



# Bone mineral density and vertebral fractures and their relationship with pulmonary dysfunction in patients with chronic obstructive pulmonary disease

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## Abstract

**Summary** To evaluate bone mineral density (BMD) and morphometric vertebral fractures (MVF) in chronic obstructive pulmonary disease (COPD) patients in comparison with two control groups. BMD was lower in the disease group (DG) and was associated with the worst disease severity and prognosis. The prevalence of MVF was high and greater in the DG than in the control groups.

**Introduction** 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 BMD and morphometric vertebral fractures (MVF) in COPD patients in comparison with two control groups and to correlate these parameters with indices of COPD severity (VEF1 and GOLD) and prognosis (BODE).

**Methods** This was a cross-sectional study in COPD patients (disease group, DG) who underwent BMD and vertebral fracture assessment (VFA). Two control groups were used: smokers without COPD (smoker group, SG) and healthy never-smoker individuals (never-smoker group, NSG).

**Results** The DG comprised 121 patients (65 women, mean age  $67.9 \pm 8.6$  years). Altered BMD was observed in 88.4% of the patients in the DG, which was more prevalent when compared with the control groups ( $p < 0.001$ ). The BMD values were lower in the DG than in the control groups ( $p < 0.05$ ). BMD was associated with the worst disease severity and prognosis ( $p < 0.05$ ). The prevalence of MVF was high (57.8%) and greater than that in the SG (23.8%) and the NSG (14.8%;  $p < 0.001$ ). The prevalence of fractures was not associated with disease severity and prognosis.

**Conclusions** COPD patients have a higher prevalence of MVF and low BMD, and the latter was associated with the severity and poor prognosis of the disease.

**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 individuals above 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 extrapulmonary disorders, including cardiovascular disease, sleep apnea, depression, anemia, chronic kidney disease, osteoporosis, cachexia, and skeletal muscle weakness [4].

Low bone mineral density (BMD) that leads to osteoporosis is common in COPD patients, 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,

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hypercapnia, hypoxia, poor nutrition, low body mass index (BMI), inflammatory cytokines, and decreased lean mass [8–10]. In addition to low BMD, COPD patients also present altered bone quality and microstructure, leading to a high prevalence of fractures. Indeed, 30–63% of COPD patients present vertebral fractures [11]. In this population, thoracic vertebral fractures are particularly concerning because 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 COPD patients is associated with disease severity and prognosis [13], and data from the literature have shown controversial results in this regard [14, 15]. In contrast, evidence suggests that newly diagnosed COPD patients 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 COPD patients compared with two control groups, one consisting of smokers without COPD and the other consisting of healthy never-smoker individuals. Secondary aims included correlating these parameters with indices of COPD severity and prognosis.

## Patients and methods

### Study groups

This was a cross-sectional study performed on a group of COPD patients treated at the Pulmonary Outpatient Clinic of the Hospital de Clinicas at Universidade Federal do Parana, Curitiba, South Brazil. All patients signed an informed consent form, and the study was approved by the Ethics Committee on Human Research of our institution.

The patients included in this study had been invited to undergo BMD and vertebral fracture assessment (VFA) between January 2010 and December 2014. The inclusion criteria were men and women older than 50 years with 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 matched by age and sex were used for comparison with the COPD group (disease group, DG): smokers without COPD (smoker group, SG) and healthy never-smoker individuals (never-smoker group, NSG). Individuals in the SG were invited to participate during their first visit to a smoking cessation clinic of the same

hospital, and individuals in the NSG 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 and VFA with 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 (kilograms) was measured on a digital electronic scale while the participants wore light clothes. Height (meters) was measured while the individuals kept their back straight, heels together, and arms extended alongside their body. Their BMI was determined by dividing the weight (in kilograms) by the squared height (in square meter) [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 DXA were the lumbar spine (LS), total femur (TF), and femoral neck (FN). The BMD results were expressed as grams per centimeter and as scores in relation to reference values determined by the International Society for Clinical Densitometry (ISCD) [18]. In our center, the least significant change (LSC) for the lumbar spine was  $0.010 \text{ g/cm}^2$  and for the proximal femur was  $0.012 \text{ g/cm}^2$ . 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] and history of exacerbations, using post-bronchodilator forced expiratory volume in the first second ( $FEV_1$ ), the modified Medical Research Council (mMRC) dyspnea scale [21], the COPD Assessment Test (CAT) [22], and a 6-min walk test [23].

Patients in the DG were classified according to the degree of airflow obstruction ( $FEV_1$ ) into categories 1 ( $\geq 80\%$ ), 2 (50–79%), 3 (30–49%), and 4 ( $< 30\%$ ) [20]. The COPD severity was determined according to the GOLD index—which is based on the post-bronchodilator  $FEV_1$ , history of exacerbations in the previous year, and symptoms such as dyspnea (measured with the mMRC or CAT)—and the study groups were classified into A, B, C, and D. The COPD prognosis was evaluated with the body mass index, airflow obstruction, dyspnea, and exercise (BODE) index [24]—which integrates the patient's BMI, the degree of airflow obstruction, grade of dyspnea, and exercise capacity—with total criteria point count varying from 0 to 10. Additionally, the patients were classified

into four quartiles, with the first being the least severe and the fourth being the most severe.

### Statistical analysis

Data are presented as the mean ± standard deviation (SD). All analyses were performed using IBM SPSS Statistics, v.20.0 (IBM Corp, Armonk, NY, USA). The normality of the distribution of the variables was evaluated by 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 the 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.

From 758 COPD patients in treatment at the pneumology clinic, 150 consecutive COPD patients were invited to participate in the study; 127 accepted the invitation, and from these, six 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<sup>2</sup>). The mean tobacco consumption was 58.9 ± 40.8 pack-years. Overall, 23 patients (19.1%) were still smoking at the time of

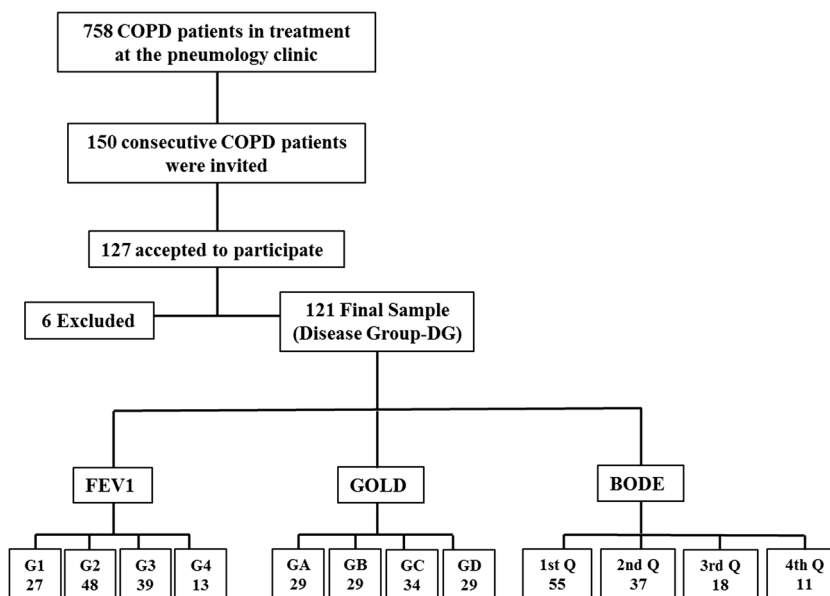
the cross-sectional evaluation. According to the degree of obstruction evaluated by the FEV1, 21 patients (17.3%) were classified as group 1, 48 (39.6%) were classified as group 2, 39 (32.2%) were classified as group 3, and 13 (10.7%) were classified as group 4. Based on the GOLD classification, the DG was subdivided as follows: GOLD A: 29 patients (23.9%), GOLD B: 29 patients (23.9%), GOLD C: 34 patients (28%), and GOLD D: 29 patients (23.9%). According to the BODE index, 55 patients (45.4%) were in the first quartile, 37 patients (30.5%) were in the second quartile, 18 patients (14.8%) were in the third quartile, and 11 (9%) were in the fourth quartile.

There were 29 patients (22.8%, GOLD A) taking short action beta 2 agonists, 92 patients (72.4%, GOLD B plus C and D) taking long action beta 2 agonists, and 63 patients (49.6%, GOLD C plus D) taking inhaled corticosteroids.

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<sup>2</sup>. All individuals were 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<sup>2</sup>, and in this group, none of the participants ever smoked. There were no differences in gender, age, or BMI among the groups, although the mean tobacco consumption in the DG was significantly higher than that in the SG (Table 1).

Abnormal BMD was observed in 88.4% of the patients in the DG; 49 (40.5%) had osteopenia [24 (36.9%) and 25 (44.6%) of women and men, respectively] and 58 (47.9%) had osteoporosis [33 (50.7%) and 25 (44.6%) of women and men, respectively]. Abnormal BMD was more prevalent in the DG than in the SG (68.2%, *p* < 0.001) and the NSG (72.8%,

**Fig. 1** Flow chart describing patients distribution in the different COPD classifications. COPD chronic obstructive pulmonary disease, FEV1 post-bronchodilator 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



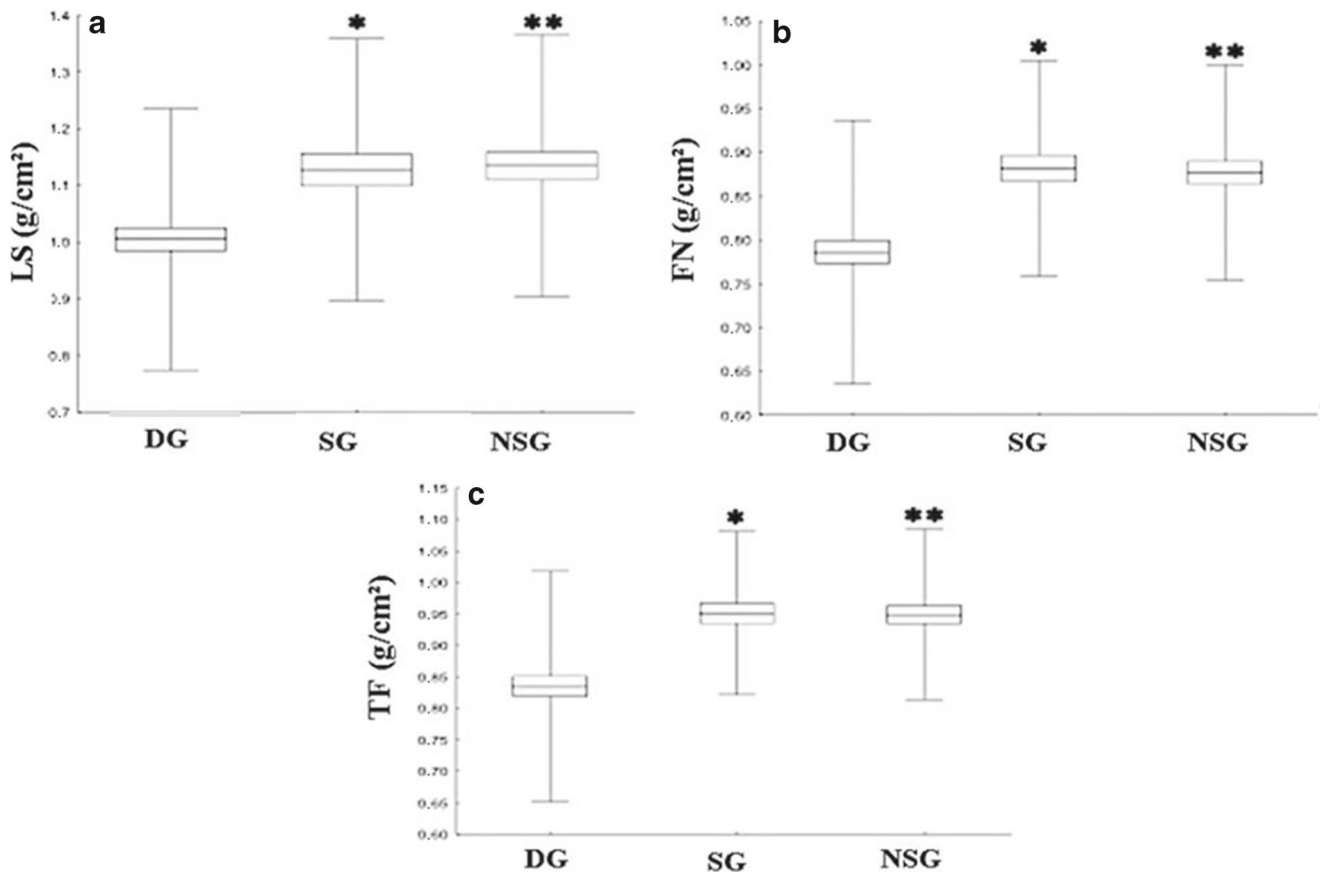
**Table 1** Clinical characteristics of the individuals from the groups

Variable	DG ( <i>n</i> = 121)	SG ( <i>n</i> = 63)	NSG ( <i>n</i> = 81)	<i>p</i>
Age	67.8 ± 8.5	65.5 ± 8.9	66 ± 8.5	0.147
BMI (kg/m <sup>2</sup> )	26.4 ± 6.1	27.6 ± 3.6	26.1 ± 2.5	0.143
Mean tobacco consumption	58.9 ± 40.8	38 ± 28.2	–	< 0.001
Abnormal BMD	88.4% ( <i>n</i> = 107)	68.2% ( <i>n</i> = 43)	72.8% ( <i>n</i> = 59)	< 0.001

COPD group (disease group, DG); smoker individuals without COPD (smoker group, SG); healthy never-smoker individuals (never-smoker group, NSG); *BMI* body mass index; mean tobacco consumption (pack-years); *BMD* bone mineral density

$p < 0.001$ , Table 1). The distribution of BMD classifications was similar in both control groups: in the SG, 31 patients (49.2%) had osteopenia [11 (31.4%) and 21 (60%) of women and men, respectively], 12 (19%) had osteoporosis [10 (28.5%) and 2 (5.7%) of women and men, respectively], and 20 (31.7%) had normal BMD [14 (40%) and 12 (34.2%) of women and men, respectively]. In the NSG, 47 patients (58%) had osteopenia [28 (59.7%) and 19 (55.8%) of women and

men, respectively], 12 (14.8%) had osteoporosis [9 (19.1%) and 3 (8.8%) of women and men, respectively], and 22 (27.1%) had normal BMD [10 (21.2%) and 12 (35.2%) of women and men, respectively]. The BMD (grams per square centimeter) values in all three sites evaluated were lower in the DG than in the control groups (Fig. 2). BMD was associated with the degree of obstruction (FEV1), GOLD, and BODE ( $p < 0.05$ , Fig. 3).

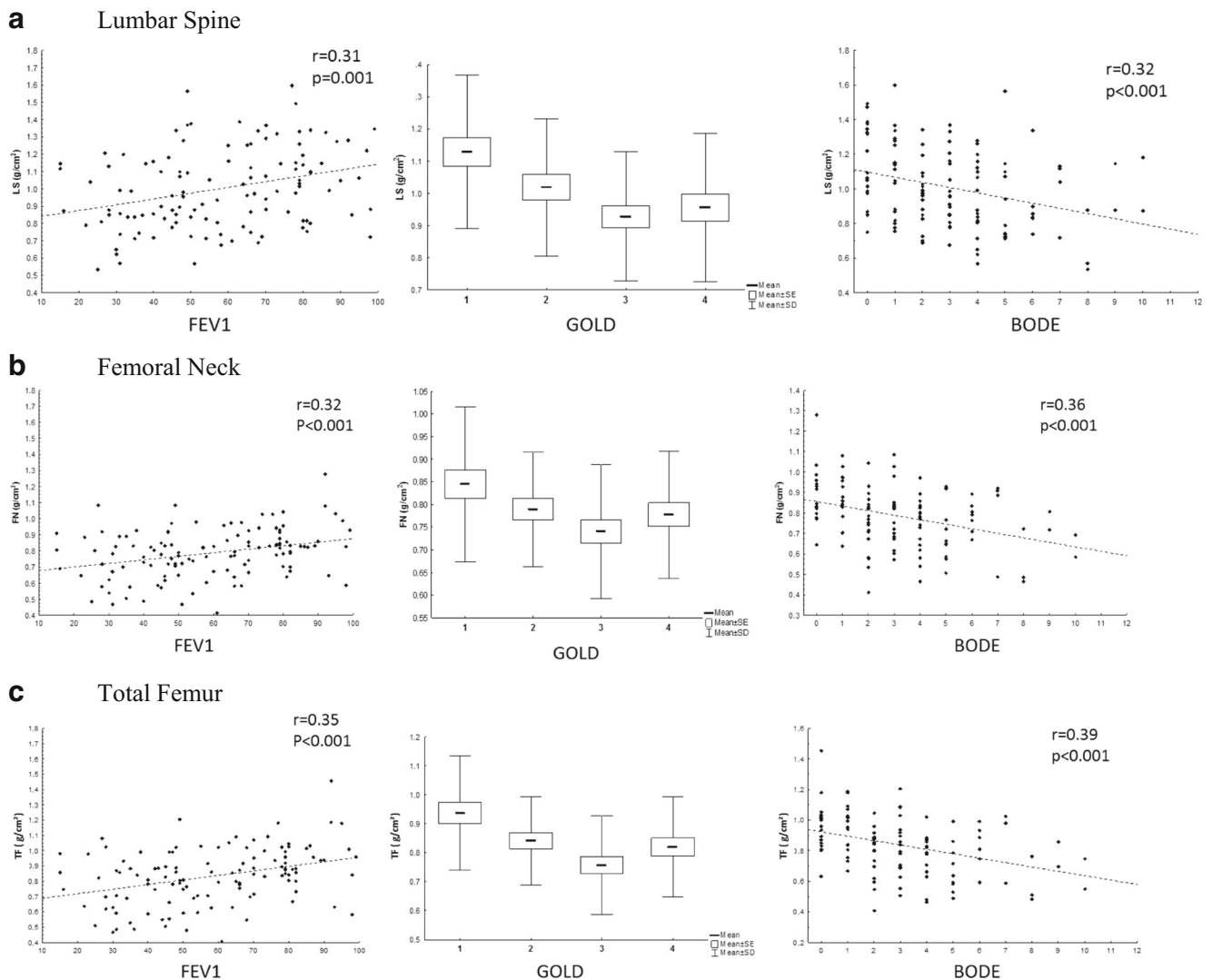


Legend: BMD: Bone Mineral Density, LS: Lumbar Spine, FN: Femoral Neck. TF: Total Femur.

\*Comparison between the DG and the SG; \*\*Comparison between the DG and the NSG,  $p < 0.05$ .

**Fig. 2** Bone mineral density at lumbar spine (LS), femoral neck (FN), and total femur (TF) in the disease group (DG) comprising 121 patients with chronic obstructive pulmonary disease (COPD), 63 smokers without COPD (SG), and 81 never-smoker healthy individuals (NSG). Horizontal

lines in the box plots indicate median and 5, 25, 75, and 95 percentiles. 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,  $p < 0.05$

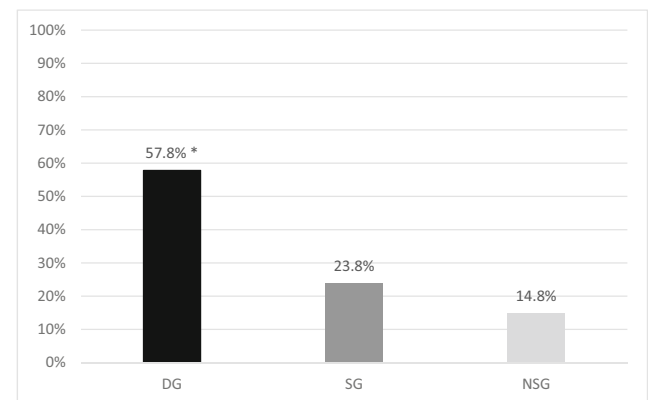


**Fig. 3** Bone mineral density according to the severity and prognosis of COPD. LS lumbar spine, FN femoral neck, TF total femur, FEV1 post-bronchodilator forced expiratory volume in the first second, BODE: B

body mass index, O airway obstruction, D dyspnea, E exercise capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease; significance =  $p < 0.05$

One hundred eighty-four vertebral fractures were found in 70 COPD patients. The prevalence of MVF was significantly higher in the DG than in the SG (57.8% vs. 23.8%,  $p < 0.001$ ) and the NSG (14.8%,  $p < 0.001$ , Figs. 3 and 4). There was no difference in the prevalence of MVF between the SG and the NSG.

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. In the DG, the prevalence of fractures was associated with low BMD in FN ( $p = 0.02$ ), but not in the LS and TF. In the control groups, there was no association between low BMD and MVF. Moreover, we did not find an association between the prevalence of fractures and FEV1, GOLD, or BODE in any of the study groups.



Legend: Asterisk denotes  $p < 0.001$  in comparison with SG and NSG

**Fig. 4** Prevalence of morphometric vertebral fractures (MVF) in 121 patients with chronic obstructive pulmonary disease (COPD), 63 smokers without COPD (SG), and 81 never-smoker healthy individuals (NSG). Asterisk denotes  $p < 0.001$  in comparison with SG and NSG

## Discussion

This is the first study comparing COPD patients with two control groups to evaluate simultaneously BMD and MVF and their association with the severity and prognosis of the disease. 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 (9–69%) [6] and is different from the prevalence of altered BMD in both control groups. Several factors may contribute to a reduction in bone mass with 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 never-smokers, which contradicts some studies in the literature that have found smoking to be 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 possible explanations for the higher BMD in GOLD 4 COPD patients than in the GOLD 3 COPD patients may be the low number of patients in each GOLD stage; the severity of the disease in GOLD 3 and GOLD 4 COPD patients may be equally as bad for the bone as shown by Watanabe R et al. [30].

The prevalence of MVF was increased in COPD patients (57.8%), similar to the literature [31, 32], 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 data regarding the association of fractures with disease severity in COPD [14, 32]. A recent study with 99 COPD patients also could not significantly correlate the number of vertebral deformities with FEV1 for men or women with COPD, and increasing age was the only factor significantly associated with vertebral fractures [33]. Majumdar et al. [32] suggested that patients with lower lung function had more severe vertebral fractures. The possible explanations for this lack of association may be the existence of decreases in bone quality starting at early stages of the disease [34, 35], limited sample size [33], or, in part, related to how “severity” is defined [32].

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

In conclusion, this was the first study that compared COPD patients 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 COPD patients, serving as an alert for physicians to weigh in 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 of COPD patients.

## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflicts of interest** None.

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