REVISTA DE INVESTIGACIÓN CLÍNICA

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PERMANYER

Rev Invest Clin. 2019;71:204-10 ORIGINAL ARTICLE

Association of Bone Mineral Density with Chronic Obstructive Pulmonary Disease in Postmenopausal Women

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ABSTRACT

Background: Osteoporosis (OP) is common in patients with chronic obstructive pulmonary disease (COPD). The relationship between OP and COPD has been primarily studied in male patients, and few reports are available in postmenopausal women. **Objective:** The purpose of this study was to investigate the association between bone mineral density (BMD) and COPD in postmenopausal women. **Methods:** This cross-sectional study included 133 clinically stable female ex-smokers with confirmed COPD, and 31 age-matched "ex-smoker" female controls. We analyzed groups according to their airway obstruction category. BMD was measured on dual-energy X-ray absorptiometry images of the left femoral neck. **Results:** Patients with COPD had lower T-scores and higher prevalence of osteopenia/OP than the control group. In the COPD group, the airway obstruction category was significantly associated with the T-score after adjustment for confounders. Multivariate logistic regression analysis showed COPD was an independent marker for increased risk of osteopenia/OP in postmenopausal women. **Conclusions:** COPD and airway obstruction category were strongly related to BMD. Postmenopausal women with COPD, especially those with severe airway obstruction, had a higher prevalence rate and a higher risk of osteopenia and OP than female controls without COPD. (REV INVEST CLIN. 2019;71:204-10)

Key words: Osteoporosis. Obstructive pulmonary disease. Postmenopausal women.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by nonreversible airflow obstruction, of which emphysema and chronic bronchitis are the most common form[1]. COPD is a systemic disease that affects lung function and is accompanied by extra-pulmonary comorbidities. Age-related osteoporosis (OP) is a major public health problem which represents an enormous burden of disability and has been recognized as one of the important comorbidities in COPD[2]. A retrospective study conducted in the US identified COPD as the leading cause of secondary OP, independently of previously known risk factors

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Received for publication: 05-12-2018
Approved for publication: 10-01-2019
DOI: 10.24875/RIC.19002935

such as glucocorticoid (GC) use or hypogonadism[3]. Meanwhile, OP has been proved to be associated with deterioration of lung function, poor quality of life, and excess mortality in COPD patients[4]. Indeed, the two conditions form a vicious cycle that significantly worsens prognosis.

Recently, increasing evidence supports the correlation between COPD and OP[5]. These disorders share some risk factors, such as menopause, a low body mass index (BMI), GC therapy, smoking, physical disability, Vitamin D deficiency, and hypogonadism[4,5]. Menopause appears to be a particularly important risk factor for OP. Unlike younger women, the risk of OP in older women exceeds that of men, coinciding with the decline in estrogen production that marks the end of the protective effect of endogenous estrogens against bone mass loss[6]. An epidemiological survey showed COPD is the third-leading cause of death in the US, with greater mortality in women than in men[7]. Management of OP is clinically important in postmenopausal patients with COPD, as they are especially susceptible to decreased quality of life, prolonged times of hospitalization, and higher mortality[4].

Several studies have clearly indicated OP to be associated with COPD in male patients; however, to date, few studies have examined the relationship between bone mass density (BMD) and COPD in postmenopausal women, remaining a matter of debate[2,8]. The aim of this cross-sectional study was to examine the association between BMD and COPD in postmenopausal women in Northwest China.

METHODS

Study population

This cross-sectional study included 133 COPD patients, and 31 age-matched female control subjects free from respiratory symptoms admitted to the Department of Geriatrics, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China, from January 1 2014 to August 31 2017. This unit mainly admits elderly patients with cardiovascular diseases and chronic respiratory diseases. The inclusion criteria were: postmenopausal women; age ≥50 years; nonsmokers; and not taking medication known to affect bone turnover. The exclusion criteria were: presence of disorders that could influence bone and calcium metabolism, such as thyrotoxicosis, hyperparathyroidism, chronic renal failure, malignancies, and current treatment with oral or inhaled GC.

Clinical features and laboratory examination

Eligible subjects had their weight and height measured, and their BMI calculated as body weight/height^2 (kg/m^2). Completion of the medical record was based on a standard questionnaire. Subjects who had been living or working with smokers were considered to be exposed to second-hand smoke.

Pulmonary function tests

The degree of airway obstruction was assessed using prebronchodilator spirometry measurements performed according to the standards of the American Thoracic Society[9]. In COPD patients, the degree of airway obstruction was categorized as follows: (a) mild (forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] <0.7, and FEV1≥80% of predicted FEV1), (b) moderate (FEV1/FVC <0.7, and FEV1≥50, and <80% of predicted FEV1), (c) severe (FEV1/FVC <0.7, and FEV1≥30m and <50% of predicted FEV1), and (d) very severe (FEV1/FVC <0.7 and FEV1 <30% of predicted FEV1).

Measurement of bone mass density

Participants were required to have had BMD of left femoral neck bone densitometry measured using a dual X-ray absorptiometry with QDR 4500A fan beam bone densitometer (Bedford, MA, USA) according to the manufacturer's instructions. BMD results were reported as T-scores. T-scores were also categorized into three groups according to the World Health Organization criteria for diagnosing OP: normal BMD (T ≥ −1 SD), osteopenia (T < −1SD and > −2.5 SD), and OP (T ≤ −2.5 SD).

Statistical analyses

Analyses were carried out using SPSS version 19.0 software (SPSS Inc., Chicago, IL). Since most continuous variables were normally distributed, as tested by the Kolmogorov–Smirnov test, they were expressed as mean ± standard deviation (SD). Differences

Table 1. Baseline characteristics of all subjects

Characteristics	Controls	Patients	p value
	n=31	n=133	
Age (years)	61.28±6.63	61.40±6.42	0.926
BMI (kg/m^2)	23.15±3.13	21.88±3.30	0.053
FEV1 (L)	2.37±0.31	1.32±0.32	<0.001
FEV1% predicted (%)	90.13±12.31	64.90±7.79	<0.001
FVC (L)	2.71±0.67	2.43±0.52	0.012
FEV1/FVC	0.87±0.05	0.53±0.08	<0.001
ALP, IU/L	242.27±73.78	264.49±80.12	0.163
25(OH)D, ng/ml	22.41±4.31	20.47±5.20	0.056
Long acting β2 agonist	0	43 (32.33%)	
Exposure to second-hand smoke	12 (38.71%)	45 (33.83%)	0.324
T-score	−0.39±1.12	−1.01±1.49	0.031
Osteoporosis	5 (16.13%)	50 (37.59%)	0.023
Osteopenia	6 (19.35%)	53 (39.85%)	0.032

Values are presented as mean ± SD or number (%).
25(OH)D: 25-hydroxyvitamin D, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, ALP, alkaline phosphatase.

between the groups were evaluated using the unpaired *t*-test. Categorical variables were compared with the Chi-square test. The four airway obstruction categories in COPD patients were reorganized into three groups (Mild, Moderate, and Severe, or very severe), to improve the statistical reliability of the estimates. To confirm the influence of COPD and airway obstruction category on the T-score, multivariate linear regression analysis was performed after adjustment for age, BMI, 25(OH)-Vitamin D levels, and alkaline phosphatase (ALP) levels.

Multivariate logistic regression analysis was used to assess the association between airway obstruction category and osteopenia/OP after adjustment for age (base model and adjustment for age), and after adjusting for all statistically significant shared risk factors (full model, adjustment for age, BMI, 25[OH] - Vitamin D levels, and ALP levels). Statistical significance was set at $p < 0.05$ (2-tailed).

RESULTS

The baseline demographics of the study population are presented in table 1. Overall, a total of 164 postmenopausal female patients (mean age 61.38 ± 6.46 years) were included in the present study; encompassing 31 normal controls (mean age 61.28 ± 6.63 years) and 133 COPD patients (mean age 61.40 ± 6.42 years). Subjects in the COPD group had lower FEV1, predicted FEV1, FVC, FEV1/FVC, and T-score, and had a higher prevalence of osteopenia/OP compared with the control group ($p < 0.05$). There were no differences between the groups with respect to age, BMI, ALP, 25(OH)D, and the prevalence of exposure to second-hand smoke.

Based on their FEV1 and predicted FEV1 values, COPD patients were allocated into airway obstruction categories as follows: a mild obstruction group (n=41), a moderate obstruction group (n=65), and a severe/very severe obstruction group (n=27, Table 2). The proportion of patients with osteopenia/OP gradually increased according to the severity of airway obstruction in COPD patients ($p < 0.05$). In the severe/very severe obstruction group, 59.26% of patients had OP, while 33.33% had osteopenia. FEV1, predicted FEV1, FVC, FEV1/FVC, and T-score were significantly lower in the severe/very severe obstruction group than in the mild and moderate obstruction groups ($p < 0.05$).

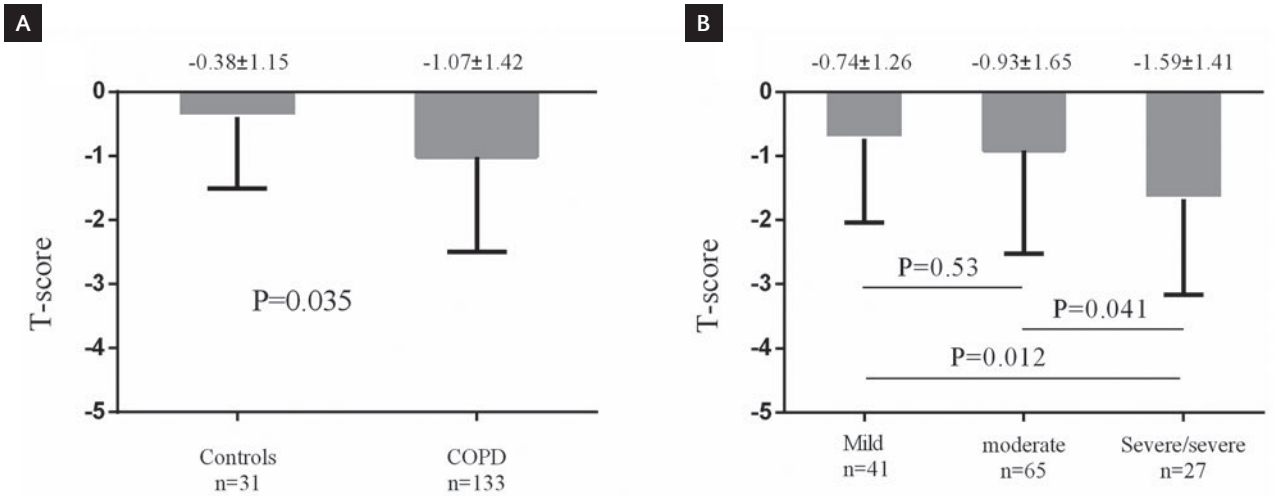
Results from the analysis of the effect of COPD on the T-score in postmenopausal women are presented

Table 2. Baseline characteristics of COPD in postmenopausal women

Characteristics	Airway obstruction			p value
	Mild	Moderate	Severe/very severe	
	n=41	n=65	n=27	
Age (years)	60.17±5.79	61.79±6.52	62.34±7.12	0.318
BMI (kg/m^2)	22.53±2.87	21.97±3.27	20.67±4.01	0.078
FEV1 (L)	1.64±0.23	1.31±0.34	0.84±0.41	<0.001
FEV1% predicted (%)	85.01±7.33	61.29±8.29	43.07±7.29	<0.001
FVC (L)	2.59±0.37	2.43±0.45	2.18±0.93	0.0149
FEV1/FVC	0.62±0.08	0.53±0.07	0.38±0.11	<0.001
ALP, IU/L	252.19±83.81	261.19±77.25	291.13±81.43	0.1356
25(OH)D, ng/ml	20.14±5.24	21.09±4.75	19.47±6.21	0.358
Long-acting β_2 agonist	11 (26.83)	17 (26.15)	15 (55.55)	0.015
Exposure to second-hand Smoke	18 (43.90)	24 (36.92)	13 (48.15)	0.087
T-score	−0.73±1.31	-0.91±1.61	-1.67±1.49	0.034
Osteoporosis	8 (19.51)	26 (40.0)	16 (59.26)	0.004
Osteopenia	11 (26.83)	33 (50.77)	9 (33.33)	0.037

Values are presented as mean ± SD or number (%).
25(OH)D: 25-hydroxyvitamin D, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, ALP: alkaline phosphatase.

Figure 1. Influence of the chronic obstructive pulmonary disease (COPD) and airway obstruction category on the T-score at the left femoral neck in postmenopausal women. **A:** Comparison between COPD patients and control subjects. **B:** Comparison between airway obstruction categories in COPD patients. p values are adjusted by age, body mass index, 25(OH)D, and alkaline phosphatase.



in figure 1. Subjects with COPD had significantly lower T-scores (−1.07±1.42) than the control group (−0.38±1.15, $p < 0.05$, adjusted). Furthermore, among COPD patients, subjects in the severe/very severe obstruction group had lower T-scores (−1.59±1.41) than the mild obstruction group (−0.74±1.26, $p < 0.05$, adjusted) and the moderate obstruction group (−0.93±1.65, $p < 0.05$, adjusted).

Table 3. Multivariate regression analysis between airway obstruction category and osteopenia, osteoporosis

Characteristics	Osteopenia			Osteoporosis		
	OR	95% CI	p value	OR	95% CI	p value
Base model[a]						
Controls	1			1		
Mild	0.75	0.045-1.689	0.175	0.87	0.312-4.874	0.582
Moderate	1.53	1.101-3.065	0.021	2.17	1.454-6.983	0.017
Severe/very severe	3.27	2.003-7.583	<0.001	4.11	2.538-9.535	<0.001
Full model[b]						
Controls	1			1		
Mild	0.68	0.031-1.896	0.245	0.73	0.543-5.564	0.643
Moderate	1.36	1.213-3.693	0.038	1.94	1.265-7.676	0.043
Severe/very severe	3.06	1.934-9.785	<0.001	3.32	1.977-7.485	<0.001

[a]Adjusted for age. [b]Adjusted for age, BMI, 25(OH)D, and ALP.
BMI: body mass index, ALP: alkaline phosphatase, OR: odds ratio, CI: confidence intervals.

A multivariate logistic regression analysis was used to assess the association between airway obstruction category and osteopenia/OP in all postmenopausal women after adjustment for age (base model), and after adjusting for all risk factors (full model) (Table 3). In the full model, subjects with COPD in the moderate and severe/very severe obstruction groups had higher risks of developing osteopenia (Moderate vs. control, odds ratio [OR] = 1.36, 95% confidence intervals [CI], 1.213-3.693, p=0.038; Severe/very severe vs. control, OR = 3.06, 95% CI, 1.934-9.785, p < 0.001) and OP (Moderate vs. control, 1.94, 95% CI, 1.265-7.676, p = 0.043; Severe/very severe vs. control, OR=3.32, 95% CI, 1.977-7.485, p < 0.001).

DISCUSSION

In this study, postmenopausal women with COPD had lower T-scores and a greater prevalence of osteopenia/OP compared with age-matched female controls. Airway obstruction categories were significantly related to left femoral neck T-scores. Subjects with COPD had higher risks of developing osteopenia and OP than controls. The selection of the study sample aimed to avoid possible confounding factors such as premenopause, smoking and exposure to GCs, and eliminating the contribution of these agents to BMD loss.

In the present study, the prevalence of osteopenia/OP was high, with 39.85% for the former, and 37.59% for the latter. These data appear to be in line with a Japanese study, which found the prevalence of osteopenia/OP in COPD patients to be high, with 46% and 24%, respectively[5]. Our findings may also be supported by observations from a British study, which showed that 23% of COPD patients had OP in the hip, and 42% had osteopenia[10]. Moreover, the prevalence of OP has also been reported to be more frequent in postmenopausal women than in age-matched men[11]. Our research results were significantly higher compared with a published meta-analysis which estimated the prevalence of OP at 35.1%, and the prevalence of osteopenia at 38.4% in COPD patients[12]. Our findings indicate OP is very common in postmenopausal women with COPD. However, the absolute prevalence is difficult to interpret, as BMD is affected by various characteristics typical of COPD patients, such as race, age, BMI, gender, and exposure to GCs[13]. OP-associated fractures have been observed to lead to excess mortality in COPD patients[4]. Therefore, awareness and treatment for OP may be crucial for the management of postmenopausal women with COPD to improve prognosis.

In our study, postmenopausal women with COPD had lower T-scores than those without COPD. The logistic regression analyses confirmed that airway obstruction categories were associated with osteopenia/OP,

even after adjustment for potential confounding factors, showing that postmenopausal women with COPD may have a higher risk of osteopenia/OP. Our finding may be supported by observations by Sakurai et al.[8], who found that the prevalence of OP in male patients with COPD was significantly higher than in those without COPD, and reduced BMD was associated with airflow limitation in male patients with COPD. Similarly, a case–control study showed that COPD was associated with low BMD in the femoral neck in male patients, reporting an OR of 1.5 for OP in COPD male patients compared with controls. However, most of these studies have been based on male COPD patients, while few have focused on postmenopausal women with COPD. A cross-sectional study investigated healthy postmenopausal women and found a correlation between lumbar spine BMD and FEV1[14]. Nevertheless, there are no reports currently available assessing BMD in postmenopausal women with COPD.

In contrast with our study, previous research has failed to find statistically significant differences between the BMD values of COPD and non-COPD subjects. The Fourth and Fifth Korea National Health and Nutrition Examination Surveys (KNHANES IV and V) examined the relationship between BMD and airway obstruction as assessed by FEV1 in 4501 Koreans aged 50 years and older. However, the results do not demonstrate a direct association between BMD and airway obstruction in either gender[15]. Important factors which could underlie these discrepancies may be the differences in subject characteristics, including race, age, BMI, smoking, Vitamin D intake, menopause, gender, daily physical activity, and GC exposure, all of which can affect BMD in COPD patients[13,16-18].

Although the association between COPD and OP has been described extensively in the literature, the exact mechanisms linking these diseases remain unclear. Thesemay include general risk factors such as older age, BMI, and reduced physical activity[16,18-20]. Weight loss in COPD has been attributed to systemic inflammation and oxidative stress, which may cause metabolic abnormalities in bone tissue indirectly through sarcopenia[20]. Low BMI has also been shown to predict OP in COPD patients[21]. Reduced physical activity may equally lead to sarcopenia and reduce sunlight exposure, resulting in Vitamin D deficiency, which may contribute to accelerated bone loss[18]. On the other hand, disease-specific risk factors, such as systemic inflammation and GC use, also play a key role. Systemic inflammation has been linked to OP and increased bone resorption[22]. COPD patients with lower BMD have been shown to have higher levels of systemic inflammation as assessed by circulating levels of C-reactive protein and inflammatory cytokines such as TNF-α and interleukin 6[17]. Systemic GC use could decrease the formation of new bone and increase bone loss[23-25]. The rate of bone loss appears to correlate with the daily dose and duration of therapy; however, reports on this aspect are scarce. Future research should investigate the common pathophysiological links between OP and COPD.

This study has some limitations. First, the cross-sectional design prevents assessment over time. Second, the major limitation of our study is the small sample size, and our findings should be verified in larger samples. Furthermore, information on impaired Vitamin D status, inflammatory cytokines, and physical activity - which may be associated with both COPD and BMD - was not available.

In this study, we investigated the association between BMD and COPD in postmenopausal women. Our results suggest the incidence of osteopenia and OP is higher in COPD patients with no GC exposure compared to ex-smoker controls. Our data also suggest airway obstruction categories may be an appropriate tool for the diagnostic assessment of BMD. This would promote the earlier identification and treatment of OP, which is an important part of the management of COPD in postmenopausal women.

ACKNOWLEDGMENTS

Rui Xu, Yuan Zhang, and Hong-Ni Yang participated in the design of this study, and they both performed the statistical analysis. Xin-Chun Chen, Yu-Qing Li, Ling-Ling Ma, and Rui Gong carried out the study and collected important background information. Rui Xu drafted the manuscript. All authors read and approved the final manuscript. No competing financial interests exist.

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