SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 151-159

Bone mineral density in patients with interstitial lung disease

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Abstract. *Objective:* To determine the prevalence of low bone mineral density (BMD) and the risk factors for osteoporosis in patients with interstitial lung disease (ILD). *Methods:* Consecutive newly diagnosed ILD patients (n=196) were included in the study. Detailed demographic and clinical data were collected at the time of diagnosis, along with BMD measurements. Univariate and multivariate logistic regression analyses were used to determine the risk factors for osteoporosis. *Results:* Forty-four percent of the patients had osteoporosis, and 36% had osteopenia. The diagnosis of usual interstitial pneumonia (UIP) was more frequently observed in the patients with osteoporosis than in those without osteoporosis (67 vs. 47%, respectively; p=0.005). The univariate analyses identified the following five variables that were associated with an increased risk of osteoporosis at any site: older age (odds ratios [OR], 1.06; 95% confidence intervals [CI], 1.04 - 1.09; p<0.0001), UIP diagnosis (OR, 2.39; 95% CI, 1.33 - 4.30; p=0.003), higher partial pressure of carbon dioxide ($PaCO_2$) (OR, 1.08; 95% CI, 1.01 - 1.14; p=0.01), hypertension (OR, 1.92; 95% CI, 1.05 - 3.49; p=0.033) and diabetes mellitus (OR, 2.38; 95% CI, 1.25 - 4.56; p=0.008). However, older age was the only independent predictor of osteoporosis (adjusted OR, 1.05; 95% CI, 1.02 to 1.08; p=0.001). *Conclusions:* We observed a high prevalence of osteoporosis and osteopenia among newly diagnosed ILD patients. Our findings suggest that there is a substantially increased risk of osteoporosis and that early screening and aggressive treatment with various anti-bone resorptive therapies are necessary in ILD patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 151-159)*

Key words: bone mineral density, interstitial lung disease, idiopathic pulmonary fibrosis, osteoporosis, osteopenia, usual interstitial pneumonia

Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders with variable etiologies, clinical presentations, radiographic patterns, and histologic appearances; it diffusely affects the lung parenchyma. Although ILD comprises more than 100 distinct entities, idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), connective tissue disease (CTD)-associated ILD, sarcoidosis, and hypersensitivity pneumonitis (HP) account for the majority of ILD cases. Although ILD is primarily a lung disease, it is associated with several comorbidities, including coronary artery disease, sleep-disordered breathing, pulmonary hypertension, gastroesophageal reflux disease and lung cancer, leading to an increased risk of morbidity and mortality in the affected patient population (1).

Received: 8 August 2014
Accepted after revision: 17 September 2014
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The World Health Organization (WHO) defines osteoporosis as a systemic disease that is characterized by low bone mineral density or micro architectural deterioration of bone tissue, leading to increased bone fragility and risk of fracture (2). Several factors have been identified that contribute to skeletal muscle weakness and osteoporosis. For example, cigarette smoking, physical inactivity, systemic and local inflammation, oxidative stress, corticosteroid use, malnutrition, and increased age were among the common factors identified in patients with chronic obstructive lung disease (COPD), which leads to an increased risk of developing osteoporosis (3). Unsurprisingly, patients with other chronic pulmonary disorders, particularly ILD, share these risk factors with COPD, contributing to the poor skeletal heath and low bone mineral density (BMD) that is observed in this population.

The estimated prevalence of osteoporosis in patients with advanced lung disease, including candidates for lung transplantation, ranges from 13-60% (4-9). However, information regarding the frequency of osteoporosis upon a patient's initial presentation with ILD is unknown. Therefore, the aim of the present study was to determine the prevalence of low BMD among newly diagnosed ILD patients. Additionally, we sought to investigate the differences in the clinical characteristics among ILD patients with and without osteoporosis to determine the risk factors associated with an increased risk of osteoporosis.

Methods

Study population

This descriptive study of consecutive patients newly diagnosed with ILD between January 2008 and December 2013 is part of an ongoing, large, prospective study of the current diagnostic assessments and outcomes of ILDs at our center. This study was approved by the Institutional Review Board and Ethics Committee of the College of Medicine, King Saud University, Riyadh, Saudi Arabia. Written informed consent was obtained from all study participants evaluated at our ILD center. A standard form was used to collect clinical information, including general symptoms, smoking history, medication use, and physical exam findings. A multidisciplinary approach involving various specialties, including pulmonology, rheumatology, radiology and pathology, was implemented for all ILD patients before a final diagnosis was rendered. Surgical lung biopsies were obtained from 46 (23%) of the patients with ILD. In addition, biopsies were obtained from 16 patients with IPF and five with CTD-associated usual interstitial pneumonia (UIP) because their high resolution computed tomography (HRCT) images were categorized as atypical for UIP (i.e. their HRCT scans lacked honeycombing and/or displayed predominantly ground glass opacities). In addition, surgical lung biopsies were obtained from eight patients with nonspecific interstitial pneumonia (NSIP), including seven with CTD-associated NSIP and one with idiopathic NSIP; and from 10 patients with chronic hypersensitivity pneumonitis; four with sarcoidosis; and three with cryptogenic organizing pneumonia.

IPF was diagnosed using established guidelines in the diagnosis and management of IPF (10, 11). Idiopathic nonspecific interstitial pneumonia (NSIP) and cryptogenic organizing pneumonia were diagnosed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) consensus classifications of idiopathic interstitial pneumonias (IIPs) (11). Sarcoidosis was diagnosed based on the criteria published by the ATS, the ERS, and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) (12). CTD was diagnosed when patients fulfilled the established classification criteria for any of the CTDs (13-20). Of the patients with CTD-UIP, 14 were diagnosed with rheumatoid arthritis, seven with systemic lupus erythematosus, five with Sjogren's syndrome, and two each with scleroderma, mixed CTD and undifferentiated CTD. Of the patients with CTD-NSIP, eight were diagnosed with scleroderma, four each with rheumatoid arthritis and Sjogren's syndrome, three with mixed CTD, two each with polymyositis/dermatomyositis and undifferentiated CTD (n = 2), and one with systemic lupus erythematosus.

Measurements

Spirometry and plethysmography, as well as the diffusing capacity of the lung for carbon monoxide

(DLco) (PFT Masterscreen; Jaeger, Hoechberg, Germany) were measured using established standard methodologies (21-23). Arterial blood gas (ABG) values (Rapid Lab 865; Bayer, Plymouth, UK) were obtained to determine the partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and oxygen saturation (SaO_2). The six-minute walk test (6MWT) was performed in accordance with ATS guidelines (24).

BMD was assessed at the lumbar spine (L1 to L4), femoral neck (right and left), and distal radius by dual energy X-ray absorptiometry (DEXA) (Lunar iDXA, GE Healthcare, Madison, WI, USA). The results of the measurements were expressed as grams per square centimeter, as T scores (the number of standard deviations from the mean peak bone masses of normal young individuals), and as Z scores (the number of standard deviations from the mean bone mass utilizing age matched reference ranges). The BMD values were classified according to the following WHO guidelines (2): normal BMD (T score >-1); osteopenia or low bone mass (T score <-1 and >-2.5); and osteoporosis (T score <-2.5). Pulmonary function tests (PFTs), ABGs, 6MWTs, blood testing, and BMD measurements were performed within 3 days of the initial evaluation if ILD was suspected.

Statistical analysis

Descriptive statistics are presented as the mean±standard deviation, median values with ranges or numbers with percentages. The unpaired Student's *t*-test, Mann-Whitney rank-sum test, chi-square test, or Fisher's exact test were used (as appropriate) to compare variables of interest. Univariate analyses were used to identify potential risk factors for developing osteoporosis at any site. Significant variables ($p<0.05$) found via univariate analyses served as independent variables in a multivariate logistic regression model. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for all significant variables. A two-sided p value <0.05 was considered to be statistically significant. SPSS (Statistical Package for the Social Sciences) version 18 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

A total of 196 consecutive patients (mean age, 58.1±14.5 years) underwent BMD measurements during their initial evaluations for ILD. There was a slight predominance of females (123, 63%), and the male-to-female ratio was 1:1.7. Eighty-six patients (44%) were identified as having osteoporosis at any site, and 70 patients (36%) had osteopenia. Among the patients with osteoporosis, the lumbar spine was the most frequently involved site (33%), followed by the distal radius (20%) and the femoral neck (13%). In patients with osteopenia, the lumbar spine was also the most frequently involved site (41%), followed by the femoral neck (40%), and distal radius (32%) (Table 1). The number of sites involved in the patients with osteoporosis was as follows: forty seven (55%) patients had one site, eighteen (21%) had two sites, and 21 (24%) had three or more sites. In patients with osteopenia, 27 (39%) had one site, 12 (17%) had two sites, and 31 (44%) had three or more sites.

The distributions of ILD between the patients with and without osteoporosis are shown in Table 2. The diagnosis of UIP was more frequently observed in the patients with osteoporosis compared to those without osteoporosis (67 vs. 47%, respectively; p=0.005). However, there were no significant between-group differences for other types of ILD.

Table 1. BMD in the study cohort.

Variables	BMD g/cm^2	T score	Z score	Normal (%)	Osteopenia (%)	Osteoporosis (%)
Lumbar spine	0.962±0.18	-1.925±1.50	-1.314±1.34	24	43	33
Femoral neck, left	0.908±0.91	-0.951±1.38	-0.309±1.26	49	39	12
Femoral neck, right	0.897±0.17	-1.038±1.38	-0.435±1.14	47	40	13
Distal radius	0.778±0.18	-1.346±2.84	-0.510±1.27	48	32	20

Data are presented as the mean±SD or as a percentage. A patient could have more than one site involvement.
Abbreviations: BMD=Bone mineral density

Table 2. Interstitial lung disease distribution between the patients with and without osteoporosis

	Without osteoporosis (n=110)	With osteoporosis (n= 86)	p value
UIP	51 (47)	58 (67)	0.005
Idiopathic	37 (73)	40 (69)	
CTD-associated	14 (27)	18 (31)	
NSIP	20 (18)	10 (12)	0.812
Idiopathic	5 (25)	1 (10)	
CTD-associated	15 (75)	9 (90)	
Sarcoidosis	21 (19)	9 (10)	0.485
Chronic HP	12 (11)	7 (8)	0.472
Cryptogenic OP	6 (6)	2 (2)	0.534

Data are presented as numbers (with percentages).
Definitions of abbreviations: UIP=usual interstitial pneumonia; CTD=connective tissue disease; NSIP=nonspecific interstitial pneumonia; HP=hypersensitivity pneumonitis; OP=organizing pneumonia

Among the patients with CTD-associated UIP patients and osteoporosis, the underlying CTDs were rheumatoid arthritis in 11 patients, systemic lupus erythematosus in three, Sjogren's syndrome in two, and scleroderma and mixed CTD in one each. Of the patients with CTD-associated NSIP and osteoporosis, the underlying CTDs were rheumatoid arthritis in three and Sjogren's syndrome, scleroderma, and mixed CTD in two each.

Comparisons of the demographic and clinical characteristics between the two groups are shown in Table 3. Patients with osteoporosis were significantly older compared to those without osteoporosis (p<0.0001). Additionally, there were more women older than 50 years of age in the osteoporosis group compared to the group without osteoporosis (88 vs. 42%, respectively; p<0.0001). A similar finding was also noted for men older than 50 years of age, as they were more frequently observed among the patients with osteoporosis compared to those without osteoporosis (90 vs. 72%, respectively; p=0.062). However, there were no significant between-group differences regarding gender, smoking status or disease duration. Furthermore, the patients with osteoporosis were more likely to be shorter in height (p=0.001) and have a lower body weight (p=0.002) than the patients without osteoporosis. Regarding comorbidities, hypertension and diabetes mellitus were more frequently noted in the osteoporosis group than in the group without osteoporosis (p=0.032 and p=0.008, respectively). Among the patients taking corticosteroids in both groups, the average daily dose was 10 mg (range, 2.5 to 40 mg). However, the frequency of corticosteroid use was similar between the two groups (p=0.621). Twenty-four percent of the patients with osteoporosis were using bisphosphonates, calcium supplements, or vitamin D alone or in combination with other therapies, compared to 26% of patients without osteoporosis. The average level of vitamin D was not significantly different when comparing the patients with and without osteoporosis (42.4±30.5 nmol/L and 38.8±26.7 nmol/L, respectively; p=0.423).

Table 3. Comparison of demographic and clinical characteristics between the patients with and without osteoporosis

	Without osteoporosis (n=110)	With osteoporosis (n= 86)	p value
Age, years	52.8±14.7	64.7±11.0	< 0.0001
Female gender	67 (61)	56 (65)	0.545
Ever smoker	23 (21)	19 (22)	0.808
Disease duration, months	30.7±30.0	31.0±21.1	0.931
Height, cm	159.6±8.1	155.5±8.9	0.001
Weight, kg	77.1±15.5	69.9±15.6	0.002
BMI, kg/m^2	30.4±6.1	29.1±6.8	0.140
Comorbidities			
Hypertension	30 (27)	36 (42)	0.032
Diabetes mellitus	21 (19)	31 (36)	0.008
Ischemic heart disease	8 (7)	8 (9)	0.607
Corticosteroid use	46 (42)	39 (45)	0.621
25-Hydroxyvitamin D	n=100	n=69	
< 50 nmol/	74 (74)	49 (71)	0.139
50 - 75 nmol/L	17 (17)	11 (16)	0.597
>75 nmol/L	9 (9)	9 (13)	0.583

Data are presented as the mean±standard deviation or as a number (percentage)

Comparisons of the physiological parameters for the ILD patients with and without osteoporosis are shown in Table 4. No differences in any PFT indices were noted between the patients with and without osteoporosis. However, the ILD patients with osteoporosis had a significantly shorter walking distance [(294.1±119.6) vs. (350.3±99.9) meters, p=0.001] and higher $PaCO_2$ values [(42.3±7.8) vs. (39.9±3.9) mmHg, p=0.007] compared with the patients without osteoporosis.

The demographic and clinical characteristics and physiological parameters of the IPF patients (n = 77) with and without osteoporosis are shown in Tables 5 and 6. IPF patients with osteoporosis were significantly older (p = 0.022) and had a lower body mass index (BMI) (p=0.022) than IPF patients without osteoporosis. However, there were no significant between group differences in gender, disease

Table 4. Comparison of physiological parameters between patients with and without osteoporosis

	Without osteoporosis (n=110)	With osteoporosis (n= 86)	p value
Pulmonary function test			
FVC, % predicted	62.1±21.1	64.4±18.6	0.446
FEV_1, % predicted	66.1±21.2	70.6±19.2	0.130
TLC, % predicted	63.0±17.5	66.1±17.3	0.238
DLco, % predicted	43.1±20.7	41.7±19.2	0.658
Six-minute walk test			
Initial Borg	0.9±1.2	0.8±1.1	0.605
Final Borg	3.1±2.4	3.7±2.4	0.067
Initial SpO_2, %	95.9±2.6	94.8±3.1	0.013
Final SpO_2, %	87.8±10.0	84.7±8.7	0.027
Distance, meters	350.3±99.9	294.1±119.6	0.001
Arterial blood gas			
PaO_2, mmHg	71.8±13.6	68.6±16.7	0.137
$PaCO_2$, mmHg	39.9±3.9	42.3±7.8	0.007
SaO_2, %	94.6±4.6	93.8±4.4	0.203

Data are presented as the mean±standard deviation or as a number (percentage).
Definitions of abbreviations: FVC=forced vital capacity; FEV_1=forced expiratory volume in one second; TLC=total lung capacity; DLco=diffusion capacity of the lung for carbon monoxide; SpO_2=oxygen saturation by pulse oximetry; PaO_2=partial pressure of oxygen; $PaCO_2$=partial pressure of carbon dioxide; SaO_2=oxygen saturation

Table 5. Demographic and clinical characteristics of IPF patients with and without osteoporosis

	Without osteoporosis (n=37)	With osteoporosis (n=40)	p value
Age, years	62.4±14.6	69.3±11.3	0.022
Female gender	11 (30)	19 (48)	0.110
Ever smoker	13 (35)	12 (30)	0.631
Disease duration, months	26.1±16.9	27.8±20.9	0.699
Height, cm	161.2±9.5	156.1±9.8	0.023
Weight, kg	78.2±15.2	66.3±13.5	<0.0001
BMI, kg/m^2	30.5±6.1	27.3±5.8	0.022
Comorbidities			
Hypertension	10 (27)	13 (32)	0.602
Diabetes mellitus	8 (22)	14 (35)	0.194
Ischemic heart disease	5 (14)	4 (10)	0.730
Corticosteroid use	13 (35)	10 (25)	0.286
25-Hydroxyvitamin D	n=35	n=33	
< 50 nmol/	24 (69)	23 (70)	0.508
50 – 75 nmol/L	10 (29)	4 (12)	0.053
>75 nmol/L	1 (3)	6 (18)	0.110

Data are presented as the mean±standard deviation or as a number (percentage).
Definitions of abbreviations: IPF=idiopathic pulmonary fibrosis

duration, smoking status, comorbidities, corticosteroid use, vitamin D level, PFTs, or 6MWT or ABG values.

The results of our univariate analyses of risk factors for osteoporosis among ILD patients are shown in Table 7. The following five variables were associated with an increased risk of osteoporosis at any site: increased age, diagnosis of UIP, higher $PaCO_2$, presence of hypertension and presence of diabetes mellitus. In assessing whether specific types of UIP were associated with increased risk of osteoporosis, we found that neither idiopathic [unadjusted OR, 1.71; 95% CI, 0.96 - 3.06; p=0.068] nor CTD-associated [unadjusted OR, 1.81; 95% CI, 0.84 - 3.89; p=0.126] UIP was associated with increased risk of osteoporosis. Conversely, the following variables were associated with a lower risk of developing osteoporosis: increased height, higher body weight, higher initial oxygen saturation, less oxygen desaturation at the end of the walking test and increasing walking distance. Multivariate logistic regression demonstrated that increased age (adjusted OR, 1.05; 95% CI, 1.02 – 1.08; p=0.001) was an independent risk factor for osteoporosis.

Table 6. Physiological parameters of IPF patients with and without osteoporosis

	Without osteoporosis (n=37)	With osteoporosis (n=40)	p value
Pulmonary function test			
FVC, % predicted	60.9±21.4	65.0±20.7	0.396
FEV_1, % predicted	68.7±22.6	75.1±21.5	0.214
TLC, % predicted	57.5±16.2	61.6±13.7	0.243
DLco, % predicted	40.4±21.1	40.3±20.5	0.980
Six-minute walk test			
Initial Borg	1.0±1.3	0.9±1.2	0.679
Final Borg	3.6±2.9	3.5±2.4	0.959
Initial SpO_2, %	95.6±2.2	94.6±2.8	0.094
Final SpO_2, %	86.7±9.2	85.3±6.2	0.443
Distance, meters	318.3±112.9	280.2±129.6	0.187
Arterial blood gas			
PaO_2, mmHg	70.8±11.3	69.6±11.2	0.647
$PaCO_2$, mmHg	41.1±3.4	42.3±6.1	0.278
SaO_2, %	94.3±5.1	94.1±3.5	0.880

Data are presented as the mean±standard deviation or as a number (percentage).
Definitions of abbreviations: IPF=idiopathic pulmonary fibrosis; FVC=forced vital capacity; FEV_1=forced expiratory volume in one second; TLC=total lung capacity; DLco=diffusion capacity of the lung for carbon monoxide; SpO_2=oxygen saturation by pulse oximetry; PaO_2=partial pressure of oxygen; $PaCO_2$=partial pressure of carbon dioxide; SaO_2=oxygen saturation.

Discussion

The present study demonstrates that 80% of newly diagnosed ILD patients had low BMD mea-

Table 7. Risk factors for osteoporosis, according to univariate analysis

Type of interstitial lung disease	Unadjusted OR	95% CI	p value
UIP	2.39	1.33 - 4.30	0.003
NSIP	0.59	0.26 - 1.34	0.209
Sarcoidosis	0.49	0.21 - 1.14	0.101
Chronic HP	0.72	0.27 - 1.92	0.517
Cryptogenic OP	0.41	0.08 - 2.09	0.286
Age	1.06	1.04 - 1.09	<0.0001
Female gender	1.19	0.66 - 2.15	0.546
Ever smoker	1.08	0.54 - 2.16	0.808
Disease duration	1.00	0.98 - 1.01	0.931
Height, cm	0.94	0.91 - 0.97	0.002
Weight, kg	0.97	0.95 - 0.98	0.002
Body mass index, kg/m^2	0.96	0.92 - 1.01	0.141
Comorbidities			
Hypertension	1.92	1.05 - 3.49	0.033
Diabetes	2.38	1.25 - 4.56	0.008
Ischemic heart disease	1.30	0.47 - 3.63	0.607
Corticosteroid use	1.15	0.65 - 2.03	0.621
Vitamin D, nmol/L	1.00	0.99 - 1.02	0.422
Pulmonary function tests			
FVC, % predicted	1.01	0.99 - 1.02	0.444
TLC, % predicted	1.01	0.99 - 1.01	0.238
DLco, % predicted	0.99	0.98 - 1.01	0.656
Six-minute walk test			
Initial SpO_2, %	0.88	0.79 - 0.97	0.016
Final SpO_2, %	0.96	0.93 - 0.99	0.033
Distance, meters	0.99	0.99 - 1.00	0.001
Arterial blood gas			
PaO_2, mmHg	0.98	0.96 - 1.00	0.140
$PaCO_2$, mmHg	1.08	1.01 - 1.14	0.010
SaO_2, %	0.95	0.89 - 1.02	0.207

Definitions of abbreviations: OR=odds ratio; CI=confidence interval; UIP=usual interstitial pneumonia; NSIP=nonspecific interstitial pneumonia; HP=hypersensitivity pneumonitis; OP=organizing pneumonia; FVC=forced vital capacity; TLC=total lung capacity; DLco=diffusion capacity of the lung for carbon monoxide; SpO_2=oxygen saturation by pulse oximetry; PaO_2=partial pressure of oxygen; $PaCO_2$=partial pressure of carbon dioxide; SaO_2=oxygen saturation.

surements. The risk factors for osteoporosis are well known and include increased age, female gender, Asian descent, malnutrition, physical inactivity, cigarette smoking and corticosteroid use (2). Additionally, several diseases and disorders have been associated with an increased risk of osteoporosis, including endocrine and metabolic diseases, gastrointestinal disorders, malignancy and COPD (2, 3). However, information regarding the specific risk factors for osteoporosis in patients with ILD is limited. Previous studies of BMD in patients with lung disease examined specific populations with advanced stages of lung disease and included candidates for lung transplantation (4-9). Additionally, these heterogeneous populations comprised patients with and without ILD and included patients with cystic fibrosis, COPD, pulmonary hypertension and other diseases (4, 5, 7-9). In the present study, we investigated the prevalence of low BMD in a large number of patients with ILDs of varying degrees of severity and who presented for the first time to our ILD clinic.

Previous studies from this region estimated the prevalence of osteoporosis in patients older than 50 years of age as ranging being between 24% and 39% for women and 21% for men (25-27). In the present study, we found that 44% of the cohort had osteoporosis, and 36% had osteopenia, according to the WHO criteria. However, when we classified our participants by age, we found that the prevalence of osteoporosis in patients older than 50 years of age was 88% for women and 90% for men. Therefore, our results reveal a substantially increased risk of osteoporosis in ILD patients.

Univariate analysis revealed five variables that are significantly associated with an increased risk of developing osteoporosis at any site: increased age, UIP diagnosis, higher $PaCO_2$ and the presence of comorbidities, including hypertension and diabetes mellitus. The association between UIP and the risk of developing osteoporosis is interesting. Perhaps patients with UIP reflect an advanced state of lung disease. However, the similarity in lung function parameters between patients with and without osteoporosis and the lack of association between PFTs and the risk of osteoporosis suggest other likely explanations. Corticosteroids are well-known risk factors for osteoporosis, and they are frequently used in patients with UIP, whether idiopathic UIP or UIP associated with CTD. However, a substantial number of UIP patients (59%) with osteoporosis never received corticosteroid treatment prior to presenting at our ILD clinic. Moreover, the number of UIP patients with and without osteoporosis who received corticosteroids was not significantly different (41% vs. 37%, respectively; p=0.55). Additionally, we found no association between corticosteroids and osteoporosis risk among the ILD patients. Our findings were consistent with a study of patients with advanced lung disease who were referred for lung transplantation; in that study, 64% of the patients had UIP (6). Nonetheless, the findings in both the present study and the cited study do not rule out the deleterious effect of corticosteroids on bone but sug-

gest that other factors are involved and may contribute to the increased risk of osteoporosis observed in UIP patients. Transforming growth factor-beta (TGF-β), is abundant in bone and plays an important role in regulating bone resorption and formation. The overexpression of TGF-β increases the activity of osteoblasts and osteoclasts, leading to increased bone turnover and, consequently, to osteoporosis (28). Given that TGF-β is one of the key markers of pulmonary fibrosis, excessive production of TGF-β may offer an alternative explanation for the association between UIP and the increased risk for osteoporosis observed in the present study. However, the association between UIP and osteoporosis was only observed in the unadjusted analysis, and future large scale studies exploring the impact of UIP on BMDs are needed.

Diabetes and hypertension are among several common diseases that have negative effects on BMD, predisposing patients to the development of osteoporosis (2, 29-31). In the present study, we found that diabetes mellitus was associated with a 2.4-fold increased risk of developing osteoporosis, and hypertension was associated with a 1.9-fold increased risk of developing osteoporosis. Thus, our results underscore the importance of recognizing these comorbidities as risk factors for osteoporosis in ILD patients. The association between high $PaCO_2$ and an increased risk of osteoporosis noted in the present study is unclear but perhaps suggests that mild and persistent elevations in $PaCO_2$, either alone or in combination with hypoxia, may result in an imbalance between osteoblast and osteoclast activity, leading to increased bone turnover, poor skeletal heath and low BMD measurements (32, 33). However, future longitudinal studies are necessary to determine the impact of chronic increases in $PaCO_2$ on BMD.

Vitamin D plays an essential role in maintaining both skeletal and extraskeletal health. Although there is no consensus regarding the definition of optimal serum 25-hydroxy(OH) vitamin D concentrations, experts define vitamin D deficiency as a serum 25(OH)D level of <50 nmol/L (<20 ng/mL), whereas vitamin D insufficiency is defined as a serum level between 50 and 75 nmol/L (20-30 ng/mL) (34, 35). Currently, there is widespread global recognition of low vitamin D levels; however, levels <25 nmol/L are more prevalent in regions in South Asia and the Middle East (36). Therefore, it was not surprising to find that >70% of our ILD patients were vitamin D deficient. However, we found no association between vitamin D levels and the risk of osteoporosis among our cohort, despite the fact that the majority of our osteoporosis patients were vitamin D deficient. Our findings align with other studies involving patients with advanced lung disease (5, 9). The absence of an association between serum vitamin D levels and BMD measurements may be attributed to our participants having higher body mass indices. This supposition is supported by the protective effects of higher body weight against osteoporosis noted in the present study. Forli et al. (37) noted that vitamin D deficiency was common in both underweight (average BMI, 17 kg m^{-2}) and normal weight (average BMI, 22 kg m^{-2}) patients with advanced lung disease. However, in the cited study, an association between vitamin D deficiency and reduced femur neck T scores was only noted in underweight patients. Forli et al.(37) suggested that underweight patients have less fat, and because adipose tissue contains a large amount of vitamin D_3, the utilization of vitamin D in underweight patients is severely compromised, which may explain the association between low fat-free mass and low BMI, and the increased risk of developing osteoporosis in COPD patients (38, 39).

The present study had several limitations. First, our clinical setting is a tertiary care hospital, wherein selection bias toward patients with advanced lung disease is often inevitable. Second, we did not have information regarding the cumulative corticosteroids doses or durations of corticosteroid use prior to each patient's presentation at our ILD clinic. However, the number of patients using corticosteroids was not significantly different between the patients with and without osteoporosis. Moreover, because approximately 60% of the patients in both groups did not receive corticosteroid treatment, we do not believe that this confounded our findings. The third limitation results from the fact that fewer than 25% of our participants received osteoporosis prophylaxis, as the association between prophylaxis and the prevention of osteoporosis among ILD patients cannot be determined because of this low number. Finally, the number of patients with ILDs other than UIP was relatively small, which may have accounted for the absence of an association between certain types of ILD and the risk of developing osteoporosis.

In conclusion, our study demonstrates a high prevalence of osteoporosis and osteopenia in patients with various types of ILD. Moreover, among the many variables associated with osteoporosis, we found that increased age was the only independent risk factor for osteoporosis. Furthermore, the majority of our ILD patients were vitamin D deficient, and only one-fourth of the participants received osteoporosis prophylaxis. Therefore, an early screening program and aggressive treatment with various antibone resorptive therapies are necessary in this patient group.

Authors' contributions

Esam H. Alhamad contributed to the study design and data collection, performed the statistical analysis, interpreted the data and drafted the manuscript. Rufai Nadama performed the data collection and helped to draft the manuscript. All authors read and approved the final manuscript.

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