bones in those treated with prednisolone, while a reduced trabecular BMD was also found in those who did not receive long-term corticosteroid treatment (Praet et al., 1992).

Pathophysiology of Osteoporosis in chronic obstructive pulmonary disease: It is likely that osteoporosis in patients with COPD is a consequence of various factors some having been present throughout the life of the patient, others due to the disease process itself and some specific to the treatment of the lung disease (Ionescu and Schoon, 2003). Increased concentrations of the circulating inflammatory mediators (tumour necrosis factor (TNF) - α, IL-6) have been reported in COPD, mainly in patients who lose weight and in those with a low FFM and skeletal muscle mass (Ionescu and Schoon, 2003; DiFrancia et al., 1994; Schols et al., 1996; Schols et al., 1999). Moreover, peripheral monocyes from patients with COPD who lose weight had an increased ability to produce TNF-α (de Godoy et al., 1996). Leukocyte-derived IL-1α and TNF-α stimulate bone resorption (Engelen et al., 1998; Gowen and Mundy, 1986; Bertolami et al., 1986) and IL-6 stimulates the formation of osteoclasts (Manolagas and Jilka, 1995). Peripheral macrophages from patients with idiopathic osteoporosis and rapid bone turnover produce increased amounts of IL-1 (Bogochetat, 2006). There is some evidence for a possible role of the inflammatory mediators on bone metabolism in COPD, which has been described in other diseases associated with weight loss, depletion of FFM and systemic inflammation such as chronic heart failure, cystic fibrosis or cancer (Anker et al., 1999; Ionescu and Schoon, 2003; Espat et al., 1995). The inflammation in COPD is also leading to a protein catabolic state. FFM is significantly decreased in these patients, (Vestbo et al., 2006) and the enzyme catalytic activity is increased, leading to muscle dysfunction and bone loss. Significant changes in the enzymatic function have been detected in sera from COPD patients in which increased activity of alkaline phosphatase has been found. This may be a sign of increased bone metabolism, and evidence of altered bone rearrangement in COPD patients (Jorgensen and Schwarz, 2008). Matrix metalloproteinase (MMP) activity (primarily MMP-9 and MMP-12) is also increased in sputum from COPD patients that are smokers and may account for both the destruction of lung tissue and the development of osteoporosis (Jorgensen and Schwarz, 2008). Most patients with COPD are not completely immobilized; however, advanced COPD often is associated with decreased functional status and mobility (Biskobing, 2002; Bourjeily and Rochester, 2000). The decreased exercise tolerance is due to multiple factors, including dyspnea and deconditioning due to respiratory and peripheral skeletal muscle weakness (Bourjeily and Rochester, 2000). Skeletal muscle dysfunction in COPD is probably multifactorial. The reduced mobility due to shortness of breath, the myopathy due to corticosteroid treatments and metabolic factors generate a vicious circle more obvious in patients with severe disease (American Thoracic Society and European Thoracic Society, 1999; Gosselin et al., 1996; Ionescu and Schoon, 2003). Patients with COPD are at risk to develop osteoporosis due to a reduced skeletal muscle mass and strength, both secondary to the disease and due to the natural process of ageing. It remains for future research to assess if training of various skeletal muscle groups improve BMD or prevent the progressive loss of bone mass (Ionescu and Schoon, 2003). It is found that BMI was the strongest predictor of osteoporosis in patients with COPD (Biskobing, 2002). Both the BMI and the mid arm muscle circumference (an index of FFM) were associated with a reduced BMD in patients with COPD (Biskobing, 2002). Such studies support the view that weight loss and mainly the depletion of FFM are factors contributing to the loss of BMD in some patients with COPD. Many patients with end-stage COPD lose weight as the disease progresses due to decreased intake and increased energy requirements (Schols and Wouters, 2000). Iqbal et al., (1999) reported that the lowest BMD was seen in a group of patients with BMI below the normal median and reported an independent correlation between BMI and BMD. Hypogonadism and the reduced availability of sex hormones, either due to ageing or to the effect of corticosteroid treatment, contribute to the development of osteoporosis. Oestrogen deficiency in females increases the bone loss after menopause, and the decline in circulating free oestrogen in elderly males has also been related to a reduction in bone mass (Raisz, 1988; Falahati-Nini et al., 2000; Ionescu and Schoon, 2003; Graat-Verboom et al., 2009; Seeman, 2002). Oestrogen regulates both bone resorption and formation, while testosterone regulates bone formation (Falahati-Nini et al., 2000; Ionescu and Schoon, 2003; Seeman, 2002).

Consequences of osteoporosis in chronic obstructive pulmonary disease: the risk of fractures: Osteoporotic or fragility fractures are extremely common, even than heart attack, stroke and breast cancer combined. At least one in three women and one in five men will suffer from an osteoporotic fracture during their lifetime (NOF, 2011). Over 80% of all fractures after age 50 are caused by osteoporosis. Despite availability of BMD testing and coverage for osteoporosis medications, over 80% of fracture patients are never offered assessment and/or treatment for osteoporosis post fracture (IOF, 2011). Once an osteoporotic fracture has occurred, another is more likely to occur in the absence of treatment (Greene and Dell, 2010). Osteoporosis is not a benign disease as both spine and hip fractures result in an increased mortality rate. Twenty-eight percent of women and 37% of men who suffer a hip fracture will die within the following year. Long term pain and disability are all too frequent. The fear of falling results in seclusion, isolation and depression (Osteoporosis Canada, 2011). Debate continues on the precise mechanisms and pathophysiology of osteoporosis in COPD, but most
Physicians are concerned about the risk of fractures, which would add to the disability of such patients. In a general population, a British epidemiological study reported that the two main independent factors for increased risk of hip fractures in the elderly were inactivity and muscle weakness (Cooper et al., 1988). The American National Health and Nutrition Examination Survey (NHANES) III found that weight loss of at least 10%, a low phalangeal bone density and the presence of any chronic condition were main factors, with smoking and low physical activity levels additional risk factors for hip fractures in White males (Mussolino et al., 1998). Such risk factors reported in a general population are likely be found in patients with COPD, who smoked or continue to smoke, are inactive and have weak skeletal muscles (Ionescu and Schoon, 2003). Fifty per cent of the patients with various disease treated with corticosteroids suffer fractures and the proportion is close to 100% in those treated for rheumatoid arthritis (Callahan et al., 1991; Van et al., 2000; Johnston et al., 1989; Cooper et al., 1995). A report on the use of oral corticosteroids and the risk of fractures, where 40% of patients were treated for respiratory disease found an increased rate of non-vertebral and hip fractures compared to the control group (relative rates (95% confidence interval (CI)) were 1.33 (1.29–1.38) and 1.61 (1.47–1.76), respectively).

The relative rate of non-vertebral fractures increased with the dose of corticosteroids from 1.17 in the low dose (<2.5 mg·day$^{-1}$) to 1.64 in the high dose group (at least 7.5 mg·day$^{-1}$) and most of the excess risk of fractures disappeared within 1 yr when the treatment was stopped (Van et al., 2000). A retrospective study on the risk of fractures in patients receiving inhaled corticosteroids, which included a 6% sample of the UK population and excluded patients with any confounding variables for fractures, reported a similar risk in patients who used inhaled corticosteroids and in those who received inhaled bronchodilators only, which suggests a role played by the chronic respiratory disease itself as a risk factor for osteoporosis. In both groups the risk of fractures was higher than in the control group, and the relative risk increased with the dose of inhaled corticosteroid treatment (beclometasone in 86.4% of cases) from 0.95 (95% CI 0.67–1.34) if <300 µg·day$^{-1}$ to 1.77 (1.31–2.40) if >700 µg·day$^{-1}$ (Van et al., 2001). Compared to the risk of fractures in postmenopausal females where for one SD reduction in BMD the risk doubles (Marshall et al., 1996). A cross-sectional study on 312 males with COPD assessed the prevalence of fractures in three groups: 1) patients who never used corticosteroids, 2) patients who received inhaled corticosteroids and 3) those receiving systemic steroids (range of the duration of corticosteroid treatments in group 3 was 2.5 to 1,300 weeks) (McEvoy et al., 1998). The prevalence of at least one vertebral fracture was 48.7% in group 1, 57.1% in group 2 and 63.3% in group 3, with ≥6 vertebral fractures found only in group 3. The high risk of fractures in the group who never used corticosteroids suggests that factors others than the treatment may be involved in the pathogenesis of osteoporosis. However, a study on a smaller number of patients with COPD and severe lung disease found no evidence of an increased risk of fractures in patients who were not receiving long-term corticosteroid treatment (Riancho et al., 1987), which suggests the need for further large prospective studies in order to investigate which patients with COPD are more at risk of fractures due to osteoporosis. The occurrence of fractures has implications for the morbidity and mortality. Severe osteoporosis with thoracic vertebral fractures and wedging with hyperkyphosis was associated with about 10% reduction in forced vital capacity (FVC) in females, with a cumulative effect of the number of fractures on the decline in FVC (Leech et al., 1990). Such a reduction in FVC would add to the lung function impairment and disability in patients with chronic lung disease. Mortality after hip fractures in the elderly is about 20% in the first year (highest mortality rate for any fractures) and 19% of these patients require residential care when discharged from hospital, which adds to the economic burden of the disease (Walker-Bone et al., 1998; Advisory Group on Osteoporosis, 1994).

**Diagnosis of osteoporosis**

**Dual-Energy X-Ray Absorptiometry:** Different methods of bone mineral density (BMD) measurements can be used. Dual energy X-ray absorptiometry (DEXA) is currently the most frequently used and is accurate, reproducible and involves very low doses of radiation. BMD is expressed in standard deviation of means, the T and Z scores. The T score is a standard deviation compared to a young adult sex-matched control population. The Z score is a standard deviation compared to an age- and sex-matched control population. One standard deviation reduction in the BMD increases the fracture risk by 1.5–3 folds (Marshall et al., 1996). The gold standard for the diagnosis of osteoporosis is DEXA (WHO, 2007). Multiple sites can be used to measure BMD by DEXA. The sites most frequently used are the hip, the lumbar spine, forearm and/or whole-body. Several studies investigated the best location for DEXA-scanning to diagnose osteoporosis (Graat-Verbroom et al., 2010-b; Arlot et al., 1997; Franck and Munz, 2000; Leslie et al., 2007; Nelson et al., 1998). DEXA scanning of the hip and the lumbar spine resulted in a higher prevalence of osteoporosis than whole-body DEXA scanning in pre- and postmenopausal women (Arlot et al., 1997). T-score is a value that compares the patient’s bone mass density to the individuals at their peak bone mineral density. Osteoporosis is defined by the World Health Organization as a T-score of <-2.5. Also, osteopenia defined as a T-score between -2.5 and -1 (Washnic, 1996). The most common BMD test is DEXA of the total hip, femoral neck, and lumbar spine, using the lowest of the 3 BMD scores for diagnosis (Sweet et al., 2009). BMD measurements are expressed in absolute terms of grams per square centimeter scanned (g/cm²) and as a relationship to two norms: compared to “young normal” adults of the same sex (T-score) or compared to the expected BMD for the patient’s age and sex (Z-score). The difference between the patient’s score and the norm is expressed in standard deviations (SD) above or below the mean. A negative value indicates a BMD measurement below the mean. Osteoporosis is defined according to T-scores as shown in the table below (National Osteoporosis Foundation, 2010).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T-score</th>
</tr>
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<tbody>
<tr>
<td>Normal bone mass</td>
<td>≥ -1.0</td>
</tr>
<tr>
<td>Osteopenia (low bone mass)</td>
<td>between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
</tbody>
</table>

A patient who has had a fragility fracture is considered to have osteoporosis regardless of the T-score (US Department of Health and Human Services, 2008). In postmenopausal women and men aged 50 years and over, the WHO diagnostic T-score criteria (normal, low bone mass and osteoporosis) are applied.
to BMD measurement by central DEXA at the lumbar spine, total hip and femoral neck. BMD measured by DEXA at the one-third (33%) radius site can be used for diagnosing osteoporosis when the hip and spine (National Osteoporosis Foundation, 2008).

**Quantitative Computed Tomography and Ultrasound:**

Quantitative computed tomography (QCT) is similar to DEXA in its ability to quantify the degree of bone loss and assess fracture risk accurately. In contrast to DEXA, QCT gives a true volumetric measurement of BMD and accurately discriminates trabecular bone from cortical bone. QCT may overestimate the extent of bone loss with age and glucocorticoid use because bone marrow fat increases in these two clinical settings. In addition to a slightly higher radiation exposure (although less than on a routine CT examination), reliance on an imaging device that is heavily utilized for other clinical applications and the higher cost of QCT have limited its widespread adoption. Quantitative ultrasound is a complementary way to measure bone mass and perhaps other properties of bone. Compared with DEXA or QCT, this method has desirable attributes of lower instrument cost, portability, and absence of ionizing radiation. Ultrasound studies are usually performed of the calcaneus, although the tibia, patella, distal radius, and proximal phalanges can also be examined. There are no universally accepted criteria for an ultrasonic diagnosis of osteoporosis and it is not possible to predict BMD by ultrasound measurements. Compared with DEXA and QCT, ultrasound is relatively insensitive for osteoporosis diagnosis. Thus, even borderline abnormalities should prompt the performance of a central DEXA (Saag, 2008).

**Conventional Radiography:**

Plain radiographs are inaccurate for the assessment of BMD. Bone loss must exceed 30% to 40% before it is visible by x-ray. Assessment of the trabecular pattern of the femoral neck has been shown to correlate with osteoporosis. Other radiographic measurements, such as hip axis length, also correlate with fracture risk. Vertebral fractures have different patterns and can be graded semiquantitatively on the basis of endplate deformities, anterior wedging, and crush fractures (Graat-Verboom et al., 2010-a).

**Biochemical Markers:**

Several biochemical tests are now available that provide an index of the overall rate of bone remodeling (Table 2-2). Biochemical markers are usually characterized as those related primarily to bone formation or bone resorption. These tests measure the overall state of bone remodeling at a single point in time. Clinical use of these tests has been hampered by biologic variability (in part related to circadian rhythm) as well as to analytical variability. For the most part, remodeling markers do not predict rates of bone loss well enough to use this information clinically. However, markers of bone resorption may help in the prediction of fracture risk, particularly in older individuals. In women ≥65 years, when bone density results are greater than the usual treatment thresholds noted above, a high level of bone resorption should prompt consideration of treatment. The primary use of biochemical markers is for monitoring the response to treatment. Inhibition of bone resorption is maximal within 3 to 6 months. Thus, measurement of bone resorption prior to initiating therapy and 4 to 6 months after starting therapy provides an earlier estimate of patient response than does bone densitometry. A decline in resorptive markers can be ascertained after treatment with bisphosphonates or estrogen; this effect is less marked after treatment with either raloxifene or intranasal calcitonin. A biochemical marker response to therapy is particularly useful for asymptomatic patients and might help to ensure long-term compliance. Bone turnover markers are also useful in monitoring the effects of PTH, or teriparatide, which rapidly increases bone formation and later bone resorption (Lindsay and Cosman, 2005).

**Treatment of osteoporosis in patients with chronic obstructive pulmonary disease:**

Despite the remarkable lack of interventional studies targeting osteoporosis in patients with COPD, some conclusions can be drawn from the treatment of corticosteroid-induced osteoporosis, postmenopausal osteoporosis and the few studies on patients with asthma and other chronic lung diseases.

**Nonpharmacologic Therapies:**

Nonpharmacologic therapies such as physical therapy can be beneficial in the prevention of falls and fractures in patients with osteoporosis (Henderson et al., 1998). Patients with COPD have been shown to have decreased activity levels due to muscle weakness and deconditioning (Bourjeily and Rochester, 2000). To reverse the decreased muscle strength and instability, which is manifested by the inability to rise from a chair, slow gait speed, decreased grip strength, and increased risk for hip fracture, (Cooper et al., 1988; Cummings et al., 1995), a physical therapy program should be designed to increase exercise endurance, muscle strength, and balance. This will not only improve the quality of life and functional status but also will decrease the risk for falls and subsequent fractures (Bourjeily and Rochester, 2000; McClung and Spencer, 1996).

**Calcium and vitamin D supplements:**

Calcium and vitamin D supplementation have been shown in some, but not all, studies to be beneficial in patients receiving long-term corticosteroid therapy. In patients with rheumatoid arthritis who were receiving relatively low doses of prednisone (average dose, 5.5 mg/d), those receiving calcium and vitamin D had significantly higher BMDs than those receiving placebo.87 High-dose 25-hydroxy-cholecalciferol significantly increased vertebral BMD by 4.9% in cardiac transplant patients after 18 months (Biskobing, 2002). In postmenopausal females, calcium and vitamin D supplements may be beneficial if the dietary intake of calcium is low, which has been reported in some elderly females (Eastell, 1998; Ionescu and Schoon, 2003; Chapuy et al., 1994). In corticosteroid-induced osteoporosis have reported that calcium and vitamin D supplements may reduce the rate of bone loss in the short term, but no increase of bone mass in the long term and in those receiving higher doses of prednisone (average dose, 18.9 mg/d).

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**Table 2-2. Biochemical Markers of Bone Metabolism in Clinical Use**

<table>
<thead>
<tr>
<th>Bone formation</th>
<th>Bone resorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bone-specific alkaline phosphatase</td>
<td>Urine and serum cross-linked N-telopeptide</td>
</tr>
<tr>
<td>Serum osteocalcin</td>
<td>Urine and serum cross-linked C-telopeptide</td>
</tr>
<tr>
<td>Serum propeptide of type I procollagen</td>
<td>Urine total free deoxypyridinoline</td>
</tr>
<tr>
<td></td>
<td>Urine hydroxyproline</td>
</tr>
<tr>
<td></td>
<td>Serum tartrate-resistant acid phosphatase</td>
</tr>
<tr>
<td></td>
<td>Serum bone sialoprotein</td>
</tr>
<tr>
<td></td>
<td>Urine hydroxylsine glycosides</td>
</tr>
</tbody>
</table>

Source: Adapted from SM Krane and MF Holick, Chap. 355 in HPIM, 14 ed, 1998.
was found (Goldstein et al., 1999; Lane and Lukert, 1998; ACR, 1996).

**Hormone replacement:** Due to the high incidence of hypogonadism with glucocorticoid use, all premenopausal women and men should be monitored for the development of hypogonadism (Adachi, 1997; Doerr and Pirke, 1976). In premenopausal women, a history of amenorrhea suggests the development of hypogonadism, which can be treated with oral contraceptives or hormone replacement therapy (HRT) (Lane and Lukert, 1998). Postmenopausal women should be considered for HRT unless there is a contraindication (Altzkorn and Yokes, 2001; Rosen and Kessench, 1997; Notelovitz, 1997). An alternative to estrogen therapy is raloxifene, a selective estrogen receptor modulator (Clemett and Spender, 2000). In postmenopausal women, these agents have estrogen-like effects on the bone but do not increase the risk of breast cancer or endometrial cancer (Clemett and Spender, 2000; Biskobing, 2002). Testosterone levels should be measured in all men who have osteoporosis. If the level is low, testosterone replacement therapy will be beneficial not only by improving BMD but also, possibly, by improving muscle mass and strength (Brodsky et al., 1996; Biskobing, 2002). Testosterone therapy has been shown to improve BMD in men patients receiving oral glucocorticoid therapy. The spine BMD improved 5% after 12 months of testosterone therapy compared to no change in BMD after the 12-month control period (Reid et al., 1996).

**Calcitonin:** Calcitonin is a peptide hormone secreted by specialized cells in the thyroid gland. Salmon calcitonin is used for treatment of osteoporosis because it is more potent and has a longer duration of action than human calcitonin. Calcitonin acts directly to reduce bone resorption by binding to specific receptors of the osteoclast. Available since 1984 for subcutaneous injection (currently marketed as Calcimar, Miacalcin, Fortical), salmon calcitonin (50–100 IU daily) results in slight gains in spinal BMD—somewhat less than the gains induced by other agents. Because of the perception of limited and perhaps only transient effectiveness, the inconvenience and discomfort of injections, relatively high cost, and limited tolerance (approximately 20% of patients given subcutaneous salmon calcitonin develop nausea or flushing), subcutaneous calcitonin was not widely used. Nasal calcitonin (Miacalcin) was introduced in 1995. Another brand, Fortical, was approved by the United States Food and Drug Administration (FDA) in 2005. The nasal form is much better tolerated than the subcutaneous form. The recommended dose of nasal calcitonin is 200 IU (one spray) daily. It is approved for treatment of postmenopausal osteoporosis but not for prevention or for use in glucocorticoid-induced osteoporosis (Saag, 2008). A 5-year study of nasal calcitonin in over 1000 women with preexisting vertebral fractures showed only a modest effect on spinal bone mass, but a 33% reduction in the incidence of new vertebral fractures (Watts, 2008). No effect of calcitonin on nonvertebral or hip fracture was shown in this study. Nasal calcitonin is extremely well tolerated. There are no concerns about long-term safety. Calcitonin may have an analgesic effect and is sometimes prescribed for patients who have acute painful vertebral fractures (Saag, 2008).

**Bisphosphonates:** Bisphosphonates share a common chemical structure (two phosphonic acids joined to a carbon) that causes them to bind avidly to hydroxyapatite crystals on the surfaces of bone. They are resistant to metabolic degradation, and work through two broad mechanisms. First, bisphosphonates reduce the ability of individual osteoclasts to resorb bone. Second, they accelerate osteoclasts apoptosis (programmed cell death). Three bisphosphonates (alendronate, ibandronate, and risedronate) are approved for prevention and treatment of postmenopausal osteoporosis. Bisphosphonates are remarkably free from systemic toxicity (Saag, 2008).

**Alendronate (Fosamax)** was the first bisphosphonates approved by the FDA (1995) for prevention and treatment of osteoporosis. In phase III trials involving almost 1000 women in their late 60s who had established osteoporosis, alendronate 10 mg daily was shown to increase spinal bone density by almost 10% after 3 years, and, to a lesser degree, to increase BMD at other sites as well (Watts, 2008). Alendronate is available in 5-mg, 10-mg, 35-mg, 40-mg, and 70-mg tablets and in unit-dose liquid of 70 mg. It is also available in a 70-mg tablet containing 2800 IU of vitamin D intended for weekly dosing. Alendronate is approved for prevention of bone loss (5 mg daily or 35 mg weekly) and treatment of osteoporosis (10 mg daily or 70 mg weekly). Alendronate is also approved for treatment of glucocorticoid-induced osteoporosis (5 mg daily for men and estrogen-replete women, 10 mg daily for estrogen-deficient women) (Saag, 2008).

**Risedronate** (Actonel) was approved by the FDA in 2000. Its effectiveness for vertebral fracture reduction was shown in two pivotal studies of over 3600 women with low BMD and prevalent vertebral fractures (Watts, 2008; Harris et al., 1999). Risedronate has been shown to prevent bone loss in recently menopausal women. Risedronate is available in 5-mg and 35-mg tablets and in a packet containing 35-mg tablets with additional tablets of calcium carbonate, to be taken separately. Risedronate is approved for the prevention and treatment of postmenopausal osteoporosis, as well as for the prevention and treatment of glucocorticoid-induced osteoporosis. The dose of risedronate is 5 mg daily or 35 mg weekly for all of these indications. Risedronate was well tolerated in clinical trials of almost 16,000 subjects; in aggregate, the adverse events rate has been no different from that of placebo. Saag, 2008).

**Ibandronate** (Boniva) 2.5 mg daily by mouth and an intermittent regimen (20 mg orally every other day for 12 doses repeated every 3 months) was shown to reduce new vertebral fractures in a study of almost 3000 women with preexisting vertebral fractures (Watts, 2008). Ibandronate, approved for prevention and treatment of postmenopausal osteoporosis, can be given orally (2.5 mg daily or 150 mg monthly) or intravenously (3 mg over 15–30 seconds every 3 months). Ibandronate has not been shown to have an effect on hip fractures. Although there was no effect on nonvertebral fractures overall, a post hoc analysis of the pivotal trial data showed a significant reduction with daily oral therapy (but not an intermittent regimen) in nonvertebral fractures in women with femoral neck T scores of −3.0 or below (Saag, 2008).

**Etidronate, pamidronate, and zoledronic acid** are other bisphosphonates available in the United States. Although they are not approved by the FDA for use in osteoporosis, they are sometimes used off label. Etidronate (Didronel) has been shown to increase BMD in two prospective, randomized, controlled trials of women with postmenopausal osteoporosis. When used to treat osteoporosis, it is given in an intermittent cyclical regimen (400 mg etidronate daily for 14 days every third month). As with all bisphosphonates, etidronate must be
taken on an empty stomach to be effective, but it may be taken between meals, at bedtime, or during the night.

**Pamidronate** (Aredia), another bisphosphonate, is not approved by the FDA for use in osteoporosis. It is given by intravenous infusion. A typical regimen is an initial dose of pamidronate 90 mg, infused over about 60 minutes, with subsequent doses of 30 mg every third month. Intravenous pamidronate is useful for patients who cannot tolerate oral bisphosphonates (Watts, 2008).

**Prevention and therapy: suggestions for the future:** The prevention of osteoporosis in COPD patients is dependent on an awareness of the magnitude of the problem. There is little impetus for screening and/or preventive therapy because patients are generally asymptomatic until they experience a fracture. However, early recognition and the institution of preventive therapy are essential in avoiding fractures (Biskobing, 2002). In order to assess the efficacy of treatments, more information on the risk factors and the pathogenesis of COPD-induced osteoporosis is needed. Such information could be gathered through prospective studies designed to assess the rate of decline of the BMD and the contributing factors such as the type of corticotherapy, the presence of hypogonadism, ongoing smoking, reduced physical activity and the weakness of the skeletal muscles (Ionescu and Schoon, 2003). In view of the relationship between the skeletal muscle mass and the BMD (Sandler, 1989; Henderson et al., 1998; Aniansson et al., 1984; Winett and Carpenterelli, 2001), it is likely that training programmes and conditioning will have beneficial effects on the maintenance of BMD in patients with COPD. However, the types of training and the specific programmes of rehabilitation need to be designed. Hormone replacement therapy is likely to be beneficial in patients with COPD and hypogonadism. In view of the age group and exposure to corticosteroid treatment, which are associated with hypogonadism, the assessment of the hormonal status should be part of the general investigation of osteoporosis in patients with COPD (Ionescu and Schoon, 2003). The intake of calcium and vitamin D should be assessed, in view of some reports that supplementation is beneficial for the preservation of the bone mass, mainly in subjects with a reduced intake (Eastell, 1998; Ionescu and Schoon, 2003; Chapuy et al., 1994). According to the current nutritional recommendations the daily intake of calcium (1,200–1,500 mg·day$^{-1}$) and vitamin D (at least 400 IU·day$^{-1}$) should be ensured (Goldstein et al., 1999; Lane and Lukert, 1998; American College of Rheumatology, 1996). More promising in view of the available research in patients with chronic lung disease is the therapy with bisphosphonates. The patients with COPD and osteoporosis treated with long-term systemic corticosteroids should be considered for such treatments. For patients with osteopenia, those on long-term inhaled corticosteroids and/or intermittent courses of oral corticosteroids without florid osteoporosis, regular monitoring of BMD by DEXA scanning should be undertaken (Ionescu and Schoon, 2003).

**DISCUSSION**

**Risk of Osteoporosis in Chronic Obstructive Pulmonary Disease:** 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 (WHO, 2008). Osteoporosis was observed to be more prevalent among Chronic Obstructive Pulmonary Disease (COPD) patients than among healthy subjects (Agusti et al., 2003; Kjensli et al., 2007). In the present study, we define osteoporosis according to the WHO criteria of osteoporosis. Katsura and Kida, (2002) defined osteoporosis according to the Japanese guidelines whereas most other studies used the WHO criteria to define osteoporosis. Interpretation of the results should be with caution as causality of the correlates needs to be confirmed. Some of these causes are determined, including female sex, advanced age, hormonal disturbances, alcohol, smoking, genetic factors, and low calcium intake (Wasnich, 1996). Furthermore, there are several factors reported to be responsible for the reduced bone density in patients with COPD, such as BMI (Iqbal et al., 1999; Katsura and Kida, 2002; Kjensli et al., 2007; Vrieze et al., 2007), FEV$_1$ (Iqbal et al., 1999; Vrieze et al., 2007), smoking (Iqbal et al., 1999), inactivity (Iqbal et al., 1999), and corticosteroid therapy (Iqbal et al., 1999; Kjensli et al., 2007; Lee and Weiss, 2004). However, the effects of these factors, with the exception of BMI, are still controversial. The present study was performed to evaluate the risk of osteoporosis in patients with COPD by measurement of bone mineral density (BMD) depending on the DEXA- scan findings. At the same time compare this group of patients with a healthy group who denies the characteristic features of COPD in addition to the exclusion criteria mentioned in chapter three.

The current study involved 106 individuals who were divided into 2 groups. The first group consists of 53 patients with COPD and the second group consists of 53 healthy individuals. The two groups were matched concerning the number of males and females (table 4-1) and their ages (table 4-2) as well as body mass index (BMI) (table 4-6) as confirmed statistically by the absence of significant differences between the studied groups. This matching of individual groups number, sex and age may exclude any effect of these parameters on the results of the study. In this study the mean age of the patients was 60 years (Table 4-2). Higher age is a risk factor for osteoporosis in the general population (WHO, 2007). However, increasing age is associated with an increasing risk of osteoporosis in COPD patients (Graat-Verboom et al., 2010-a). Three other studies (Mineo et al., 2005; Katsura and Kida, 2002; Biskobing, 2002) found a relatively high prevalence of osteoporosis in COPD (50%, 49% and 60%, respectively). However, the mean age of these patients was (72, 70 and 71 years, respectively), whereas in our study the mean age was 60 years. The present study is in line with the preceding studies that there was decreased bone mineral density with increasing the mean age in the studied group of COPD patients (figure 4-3). In osteopenia, the mean age was (58.40) while in osteoporosis was (62.27); this means that there is a strong correlation between aging and development or severity of osteoporosis, so the advancing age considered one of the famous factors in predisposing low bone density. The explanation for this high percentage of osteoporosis in old age group in these patients in women and men is probably that osteoporosis occurs as a result of decreased formation of bone and decreased renal production of 1,25(OH)$_2$D3 occurring late in life. 1,25(OH)$_2$D3 is the active form of vitamin D and as a result of decreased production of vitamin D, there will be decreased calcium absorption and eventually decreased formation of bone. Accumulation of fat in the bone marrow space may be also responsible for the reduction in bone mass, where stem cells tend to differentiate into adipose tissue rather than osteoblast. The genetic and environmental factors that...
include calcium intake during growth, smoking, exercise, alcoholism are also responsible for the individual variation in age related osteoporosis. Furthermore, the disease itself is an additive factors to osteoporosis in this age group secondary the inflammatory process and other consequences of the disease. The prevalence of osteoporosis is highest in individuals over 50 years and about 90% of hip fractures occur in persons aged 50 years or older (Smith and Wordsworth, 2005). Bonno and Einhorn, (2003) suggested that senile osteoporosis occurs in old aged individual and in both sex because of decreased formation of bone and decreased renal production of 1,25(OH)2 D3. The consequence is a loss of cortical and trabecular bone and increased risk for fractures of the hip, long bones, and vertebrae. In the current study, the combination of DEXA-scan of both lumbar spine and hip and the clinical manifestations resulted in an osteoporosis percentage of (41%) in patients with clinically stable COPD according to the T-score reading of (≤ 2.5) on DEXA- scan findings (Table 4-3).

In the present trial, a consecutive sample consisting of (53) COPD outpatients representing three GOLD stages (from stage 0 to stage II included) were screened for osteoporosis. Significant differences were found in the proportion of osteoporotic COPD patients after stratification for GOLD stages. Naghshin et al., (2004) noticed a significant association between osteoporosis and COPD severity. This study was in agreement with our results where it shows significant increase in the percentage of osteoporosis from (35%) in GOLD stage I to (50%) in GOLD stage II (Table 4-4 and Figure 4-1). In other study, the percentage of osteopenia and osteoporosis are increased with advancing GOLD stage (Vrieze et al., 2007). Vrieze et al., (2007) found a low prevalence of osteoporosis compared with other studies. This may, at least in part, be because none of the GOLD stage II patients had osteoporosis. In contrast, Bolton et al., (2004) found a prevalence of osteoporosis in (20%) of GOLD stage II patients. A possible explanation for these conflicting results could be the use of quantitative ultrasound by Vrieze et al., (2007) instead of DEXA scan, which is the gold standard to assess osteoporosis (WHO, 2008). The highest prevalence (69%) of osteoporosis in COPD was reported by Graat-Verboom et al., (2009). In two other studies conducted in COPD patients considered for lung transplantation, the prevalence of osteoporosis was lower (48% and 59%) (Graat-Verboom et al., 2009; Aris et al., 1996). This difference in prevalence may be due to differences in patient characteristics. However, in the absence of clinical characteristics for COPD patients only, this was hard to check (Graat-Verboom et al., 2009). Furthermore, low bone mass was correlated with low fat free mass (FFM) in GOLD IV patients, and FFM could thus be used as a determinant of bone loss in this population. These findings were supported by a case-control study, (Kjensli et al., 2007), in which patients with COPD were found to have lower bone mass than controls, and decreasing BMD was found with increasing GOLD stage. In another hand, (68%) of COPD patients had either low bone mass (osteopenia or osteoporosis) or a previously undiagnosed vertebral fracture, with (25%) of the included patients having a vertebral fracture (Jorgensen et al., 2007).

These studies are in line with the present study, the percentage of osteoporosis in GOLD stage 0 patients with COPD was (28.6%), in GOLD stage I patients with COPD was (35%) while in GOLD stage II was (50%). It is clear that the risk of osteoporosis correlates positively with the severity of COPD that there was increase in the percentage of osteoporosis with increasing the severity of COPD (figure 4-1). Jorgensen et al., (2007) showed that (68%) of 62 COPD patients with a mean FEV1 of (33%) pred. had osteopenia or osteoporosis, assessed by DEXA or spinal X-ray. In our study, the percentage of osteoporosis was (41%) in the patients with a mean FEV1%pred. of (76.4), while the percentage of osteopenia was (47.2%) with a mean FEV1%pred. of (88.3) (Table 4-10). These findings suggest that extra-pulmonary features like osteoporosis can be predicted by the degree of airflow limitation. It has been recognized that COPD involves several extra-pulmonary features, indicating that it is a systemic disease, and that one of the major systemic features is osteoporosis. On average, in the present study, the percentage of osteoporosis and/or a low BMD was significantly higher in COPD patients than in healthy subjects (table 4-3). Furthermore, our results showed the degree of osteoporosis is in increasing with increasing the severity of COPD. This explains the stone impact of inflammatory process on the bone biophysicsology with its consequences. There may be several explanatory mechanisms for our results. The first is the presence of systemic inflammation. It is found that reduced lung function is associated with increased levels of systemic inflammatory markers that lead to the inflammatory process in patient with COPD and eventually cause acceleration and increase in bone resorption leading to osteoporosis. It is likely that osteoporosis in patients with COPD is a consequence of various factors some having been present throughout the life of the patient, others due to the disease process itself and some specific to the treatment of the lung disease (Ionescu and Schoon, 2003).

Increased concentrations of the circulating inflammatory mediators (tumour necrosis factor (TNF) - α, IL-6, IL-1α) have been reported in COPD (Gan et al., 2004). Leukocyte-derived IL-1α and TNF-α stimulate bone resorption (Engelen et al., 1998; Gowen and Mundy, 1986; Bertolini et al., 1986) and IL-6 stimulates the formation of osteoclasts (Manolagas and Jilka, 1995). The second mechanism of reduced bone mass in COPD may be the low level of physical activity. Patients with COPD experience dyspnea during exertion, which may lead to a vicious circle of inactivity, deconditioning and increased dyspnea on exertion. Most patients with COPD spend less time walking and standing and more time sitting and lying in daily life when compared with sedentary healthy elderly subjects. Most patients with COPD are not completely immobilized; however, advanced COPD often is associated with decreased functional status and mobility (Biskobing, 2002; Bourjeily and Rochester, 2000). The decreased exercise tolerance is due to multiple factors, including dyspnea and deconditioning due to respiratory and peripheral skeletal muscle weakness (Bourjeily...
and Rochester, 2000). In addition to the advanced age of the patient, genetic factors and other environmental factors that all contribute to osteoporosis. The elevated percentage in the osteoporosis in patients with COPD in the present study may add some light on the fact that COPD is one of the most important risk factors that may contribute to the high morbidity and mortality in this group of patients in presence of this high percentage of osteoporosis especially if we regard to its consequences.

**Correlates of osteoporosis in COPD:** In the current study, there was a negative correlation between the BMI and the severity of osteoporosis and/or reduced BMD. Bone mass is directly correlated with Body mass index (BMI) (Ionescu and Schoon, 2003; Heaney, 1998). As presented, osteoporosis met the lower mean BMI as shown in table (4-6). Many studies found body composition measures (low BMI, low FFMI and % of ideal body weight) to have a significant correlation with osteoporosis and/or BMD (Bolton et al., 2004; Vrieze et al., 2007; Katsura and Kida, 2002; Biskobing, 2000; Graat-Verboom et al., 2010-a), these studies are in agreement with our study. In the general population, low body weight and/or low BMI have also been identified as risk factors for osteoporosis and incorporated in guidelines (WHO, 2008; Graat-Verboom et al., 2009). Furthermore, in this study, if we talk in numbers about the BMI to compare between the patients and control group, we note that the mean BMI in patients was (25.74± 5.05) while in control group was (27.23± 5.78), and in more accurate expression, the mean BMI in presence of osteoporosis in patients and control group was (23.61± 3.76 and 24.03±5.72, respectively) (table 4-6). According to our results regarding the BMI, it is clear that BMI is less in presence of osteoporosis in both patients and control group. This means BMI is another risk factor for osteoporosis that correlate with the COPD and exist additive impact on the bone density in the opposite direction. The link between low BMI and osteoporosis or low BMD in COPD could be due to increased inflammation, decreased physical activity and/or other mechanisms leading to proteolysis. Another explanation for more osteoporosis in patients with lower BMI measurements could be that bone formation is decreased because there is relatively low mechanical loading on these bones. The relationship between BMI and bone mass suggests that the load of soft tissues is important in the preservation of bone mass. In underweight elderly the bone mineral content was reduced compared to age-matched subjects with a normal BMI (Ionescu and Schoon, 2003; Biskobing, 2002). COPD patients have been shown to be physically inactive compared with age-matched healthy subjects (Van et al., 2005).

In this study, there were no adequate and precise data available on the physical activity in the COPD patients studied. In another hand, there was a higher risk of fragility fractures in COPD patients than in healthy subjects by 3.7 times (table 4-8). Furthermore, in the present study, the number and percentage of vertebral, hip, wrist and chest fractures in the patients were 2(3.8%), 3(5.7%), 4(7.6%), 2(3.8%); while in the controls were 0(0.0%), 1(1.9%), 1(1.9%), 1(1.9%), respectively. The risk of vertebral fracture among all fractures in the patients was 11%, while risk of all fractures was 20.8% of the patients. This parallels the findings of a cross-sectional study on 312 males with COPD assessed the prevalence of fractures in three groups: 1) patients who never used corticosteroids, 2) patients who received inhaled corticosteroids and 3) those receiving systemic steroids (McEvoy et al., 1998). The prevalence of at least one vertebral fracture was 48.7% in group 1, 57.1% in group 2 and 63.3% in group 3, with ≥6 vertebral fractures found only in group 3. The high risk of fractures in the group who never used corticosteroids suggests that factors others than the treatment may be involved in the pathogenesis of osteoporosis. These factors include the same factors contribute to osteoporosis mentioned previously in the preceding text.

**In Summary, the present study had several main findings**

- Forty - one % of patients with clinically stable chronic obstructive pulmonary disease (COPD) attending a regular visit at the respiratory outpatient consultation in the Ibn Sina teaching hospital in Mosul had evidence for osteoporosis depending on DEXA- scan findings.
- Combining the results of dual energy X-ray absorptiometry (DEXA)-scans with clinical manifestations augmented the proportion of COPD patients with osteoporosis.
- The proportion of COPD patients with osteoporosis was statistically significantly different after stratification for Global Initiative on Obstructive Lung Disease (GOLD) stages.
- A large proportion of the osteoporotic COPD patients did not use physician prescribed bone medication.
- Age and BMI were clear correlates of osteoporosis in COPD patients in positive and negative direction, respectively.
- The severity and level of osteoporosis was significantly negatively correlated with FEV1% predicted.

There is increase in the prevalence of osteoporotic or fragility fractures in patients with COPD by about 4 folds than healthy Parsons, this will affect the quality of life which contributed to the high rate of morbidity and mortality in those patients.

**Conclusion**

On the basis of the results obtained in the present study, the followings can be concluded:

- Chronic obstructive pulmonary disease (COPD) is a risk factor for osteoporosis.
- Patients with COPD showed a significantly increased risk of osteoporosis as compared to that in healthy age-matched control subjects.
- The present study showed that patients with chronic obstructive pulmonary disease had 2 times the risk of osteoporosis compared with healthy age-matched control subjects.
- Patients with COPD risk developing osteoporosis even if they are not taking corticosteroids.
- As the risk of osteoporosis was increased even in people with COPD not taking corticosteroids, the present study said mechanisms that may possibly be involved included reduced physical activity, low body mass index (BMI) and advanced age.
- Low BMI, reduced physical activity, aging and severity of COPD are well known additive risk factors in patients with COPD regarding osteoporosis development.
The degree, incidence and severity of osteoporosis were increased with increasing the severity of COPD.

There was a higher risk of fragility fractures in COPD patients than in healthy subjects by 3.7 times, so there will be bad effect on the quality of life in chronic obstructive pulmonary disease patient and eventually increase the morbidity of the patient.

**Suggestions for Further Studies**

1. Longitudinal studies that investigate the contribution of potential factors leading to osteoporosis such as the nutrition, smoking, levels of physical activity, body habitus and composition, peripheral skeletal muscle mass and function.

2. Future researches that explore the incidence of hypogonadism in patients with COPD and if hormone manipulation has long-term effects on the preservation of bone mass. Other possible hormonal changes will need to be investigated, such as the potential imbalance between anabolic (IGF-1) and catabolic (corticosteroids) hormones that may contribute to the loss of skeletal muscle and bone mass in COPD.

3. The relationship between the persistent systemic inflammation and the depletion of skeletal muscles and bone in some patients with COPD will need to be further explored, in order to clarify if circulating inflammatory mediators have an effect at the tissue level or if other factors stimulate increased inflammation in the peripheral tissues, including the bone tissue.

4. Randomized placebo-controlled trials are required to assess the effects of bisphosphonates on the prevention and treatment of osteoporosis and fractures in various groups of patients with chronic obstructive pulmonary disease (exposed to oral or inhaled corticosteroids, affected by hypogonadism, as well as those who might have low bone mineral density due to other causes). Such trials should have clear outcome measures, such as the change in bone mineral density (BMD) or the assessment of the fracture rates and should investigate potential short-term and long-term side effects of the treatment.

**Recommendation**

- Chest physicians should be aware of the high risk of osteoporosis in chronic obstructive pulmonary disease even in case of a low Global Initiative for Chronic Obstructive Lung Disease score, especially in elder chronic obstructive pulmonary disease patients with a low body mass index and/or an advanced disease.
- It is necessary for pulmonologist to accentuate for preventive and cure strategies to reduce morbidity of osteoporosis in these patients.
- Prevention of osteoporosis should be a part of medical care for COPD patients.
- BMD measurement should be considered in COPD patients at high risk for osteoporosis such as those receiving high-dose inhaled glucocorticoid therapy, postmenopausal women, premenopausal women, or men with hypogonadism, low BMI, or a history of osteoporotic fracture.
- Patients should be encouraged to participate in physical therapy programs to increase exercise endurance and to maintain muscle strength.
- Awareness of the problem and of strategies to prevent the development of osteoporosis during the course of COPD therapy are essential to increase BMD and, likely, to decrease the incidence of fractures in these patients.
- It is recommended to suggest a minimum daily intake of 1,200 mg of calcium in adults older than 50 years.
- Replacement therapy is beneficial for the preservation of bone mass in patients with COPD and postmenopausal or corticosteroid-induced hypogonadism, only after considering potential risks of such treatments.
- Without appropriate diagnosis and treatment, these patients remain at substantial risk for recurrent, debilitating and life threatening osteoporotic fractures.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>The original form</th>
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<tr>
<td>ACR</td>
<td>American college of rheumatology</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CS</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>DEXA / DXA</td>
<td>Dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat-free mass</td>
</tr>
<tr>
<td>FM</td>
<td>Fat mass</td>
</tr>
<tr>
<td>FIT</td>
<td>Fracture Intervention Trial</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>ICTP</td>
<td>Type I carboxyl terminal telopeptide</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
</tbody>
</table>

**REFERENCES**


Global Initiative for Chronic Obstructive Lung Disease (GOLD) Committee 2006. COPD guideline: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. MCR Vision.


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