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ORIGINAL ARTICLE

The association of low bone mineral density with systemic inflammation in clinically stable COPD

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Abstract Chronic obstructive pulmonary disease (COPD) is known to be a systemic inflammatory disease which affects the function of many organs, and the low bone mineral density (BMD) may be the result of systemic inflammation. The aim of the present study was to explore the association of BMD with systemic inflammation in patients with clinically stable COPD. BMD and inflammatory markers, including C-reactive protein, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), were determined in all the recruited patients with clinically stable COPD. The patients were classified according to T scores, and the relationship between BMD with markers of systemic inflammation and that with other osteoporosis risk factors was assessed. There were no differences in age, female sex, body composition, tobacco exposure, and the use of respiratory medications among these groups. As the abnormality of BMD went severer, COPD patients with osteoporosis had significantly higher levels of systemic inflammation than those with either normal BMD or osteopenia. The presence of systemic inflammation was associated with a greater likelihood of low BMD, and multivariate logistic regression analysis showed that TNF-α and IL-6 were independent predictors of low BMD. It can be concluded that systemic inflammation is a significantly independent predictor of low BMD in patients with clinically stable COPD.

Keywords Chronic obstructive pulmonary disease · Inflammation · Osteoporosis · Bone mineral density

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Introduction

Chronic obstructive pulmonary disease (COPD), one of the major causes of mortality in the world, is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke [1]. Recently, there is an increasing awareness of systemic manifestations of COPD, such as osteoporosis, arterial stiffness, skeletal muscle dysfunction, and anemia, which may be related to systemic inflammation [2].

A low bone mineral density (BMD) leading to osteoporosis is a major comorbidity in COPD and a recent meta-analysis of 13 studies in patients with COPD indicated the overall mean prevalence of osteoporosis was 35.1% (range 9–69%) [3]. Nevertheless, the loss of BMD remains underdiagnosed and undertreated in these patients, and the underlying mechanisms remain poorly understood. The significant loss of BMD in those with milder airflow limitation, and in the absence of corticosteroid use [4, 5], implicates that other mechanisms distinct from traditional risk factors might contribute to the increased prevalence of low BMD in COPD.

The association between low BMD and systemic inflammation has been examined in several inflammatory diseases, such as systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD) [6, 7]. Recently, the knowledge about high levels of circulating inflammatory markers and high risk of osteoporotic fractures in COPD have been identified [8], but it remains unknown whether there is a relationship between systemic inflammation and low BMD in patients with COPD.

The aim of the study was to evaluate the relationship between the markers of systemic inflammation and low

BMD in patients with clinically stable COPD. The identification of the association may allow physicians to better monitor and prevent low BMD in patients with COPD.

Materials and methods

Study subjects

According to the diagnostic criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1], patients with clinically stable COPD were enrolled at the outpatient clinic, West China Hospital of Sichuan University, from May 2005 to April 2010. Patients with acute exacerbations of COPD in the preceding 3 months, known diagnosis of or receiving treatment for rheumatic diseases, diabetes mellitus, osteoporosis, and any disorder with an inflammatory or metabolic component, maintenance treatment with systemic corticosteroids (oral, parenteral), acute or unstable medical illnesses, and cardiovascular diseases were excluded, and there were no other known secondary causes of osteoporosis. The study protocol was approved by the ethics committee of West China Hospital of Sichuan University and all patients gave written informed consent. Portable spirometers (Master Scope, Jaeger, Germany) were used on all patients in the study following the procedure for spirometry recommended by American Thoracic Society (ATS)/European Respiratory Society (ERS), and the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured [9].

Data on demographic, lifestyle, and biological factors, including gender, age, height, and body weight, smoking habits, and the use of respiratory medications, were obtained from the questionnaires. All prescriptions of corticosteroid medications during the preceding 2 years before the study were collected. To combine the different inhaled corticosteroids (ICS), dose equivalencies were established [10]. The cumulative dose during the 2-year span was computed by summing the dose equivalents of all prescriptions of the inhaled formulations, and the mean daily dose was taken as the cumulative dose divided by the treatment periods.

Dual-energy X-ray absorptiometry (DXA)

BMD at the hip (total and femoral neck) and lumbar spine were determined by lunar iDXA Series X-ray Tube Housing Assembly (GE Medical Systems Lunar, Madison, USA). The BMD was expressed as an absolute value (gram per square centimeter, g/cm^2) and as a T-score, the number of standard deviations from a young, sex-specific reference mean, using the health population of multicenter in China for BMD measurements [11]. Diagnosis of osteoporosis was based on the lowest T-score of the three measured locations and defined as follows: osteoporosis: T-score ≤ -2.5; osteopenia: T-score between -2.5 and -1; normal BMD: T-score > -1 [12].

Biomarkers measurement

Peripheral venous blood samples were collected to measure the serum levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). CRP was assessed with rate nephelometry assay by a Beckman Coulter Immage 800 immunochemistry system (Beckman Coulter, Inc, Chicago, USA), which had a detection limit of 0.1 mg/l. TNF-α and IL-6 was measured by enzyme linked immunosorbent assay and electro-chemiluminescence immunoassay using Benchmak microplate reader (Bio-rad Corporation, USA) and modular analytics E170 (Hitachi High-Technologies Corporation, Tokyo, Japan) with a lower limit of detection of 0.5 and 0.1 pg/ml, respectively.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 statistical software package (SPSS Inc., Chicago, USA). Continuous variables were presented as Means ± Standard Deviation (M ± SD) and categorical variables as frequencies and group percentages. Continuous and categorical variables were compared among groups by analysis of variance (ANOVA) and X^2 analysis, respectively. Univariate logistic regression analyses were performed to assess the impact of systemic inflammation, airway obstruction, age, sex, body mass index (BMI), tobacco exposure, and the use of respiratory medications on the likelihood of low BMD. Established osteoporosis risk factors and those factors with a significance level of less than or equal to 0.20 in univariate analysis were included in the multivariate logistic regression analysis model. The odds ratios (OR) and 95% confidence intervals (CI) were then calculated. A value of $P < 0.05$ was considered statistically significant, and all reported P values were two-sided.

Results

672 patients with COPD (583 men and 89 women) were enrolled, and their demographic and biochemical characteristics were demonstrated in Table 1. They mainly had moderate airway obstruction (mean FEV_1% 58.3 (SD 14.1)), and only 128 (19.0%) and 66 (9.8%) patients with severe and very severe COPD, respectively. The patients were classified into three groups: 37.5% patients with normal BMD, 33.8% patients with osteopenia, and 28.7% patients with osteoporosis. There were no differences in age, sex, BMI, tobacco exposure, the use of ICS, inhaled

Table 1 Baseline characteristics

	Normal BMD	Osteopenia	Osteoporosis	*P* value
Patients (*n*, %)	252 (37.5)	227 (33.8)	193 (28.7)	
Age (years)	61.2 ± 11.1	63.0 ± 5.3	63.7 ± 10.4	0.908
Female gender (*n*, %)	35 (13.9)	30 (13.2)	24 (12.4)	0.696
BMI (kg/m^2)	23.2 ± 2.0	23.8 ± 4.7	22.4 ± 3.9	0.766
Respiratory medications				
Use of ICS (*n*, %)	40 (15.9)	39 (17.2)	39 (20.2)	0.058
Mean daily dose[a] of ICS in user (μg)	341.2 ± 211.0	372.3 ± 224.4	420.6 ± 199.2	0.063
Cumulative dose of ICS in user (mg)	266.9 ± 243.1	286.4 ± 231.3	310.1 ± 252.6	0.069
Use of inhaled LABA (*n*, %)	192 (76.2)	191 (84.1)	175 (90.7)	0.577
Use of inhaled anticholinergic (*n*, %)	90 (35.7)	74 (32.6)	75 (38.9)	0.618
Smoking status				
Current smoker (*n*, %)	71 (28.2)	60 (26.4)	59 (30.6)	0.836
Pack-years (years)	37.2 ± 2.0	38.8 ± 4.7	41.4 ± 3.9	0.623
Spirometry				
FEV$_1$/FVC ratio (%)	62.4 ± 3.9	59.7 ± 4.0	56.0 ± 6.2	*0.037*
FEV$_1$%pred (%)	70.5 ± 5.3	62.0 ± 6.8	53.2 ± 8.7	*0.022*
DXA				
Total hip T-score	−0.2 ± 1.0	−1.5 ± 1.7	−2.7 ± 0.8	*<0.001*
Femoral neck T-score	−0.3 ± 1.1	−1.4 ± 1.5	−2.5 ± 0.8	*<0.001*
Total lumbar spine T-score	−0.2 ± 1.2	−1.7 ± 1.3	−2.9 ± 0.7	*<0.001*
Systemic inflammation				
CRP (mg/l)	2.31 ± 1.22	3.20 ± 1.00	3.92 ± 0.97	*0.014*
TNF-α (pg/ml)	22.06 ± 5.12	33.21 ± 6.45	40.76 ± 9.82	*<0.001*
IL-6 (pg/ml)	39.52 ± 12.13	49.75 ± 11.53	63.11 ± 14.08	*<0.001*

BMD bone mineral density, *ICS* inhaled corticosteroids, *LABA* long-acting β-2 agonists, *FEV$_1$/FVC* ratio of forced expiratory volume in one second to forced vital capacity, *FEV$_1$%pred* forced expiratory volume in one second of predicted value, *DXA* dual-energy X-ray absorptiometry, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-alpha, *IL-6* interleukin-6

[a] Mean daily dose (in μg of budesonide-equivalent units) estimated by the cumulative dose divided by the treatment period

long-acting β-2 agonists (LABA), and inhaled anticholinergic among these groups. The majority of ICS during the 2-year period were budesonide (46%), fluticasone (38%), or beclomethasone (16%), and the mean daily and cumulative doses were computed in budesonide equivalent units. Although patients with osteoporosis used more daily and cumulative doses of ICS than those with either normal BMD or osteopenia, no differences were observed among them (*P*, 0.063 and 0.069, respectively). As the abnormality of BMD reached severer levels across groups, COPD patients had gradually decreased values of FEV$_1$/FVC ratio and forced expiratory volume in one second of predicted value (FEV$_1$%pred). Compared with patients without osteoporosis, those with osteoporosis had significantly higher serum levels of CRP, TNF-α, and IL-6.

BMD and systemic inflammation

Because the relationship between COPD and low BMD is complicated by the overlapping risk factors, univariate logistic regression analyses were performed to examine the relationship between the potential risk factors and the likelihood of low BMD (Table 2). The presence of systemic inflammation was associated with a greater likelihood of low BMD (OR 3.01; CI 1.52–4.27). Patients with severer airflow obstruction were more likely to have lower BMD, but it did not reach statistical significance (OR 2.29; CI 0.92–4.11). A statistically insignificant trend toward lower BMD was associated with other pertinent risk factors, such as BMI, smoking, the use of inhaled LABA, and anticholinergic.

Multivariate logistic regression analyses were performed based on a model of risk factors that either reached a significance threshold of 0.20 in univariate analyses or that have been established as having a potential impact on BMD. In a model that included the levels of systemic inflammatory markers, the severity of airflow obstruction, age, sex, and the use of ICS, only the higher levels of TNF-α and IL-6 significantly increased the likelihood of low BMD (OR 3.22 and 2.58, respectively), whereas no

Table 2 Univariate analysis for low BMD in patients with clinically stable COPD

	OR	95% CI	*P* value
Age (years)	1.12	0.65–1.37	0.089
Female gender (*n*, %)	1.51	0.92–3.04	0.095
BMI (kg/m^2)	0.86	0.59–2.71	0.41
Use of ICS (*n*, %)	2.13	0.87–4.01	0.13
Mean daily dose of ICS (μg)	1.49	0.90–3.12	0.33
Cumulative dose of ICS (mg)	2.93	0.94–3.66	0.27
Use of inhaled LABA (*n*, %)	1.33	0.76–1.92	0.52
Use of inhaled anticholinergic (*n*, %)	1.01	0.71–1.12	0.73
Pack-years (years)	1.27	0.63–2.35	0.67
FEV_1%pred (%)	2.29	0.92–4.11	0.070
Systemic inflammation			
Present vs. none	3.01	1.52–4.27	*0.009*

For definition of abbreviations see Table 1

association was observed for obstruction severity or other potential risk factors. Thus, the levels of TNF-α and IL-6 seem to be strong, independent predictors of low BMD (Table 3).

Discussion

In our study, it was proved that there was a significantly high prevalence of osteoporosis in patients with clinically stable COPD, in which the presence of systemic inflammation was associated with a greater likelihood of low BMD. Most importantly, the pro-inflammatory cytokines, including TNF-α and IL-6, were independent predictors of low BMD after established osteoporosis risk factors, such as age, sex, the use of inhaled respiratory medications and airway obstruction were adjusted.

Several studies have shown the prevalence of osteoporosis in patients with COPD. However, the association might be attributed to the effect of many confounders, such as age and female sex [13], body composition [14, 15], tobacco exposure [16], the use of ICS [4, 14, 17], and disease severity [5, 15]. Particularly the relationship between the use of respiratory medications with increased risk of osteoporosis has been frequently reported [14, 17, 18]. Nevertheless, adjustment for underlying disease severity was limited in these studies. The importance of controlling for severity of underlying disease in this type of research has recently been emphasized [19]. Also, it has been reported that there was no increased risk of osteoporosis and fracture in patients using ICS [20] or inhaled β-2 agonists [18] after adjustment for the presence of obstructive airway diseases (OAD). Patients with OAD have been found to have a low BMD, independent of the use of respiratory medications [21]. In our study, the impact of inhaled β-2 agonists on the likelihood of low BMD seemed to be minimal because most of the COPD patients among BMD groups were using the drug. Although the use of ICS tended to be more frequent in COPD with osteoporosis, and the mean daily and cumulative doses were more than those with either normal BMD or osteopenia, it was not translated into significant effect to the induction of osteoporosis in our study population (all $P > 0.05$). To explore the possibility of confounding as a result of these factors suggested in the previous studies, we performed different logistic regression analyses. After adjustment for age, female sex, BMI, pack-years, the use of inhaled respiratory medications, and FEV_1%pred, the association between systemic inflammation and low BMD remained statistically significant, and TNF-α and IL-6 were independent predictors of low BMD. The robustness of this association may reflect a true relationship as a result of the fact that COPD is principally a progressive inflammatory disease [1], and the low BMD or osteoporosis is quite prevalent [3, 15] even in patients with moderate clinically stable COPD [5]. Therefore, it seems plausible that systemic inflammation is correlated with low BMD, though the mechanism is not fully understood.

Table 3 Multivariate analysis for low BMD in patients with clinically stable COPD

	OR	95% CI	*P* value
Age (years)	1.09	0.61–1.32	0.082
Female gender (*n*, %)	1.38	0.86–2.97	0.098
Use of ICS (*n*, %)	2.01	0.69–3.72	0.26
FEV_1%pred (%)	1.37	0.78–3.24	0.17
Systemic inflammation			
Present vs. none	3.10	1.48–5.06	*0.014*
CRP (mg/l)	1.55	0.92–3.03	0.062
TNF-α (pg/ml)	3.22	1.48–6.77	*0.010*
IL-6 (pg/ml)	2.58	1.32–4.56	*0.023*

For definition of abbreviations see Table 1

With increasing recognition of the inflammatory components in both COPD and osteoporosis, the inflammatory process in each disease and the potential interplay between them are considered to be very important pathogenesis of both conditions [1, 8, 22–24]. The current model for the pathogenesis of COPD involves up-regulated inflammatory condition, in which epithelial cells and macrophages, once stimulated by irritants (mainly cigarette smoke), start to release various inflammatory mediators. Many elevated levels of mediators, including CRP and pro-inflammatory cytokines, which both directly and indirectly affect pulmonary tissue and other specific organ functions, could be detected in the systemic circulation and have been implicated in the pathogenesis of the majority of COPD

systemic effects. A recent meta-analysis has shown that systemic inflammation is present during COPD exacerbations and stable phases of the disease, and increased numbers of leukocytes, levels of CRP, and pro-inflammatory cytokines are present in the peripheral blood of COPD patients [25].

Several studies have identified a very high prevalence of low BMD and osteoporosis in patients with COPD. The etiology of COPD-related osteoporosis is almost certainly multifactorial, because they often have advanced age, poor mobility, smoking, and high doses of corticosteroids that might predispose to low BMD. However, these pertinent risk factors have been adjusted in the study, and it seems that COPD itself may be a risk factor for osteoporosis, and the relationship may be related to systemic inflammation. In fact, all diseases involving bone loss have a common pattern: the osteoclast is the cell exclusively responsible for bone resorption, and osteoporosis occurs when osteoclast activity overcomes osteoblast activity [26]. The relation between osteoclast activity and systemic inflammation has been demonstrated [8, 27]. Several inflammatory mediators, including TNF-α, IL-6, and IL-1, increased circulating concentrations of which also could be found in COPD patients, are associated with increased osteoclast numbers and related to osteoclast bone resorption. Moreover, Gianni et al. have confirmed that Raloxifene was able to decrease TNF-α transcription and serum levels while increasing bone density. Again these data support a close association between the pro-inflammatory processes and osteoporosis [28]. The role of pro-inflammatory cytokines may therefore be central to the osteoporosis associated with inflammatory diseases. In the present study, we investigated the association between systemic inflammation and the severity of BMD evaluated by DXA, and the results suggested that TNF-α and IL-6 were independent predictors of low BMD.

Moreover, in recent years, it has become one of hot issues that COPD is not only a disease of the lungs but is also a systemic inflammatory disorder, and Fabbri and Rabe [29] suggested adding the term "chronic systemic inflammatory syndrome" (CSIS), which includes such entities as COPD, chronic heart failure, and metabolic syndrome (MS), to the diagnosis of COPD. It has been well documented that presence of MS is very frequent in patients with COPD, and systemic inflammation may be the common pathophysiologic features and has been implicated as a major causative factor for both the conditions [30]. MS is featured by the combination of obesity, dyslipidemia, hyperglycemia, and hypertension. Although the association between each component of MS and osteoporosis has been extensively studied, the results of these studies have been inconsistent. BMD and fracture risk in patients with MS may be determined by the balance between beneficial effects of obesity and dyslipidemia versus detrimental ones of hyperglycemia on bone [31]. A study on the combined effects of MS on BMD demonstrated that patients with MS have significantly lower BMD after adjusting for confounding variables, and BMD decreased with increasing numbers of MS components [32]. Although the mechanism underlying this relationship is not clear, it has been widely accepted that the releases of the adipokines and cytokines, including pro-inflammatory molecules, such as TNF-a and IL-6, derived by visceral adiposity in MS patients may play an important role in osteoclastic bone resorption and in the pathogenesis of osteoporosis [33]. Therefore, the possible involvement of MS associated with COPD in determining osteoporosis may be eventually attributed to the systemic inflammation of COPD, which termed as CSIS.

Our study has several limitations that deserve mention. First, the sample of this study composed of mainly moderate COPD and a larger sample with a range of COPD severities would better explore this possible relationship. Second, other risk factors for osteoporosis, including vitamin D deficiency, limited physical activity, and hypogonadism, could not be assessed in the study, and future studies using more all-round methods to exclude more pertinent risk factors would better confirm the association between systemic inflammation and low BMD. Third, although the association of low BMD with COPD independent of the use of ICS has been reported in previous investigations and found in our study, it deserves to be specially noted that the increased risk of osteoporosis associated with glucocorticoid and the most common side-effect of glucocorticoid-induced osteoporosis in patients receiving long-term ICS treatment have been confirmed in other numerous studies [34–36]. Differences in the characteristics of the studied subjects (e.g., age, sex, and the severity of underlying disease) may contribute to these conflicting results. Analytic methods also varied as some studies adjusted for the presence of OAD [20, 21], but others did not [34, 35]. Long-term prospective studies to confirm the relationship between the use of ICS and the increased risk of osteoporosis are warranted. In addition, the cross-sectional study has some methodological considerations, and the interpretation of the association should be approached with caution in a cross-sectional design.

In conclusion, the study showed the presence of systemic inflammation in clinically stable COPD was associated with a greater likelihood of low BMD. Most importantly, TNF-α and IL-6 were independent predictors of low BMD. To better clarity the association, further prospective studies are needed.

Conflict of interest The authors state that they have no conflict of interest.

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