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Patients with Chronic Obstructive Pulmonary Disease Have a High Prevalence of Osteopenia and Osteoporosis associated with the Worst Degrees of Pulmonary Function and Prognosis

Dra Tatiana Costa*

Service of Endrocrinology and Metabolism of the Federal University of Paraná, Brasil

Abstract

Introduction/Background: Chronic obstructive pulmonary disease (COPD) is associated with osteoporosis and vertebral fractures. It is still unclear whether the presence of fractures and changes in bone mineral density (BMD) are associated with disease severity and prognosis. The aim of this study was to evaluate low BMD, and morphometric vertebral fractures (MVF) in patients with COPD compared with two control groups and correlate these parameters with indices of COPD severity (FEV_1 and GOLD) and prognosis (BODE).

Methodology: This was a cross-sectional study in COPD patients (disease group, DG) that undergone BMD and vertebral fracture assessment (VFA). Two control groups were used, one group of smokers individuals without COPD (smokers group, SG), and another group of healthy never smokers individuals (never smokers group, NSG).

Results: DG comprised 121 patients (65 women, mean age 67.9 ± 8.6 years). Altered BMD was observed in 88.4% of the patients in the DG which was more prevalent when compared to control groups ($p<0.001$). The BMD values were lower in the DG than in controls ($p<0.05$). BMD was associated with the worst degree of obstruction (FEV_1), GOLD, and BODE ($p<0.05$). The prevalence of MVF was high (57.8%) and greater than that in the SG (23.8%), and NSG (14.8%; $p<0.001$). The prevalence of fractures was not associated with FEV_1, GOLD, or BODE.

Conclusions: This study showed a high prevalence of low BMD in COPD patients and an association with a worse degree of FEV_1, GOLD, and BODE. MVF in patients with COPD were also higher but were not associated with disease gravity and prognosis.

Keywords: BODE; Bone mineral density; COPD; GOLD; Vertebral fractures

Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by progressive and not fully reversible airflow limitation [1]. Respiratory exacerbations, along with the presence of comorbidities, contribute to the overall severity of the disease [2]. COPD has a high prevalence, affecting up to 10% of the individuals above the age of 40 years, and is associated with high morbidity and mortality rates [3]. Despite being primarily a lung disease, COPD is associated with several extra pulmonary disorders, including cardiovascular disease, sleep apnea, depression, anemia, chronic kidney disease, osteoporosis, cachexia, and skeletal muscle weakness [4].

Low bone mineral density (BMD) leading to osteoporosis is common in patients with COPD, and previous studies have reported rates of osteoporosis of 9-69% in this population [5-7]. The etiology of low BMD in these patients is likely multifactorial and includes smoking, vitamin D deficiency, hypercapnia, hypoxia, poor nutrition, low body mass index (BMI), inflammatory cytokines, and decreased lean mass [8-10]. In addition to low BMD, patients with COPD also present altered bone quality and microstructure, leading to a high prevalence of fractures. Indeed, 30-63% of the patients with COPD present vertebral fractures [11]. In this population, thoracic vertebral fractures are particularly concerning since each vertebral fracture is estimated to lead to a 9% decline in the patient's forced vital capacity (FVC) [12].

It is still unclear whether the presence of fractures and changes in BMD in patients with COPD are associated with disease severity and prognosis [13-15], and data from the literature have shown controversial results in this regard. In contrast, evidence suggests that patients with newly diagnosed COPD already have a high prevalence of osteoporosis and fractures [16].

The main aim of this study was to evaluate BMD and morphometric vertebral fractures (MVF) in patients with COPD compared with two control groups (one group of smokers individuals without COPD and another with healthy never smokers individuals). Secondary aims included the correlation of these parameters with indices of COPD severity and prognosis. It is the first study that compared patients with COPD with two control groups and evaluated simultaneously the BMD and MVF with the severity and prognosis of the disease.

Materials and Methods

Subjects

This study is a cross-sectional part of a larger study with patients with COPD treated at the Pulmonary Outpatient Clinic of the Hospital de Clinicas at Universidade Federal do Paraná. All patients signed an informed consent form, and the study was approved by the Ethics Committee on Human Research at our institution.

***Corresponding author:** Dra Tatiana Costa, Service of Endrocrinology and Metabolism of the Federal University of Paraná, Brasil, Tel: 554133605000; E-mail: tatimrlemos@yahoo.com.br

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The patients included in this study were invited to undergone BMD and vertebral fracture assessment (VFA) between January 2010 and December 2014. The inclusion criteria were: Men and women older than 50 years, previous diagnosis of tobacco-induced COPD. COPD was evaluated by spirometry (KoKo PFT Spirometer, Occupational Health Dynamics, Hoover, AL, USA) with a post-bronchodilator FEV_1/FVC<0.70, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. Patients were excluded if one of the required tests was unavailable or if the patient was taking medications (including continuous oral glucocorticoid) or had another disease known to interfere with bone mass. Two control groups were used for comparison with the COPD group (disease group, DG), one group of smokers without COPD (smokers group, SG), and another group of healthy never smokers individuals (never smokers group, NSG). Individuals in the SG were invited to participate during their first visit to a smoking cessation clinic of the same hospital and the SSG were volunteers of both sexes from a random population invited to participate in the study. All individuals in the control groups were older than 50 years and had undergone evaluation of BMD as well as VFA in the same equipment as those in the DG. Exclusion criteria were the use of medications or the presence of diseases known to interfere with bone mass. All individuals in the SG underwent spirometry using the same spirometer used for the patients in the DG and were excluded from the study if diagnosed with COPD.

Weight (kg) was measured on a digital electronic scale while the participants wore light clothes. Height (m) was measured while the individuals kept their backs straight, heels together, and arms extended alongside the body. Their BMI was determined by dividing the weight (kg) by the squared height (in m^2) [17].

All participants underwent a BMD assessment and VFA using dual-energy X-ray absorptiometry (DXA) on a Lunar Prodigy whole-body scanner (GE Medical Systems, Madison, WI, USA). The regions evaluated in the test were the lumbar spine (LS), total femur (TF), and femoral neck (FN). The BMD results are expressed as g/cm^2 and as scores in relation to reference values determined by the International Society for Clinical Densitometry (ISCD) [18]. The least significant change (LSC) for the lumbar spine is 0.010 g/cm^2 and for proximal femur 0.012 g/cm^2 in the Bone Metabolism Unit of SEMPR. The VFA was performed simultaneously and was analyzed by a single experienced physician using the Genant semiquantitative method [19].

COPD severity and prognosis

We collected the patients' clinical data, including information about their lifetime smoking exposure (quantified in pack-years) [20], history of exacerbations, postbronchodilator forced expiratory volume in the first second (FEV_1), modified Medical Research Council (mMRC) dyspnea scale [21], COPD Assessment Test (CAT) [22], and 6-minute walk test [23].

Patients in the DG were classified according to the degree of airflow obstruction (FEV_1) into categories 1 (≥ 80%), 2 (50-79%), 3 (30-49%), and 4 (<30%) [1]. The COPD severity was determined according to the GOLD index, which is based on the postbronchodilator FEV_1, history of exacerbations in the previous year, and symptoms such as dyspnea (measured with the mMRC or CAT), and classified the study groups A, B, C, and D. The COPD prognosis was evaluated with the BODE index [24] (which integrates the patient's BMI, the degree of airflow obstruction, grade of dyspnea, and exercise capacity), and the patients were classified into four quartiles, with the first being the least severe and the fourth the most severe one.

Statistical analysis

The data are presented as the mean ± standard deviation (SD). All analysis was performed using IBM SPSS Statistics, v.20.0 (Armonk, NY: IBM Corp.). The normality of the distribution of the variables was evaluated with the Kolmogorov-Smirnov test. The comparison between two groups of quantitative variables was performed with Student's t-test for independent samples or using the nonparametric Mann-Whitney test. When comparing more than two groups, we used analysis of variance (ANOVA) with one factor and the least significant difference (LSD) test for multiple comparisons or the nonparametric Kruskal-Wallis test. For the preliminary statistical analysis, we used Fisher's exact test and the chi-square test to assess the association between two qualitative variables. P values below 0.05 were considered statistically significant.

Results

Figure 1 is the flow chart of the participants. Of the 758 COPD invited patients, 126 accepted to participate in the study, five were excluded for not having all required tests in their records. The final DG comprised 121 patients (65 women, mean age 67.9 ± 8.6 years, mean BMI 26.5 ± 6.2 kg/m^2). The mean tobacco consumption was 58.9 ± 40.8 pack-years. Overall, 23 patients (19.1%) were still smoking at the time of the study evaluation. According to the degree of obstruction evaluated by the FEV_1, 21 (17.3%) patients were classified as group 1, 48 (39.6%) as group 2, 39 (32.2%) as group 3, and 13 (10.7%) as group 4. Based on the GOLD classification, the study group was subdivided as follows: 29 (23.9%) patients, GOLD A; 29 (23.9%), GOLD B; 34 (28%), GOLD C; and 29 (23.9%), GOLD D. Regarding to the BODE index, 55 (45.4%) patients were in the first quartile, 37 (30.5%) in the second quartile, 18 (14.8%) in the third quartile, and 11 (9%) in the fourth quartile.

The SG comprised 63 individuals (29 women) with a mean age of 65.5 ± 8.9 years and a mean BMI 27.6 ± 3.6 kg/m^2. All individuals were current smokers at the time of the study evaluation. The mean tobacco consumption was 38 ± 28.2 pack-years. The NSG comprised 81 individuals (47 women) with a mean age of 66 ± 8.5 years and a mean BMI of 26.1 ± 2.6 kg/m^2, and in this group none of the participants ever smoked.

There were no differences in gender (p=0.612), age (p=0.147), or BMI (p=0.143) among the groups, except for the mean tobacco consumption in the DG, which was greater than that in the SG (p<0.001).

Altered BMD was observed in 88.4% of the patients in the DG (mostly comprising patients with osteoporosis), which was more prevalent when compared with in the control groups (p<0.001). Only 14 (11.6%) patients in the DG had a normal BMD, 49 (40.5%) had osteopenia, and 58 (47.9%) had osteoporosis. The distribution of BMD classifications was similar in both control groups: in the SG, 31 (49.2%) patients had osteopenia, 12 (19%) had osteoporosis, and 20 (31.7%) had a normal BMD evaluation. In the NSG, 47 (58%) patients had osteopenia, 12 (14.8%) had osteoporosis, and 22 (27.1%) had a normal BMD. The BMD (g/cm^2) values in all three sites evaluated were lower in the DG than in controls (Figure 2).

BMD was associated with a worse degree of obstruction (FEV_1), GOLD, and BODE (p<0.05) (Tables 1a-1c).

In patients with COPD, 184 vertebral fractures were found in 70 patients. The prevalence of MVF was high in the DG (57.8%) and greater than that in the SG (23.8%), 18 fractures in 12 patients and NSG (14.8%) 30 fractures in 15 patients (p<0.001) (Figure 3). In contrast, the

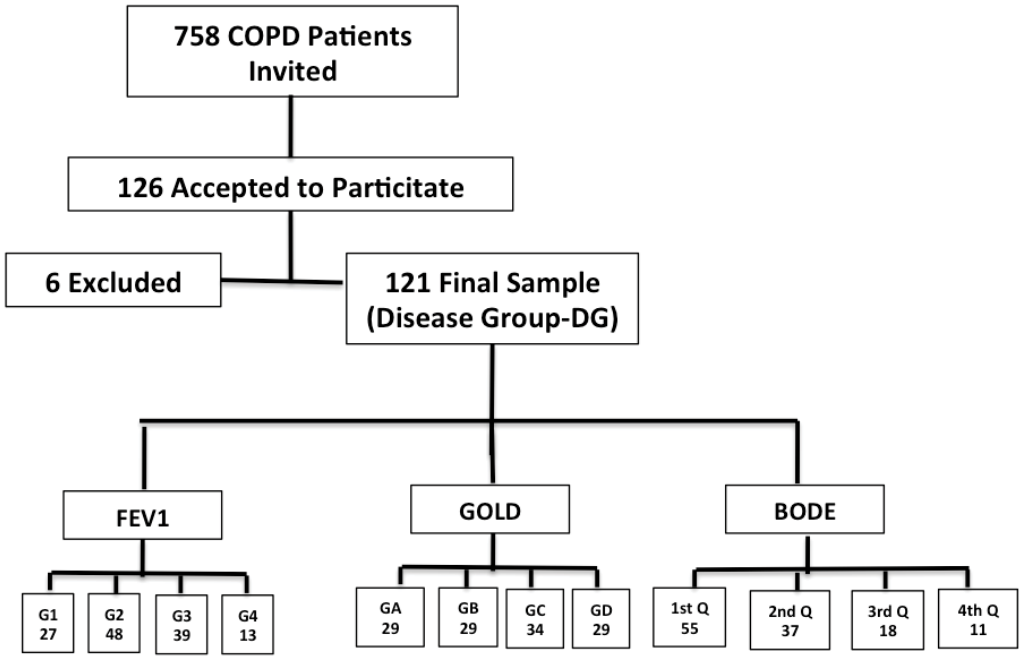

Figure 1: Flow chart describing patients distribution in the different COPD classifications.
COPD: Chronic Obstructive Pulmonary Disease; FEV1: Postbronchodilator Forced Expiratory Volume in the First Second; BODE: B, body mass index; O, airway obstruction; D, dyspnea; E, exercise capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease

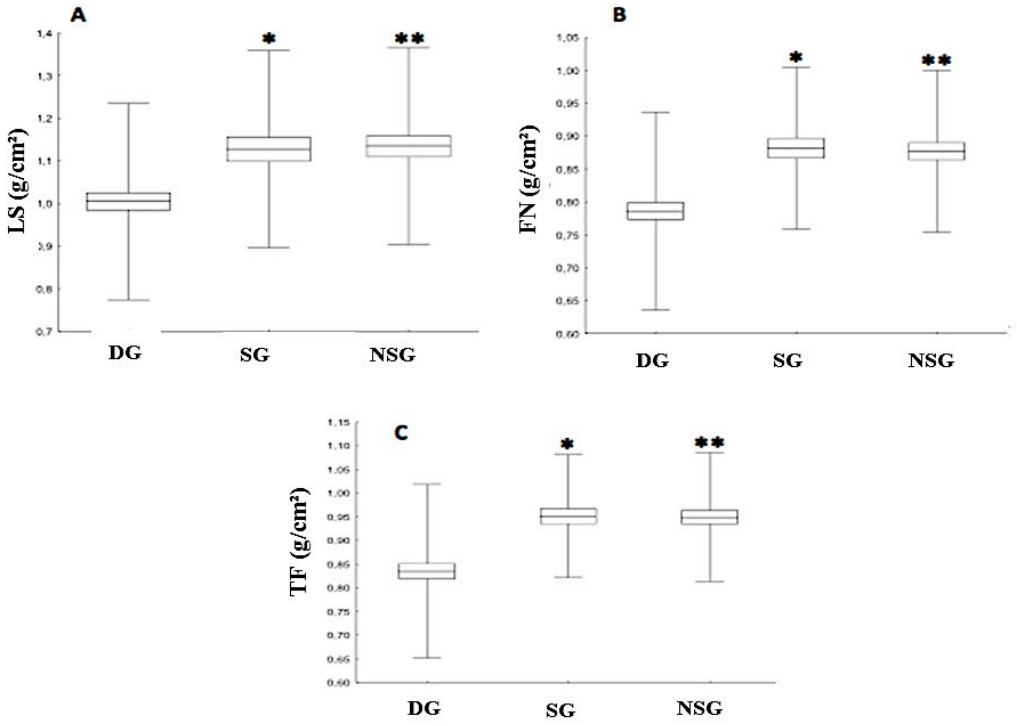

Figure 2: Bone mineral density in patients and controls.
DG: Disease *Group* (*COPD); SG:* smokers group, NSG: never smoked group; BMD: bone mineral density; LS= Lumbar Spine; FN=Femoral Neck; TF: Total Femur; *Comparison between the DG and the SG; **Comparison between the DG and the NSG, p<0.05.

(a) FEV_1

BMD/FEV1	1	2	3	4	P
LS (g/cm²)	1.07 ± 0.23	1.04 ± 0.23	0.96 ± 0.23	0.90 ± 0.22	0.049
FN (g/cm²)	0.84 ± 0.16	0.81 ± 0.13	0.74 ± 0.14	0.75 ± 0.18	0.031
TF (g/cm²)	0.91 ± 0.20	0.87 ± 0.16	0.77 ± 0.18	0.78 ± 0.20	0.011

(b) GOLD

BMD/GOLD	A	B	C	D	P
LS (g/cm²)	1.13 ± 0.24	1.02 ± 0.21	0.93 ± 0.20	0.96 ± 0.23	0.003
FN (g/cm²)	0.85 ± 0.17	0.79 ± 0.13	0.74 ± 0.15	0.75 ± 0.15	0.040
TF (g/cm²)	0.94 ± 0.20	0.84 ± 0.15	0.76 ± 0.17	0.82 ± 0.17	0.001

(c) BODE

BMD/BODE	1	2	3	4	P
LS (g/cm²)	1.07 ± 0.22	0.97 ± 0.21	0.92 ± 0.24	0.92 ± 0.23	0.017
FN (g/cm²)	0.83 ± 0.15	0.77 ± 0.14	0.74 ± 0.13	0.70 ± 0.17	0.017
TF (g/cm²)	0.90 ± 0.18	0.80 ± 0.17	0.77 ± 0.17	0.74 ± 0.20	0.003

BMD: Bone Mineral Density; LS: Lumbar Spine; FN: Femoral Neck; TF: Total Femur; FEV_1: Postbronchodilator Forced Expiratory Volume in the First Second; BODE: B, body mass index; O, airway obstruction; D: Dyspnea; E: Exercise Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; Significance: $p<0.05$.

Table 1: Bone mineral density according to the severity and prognosis of COPD.

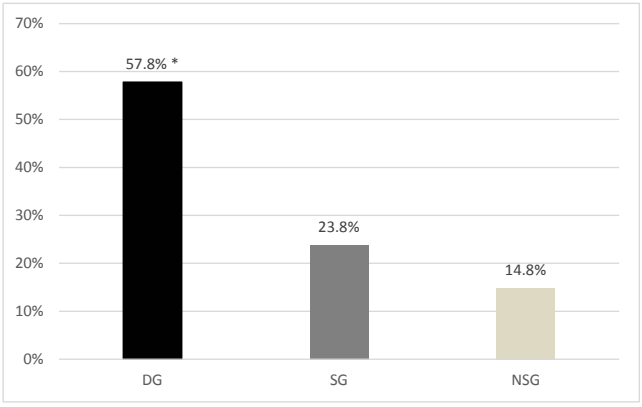

Figure 3: Prevalence of morphometric vertebral fractures in COPD patients and controls.
DG: Disease Group (COPD); SG: Smokers Group; NSG: Nonsmokers Group; Comparison between the DG and the SG and NSG.

prevalence of MVF showed no difference in the SG and NSG (p=0.124). The thoracic region was the location mostly affected with MVF in all groups, with the prevalence of 87.7%, 93.3%, and 100% in the DG, SG, and NSG, respectively. The prevalence of fractures was associated with low BMD in FN (p=0.02) in COPD patients, but not with LS and TF BMD. In control groups, there was no association with low BMD and vertebral fractures. The prevalence of fractures was not associated with FEV_1, GOLD or BODE.

Discussion

This study evaluated the relationship of BMD results and the prevalence of MVF with criteria of severity and prognosis in patients with COPD. The evaluation also included a comparison of these results with those obtained in two control groups, one group of smokers without COPD and another that never smoked. The smoking load was higher in the DG when compared with the SG, which was expected considering that the number of pack-years is related to the development of COPD, although other factors are also involved in this process [25,26].

The high prevalence of altered BMD in the DG (88.4%), in which approximately 50% of the patients showed osteoporosis, is consistent with rates described in the literature (9% to 69%) [6] and different from the prevalence of altered BMD in both control groups. Several factors may contribute to a reduction in bone mass in COPD, including inflammatory cytokines, hypercapnia, hypoxia, impaired nutrition, immobilization, hypogonadism, vitamin D deficiency, low BMI, lean mass reduction, and decreased exercise capacity [8,9]. We observed no differences in the prevalence of osteopenia or osteoporosis among smokers and nonsmokers, which contradicts some studies in the literature showing that smoking is an independent risk factor for osteoporosis [27-29]. Decreased BMD was associated with the degree of obstruction, clinical staging, and COPD's BODE prognostic index results that confirm others in the literature [13,28].

The prevalence of MVF was increased in patients with COPD (57.8%), like findings in the literature [30,31], and was higher than that in both control groups. Despite the high prevalence of fractures, they were not associated with disease severity or prognosis in COPD. The literature has controversial results in regards to the association of fractures with disease severity in COPD [14,31], and a possible explanation for this lack of association may be the existence of decreases in bone quality starting at early stages of the disease [32,33].

The limitations of the study are that no laboratory evaluation related to the bone metabolism of these patients was performed. And spine X-ray was also not done to corroborate the diagnosis of vertebral fractures.

Conclusions

In conclusion, this was the first study that compared patients with COPD with two control groups and evaluated simultaneously the BMD and MVF with the severity and prognosis of the disease. This study showed a high prevalence of low BMD and vertebral fractures in patients with COPD, serving as an alert for physicians to weight on potential skeletal changes that occur in these patients, in addition to the changes related to aging. These results may provide evidence for the need to implement interventions for prevention of osteoporosis and fractures, thus improving the quality of life in patients with COPD.

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