**Title: Bone mineral density in patients with idiopathic pulmonary fibrosis**

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**Abstract**

**Background**: Decreased bone mineral density (BMD) has been reported in patients with interstitial lung disease. However, BMD has not been evaluated in steroid-naïve patients with idiopathic pulmonary fibrosis (IPF). We aimed to measure vertebral BMD and investigate its relationship with clinical features in steroid-naïve patients with IPF.

**Methods**: We recruited 55 consecutive male patients with steroid-naïve IPF; 55 male smokers without chronic obstructive pulmonary disease or interstitial lung disease, matched by age, body mass index, and pack-years of smoking (control smokers); and 27 healthy young adults. Thoracic vertebral BMD was measured by computed tomography (CT). We further investigated the relationship of BMD with clinical features and quantitative CT indices of lung density in patients with IPF.

**Results:** The thoracic vertebral BMD of patients with IPF was significantly lower than that of control smokers (139.9 ± 28.5 mg/mL vs 160.9 ± 39.5 mg/mL, $p < 0.01$). Fifteen patients (27.2%) had BMD more than 2.5 SD below the mean BMD of young adults. In patients with IPF, emphysema volume (EV) and its ratio to total lung volume (EV%) had a significantly negative correlation with BMD ($r = -0.28$, $p = 0.04$ and $r = -0.39$, $p < 0.01$, respectively). In stepwise multiple regression analysis, EV% was an independent explanatory variable for thoracic vertebral BMD.

**Conclusion:** A substantial percentage of steroid-naïve IPF patients had decreased BMD, and a significant association was observed between the extent of emphysema and BMD in IPF.

**Key words:** bone mineral density, combined pulmonary fibrosis and emphysema, idiopathic pulmonary fibrosis

**Table of Abbreviations**

| | |
|---|---|
| 6MWT | 6 min-walk test |
| A-a$DO_2$ | alveolar-arterial oxygen pressure difference |
| ATS | American Thoracic Society |
| BMD | bone mineral density |
| BMI | body mass index |
| COPD | chronic obstructive pulmonary disease |
| CPFE | combined pulmonary fibrosis and emphysema |
| CPI | composite physiologic index |
| CT | computed tomography |
| DEXA | dual energy X-ray absorptiometry |
| DLCO | diffusing capacity of the lung for carbon monoxide |
| EV | emphysema volume |
| $FEV_1$ | forced expiratory volume in 1 second |
| FLV | functional lung volume |
| FVC | forced vital capacity |
| HRCT | high-resolution computed tomography |
| HU | Hounsfield units |
| ILD | interstitial lung disease |
| ILDV | interstitial lung disease volume |
| IPF | idiopathic pulmonary fibrosis |
| MMP | matrix metalloproteinase |
| PFT | pulmonary function test |
| ROI | region of interest |
| SD | standard deviation |
| $SpO_2$ | oxygen saturation |
| TLV | total lung volume |

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|---|---|---|
| 1 | YAM | young adult mean |

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing pneumonia of unknown cause [1]. Although the primary disorder is limited to the lungs, extrapulmonary comorbidities such as gastroesophageal reflux and cardiovascular disease have been reported [2]. Previously, we also reported an impairment of the endothelium-dependent vasodilator response in patients with pulmonary fibrosis, including IPF [3].

Bone loss, which leads to clinical osteoporosis or osteopenia, may also be an extrapulmonary complication of IPF. Osteoporosis and osteopenia are diagnosed based on the measurement of bone mineral density (BMD). A previous study showed that reduced BMD was common in patients with diffuse interstitial lung disease (ILD), including IPF [4]. However, participants in that study had ILD with known causes, and many of them had a history of systemic corticosteroid use. To date, no study has investigated BMD in patients with steroid-naïve IPF.

Decreased BMD in patients with lung diseases such as chronic obstructive pulmonary disease (COPD) [5-7] and cystic fibrosis [8, 9] has been more widely reported. Among patients with COPD, several risk factors for osteoporosis have been identified, including smoking, low body mass index (BMI), age, physical inactivity, corticosteroid use, and the extent of emphysema [5, 10]. Although the radiological and histopathological features of IPF are strikingly different from those of COPD, IPF has similar features that may lower BMD. Most patients with IPF are elderly and have a history of cigarette smoking [1], and their physical activity becomes increasingly limited as the disease progresses [11, 12]. Oral corticosteroids are frequently used for acute exacerbations and for immunosuppressive treatment after lung transplantation [1, 13]. Moreover, combined pulmonary fibrosis and emphysema (CPFE) has been recently proposed as a clinical phenotype characterized by the coexistence of pulmonary fibrosis and emphysema [14]. These clinical features suggest that bone loss could occur in patients with IPF. In addition, the factors related to the pathogenesis of IPF such as matrix metalloproteinase-9 (MMP-9) activation [15] may affect low BMD [16].

In the present study, we hypothesized that BMD would be decreased among patients with IPF and that disease severity and specific clinical phenotypes would be associated with low BMD.

To test this hypothesis, we assessed BMD in the thoracic vertebrae by high-resolution computed tomography (HRCT) of the chest, and investigated the relationships of clinical features, quantitative CT indices of lung density with BMD in steroid-naïve patients with IPF.

## Methods

### Study population

This was a cross-sectional cohort study analysis. Between July 2008 and October 2014 at Kyoto University Hospital, we recruited 55 men with IPF. IPF was diagnosed based on the current official joint statement on IPF from the American Thoracic Society (ATS)/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association [1]. Patients with any of the following were excluded: 1) current or previous oral corticosteroid use; 2) malignancy within the previous 5 years; 3) past bone disease, hyperthyroidism, or chronic liver disease; and 4) current osteoporosis treatment. As controls, we recruited 55 male smokers without COPD or ILD who underwent chest CT for medical checkup at Kitano Hospital. The controls were matched by age, BMI, and pack-years of smoking. To set the standard values of thoracic vertebral BMD, we also recruited 27 healthy young adults (9 females and 18 males). The study was approved by the Ethics Committee of Kyoto University (approval No. E2320) and Kitano Hospital (approval No. P14-11-011), and informed consent was obtained from all participants.

### Data collection

Pulmonary function tests (PFTs) (Chestac-65V; Chest MI Corp, Tokyo, Japan) were performed, and the diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method. Percent-predicted values were used for analyses. The composite physiologic index (CPI), which represents the extent of fibrosis, was calculated from the following formula: 91–(0.65 × percent predicted DLCO [%DLCO]–(0.53 × percent predicted forced vital capacity [%FVC]) + (0.34 × percent predicted forced expiratory volume in 1 second [%$FEV_1$]) [17]. Arterial blood gas was obtained while patients were breathing room air, at rest, in the supine position. The alveolar-arterial oxygen pressure difference (A-a$DO_2$) was calculated according to the standard

formula using a respiratory exchange ratio of 0.8. A 6-min walk test (6MWT) was performed according to the ATS guidelines [18], and oxygen saturation ($SpO_2$) was monitored throughout. Peripheral venous blood samples were collected and analyzed for 25-hydroxy (OH) vitamin D, albumin, calcium, phosphorus, alkaline phosphatase, and creatinine. Serum concentrations of MMPs (MMP-1, 2, 3, 7, 8, 9, 10, 12, and 13) were determined using the Bio-Plex Pro Human MMP panel (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions.

**Visual assessment of emphysema**

Emphysema was defined as a hyperlucent lung area that lacked a distinct wall. Emphysema score was visually determined by estimating the percent of emphysema in the upper, middle, and lower areas of each lung, and averaging them to produce a total emphysema score [19]. In patients with IPF, we diagnosed CPFE when the total emphysema score was at least 10%. The emphysema scores were independently calculated by two observers (K.I. and T.K.) who were blinded to clinical information. Interobserver disagreements in the diagnosis of CPFE were resolved by consensus.

**Quantitative CT analysis of lung density**

We performed three-dimensional (3D) CT volumetry to analyze CT images quantitatively [20, 21]. Briefly, all participants underwent thin-section CT examination using a multidetector Aquilion 64 CT scanner (Toshiba Medical Systems, Tochigi, Japan) in the supine position at full inspiration. Whole lung scans were performed at a peak tube voltage of 120 kVp. Contiguous 0.5-mm thick images, reconstructed with a high-spatial-frequency reconstruction algorithm (FC 56), were used for volumetric analysis. Then, the CT images were transported to a commercial workstation (AZE Virtual Place Lexus; AZE Co., Ltd., Tokyo, Japan) for 3D-CT volumetry. The workstation software automatically detected the entire perimeter of the lungs, and correctness of the lung segmentation was confirmed using volume-rendered images. After a CT attenuation histogram of the lung segmentation was generated, total lung volume (TLV) was calculated as the area under the curve, and emphysema volume (EV), functional lung volume (FLV), and ILD volume (ILDV) were acquired as quantitative indices. According to a previous report [21], EV, FLV, and ILDV were defined as the integration of the area with attenuations less than −950 Hounsfield units (HU),

between −700 and −950 HU, and between −500 and −700 HU, respectively. The ratios of FLV, ILDV, and EV to total lung volume (TLV) were designated FLV%, ILDV%, and EV%, respectively.

**Measurement of BMD in vertebral bone using chest CT**

Using a previously reported method [22, 23], BMD was measured in thoracic vertebral bones (T4, T7, and T10) derived from CT density scan. Briefly, a mid-vertebral slice was selected using the reconstructed images from 0.5-mm slices. Then, the elliptical region of interest (ROI) was encompassed manually as the possible largest area at the anterior portion of each vertebral body on the selected slice. Finally, the mean CT scan density of the ROI was measured. BMD was calculated as the mean CT scan density using the following formula: BMD (mg/mL) = 0.767 × CT scan density (in HU) + 3.37. This formula was derived from the previous report in our institute using a calibration phantom that contained eight tubes of known concentrations of hydroxyapatite [22]. All images were measured by two observers (K.I. and S.H.) to minimize interobserver variability of the measurements, and their measurements were averaged to obtain the final reported values. We defined thoracic vertebral BMD as the average of T4, T7, and T10. To validate the thoracic vertebral BMD measurement, we also performed dual energy X-ray absorptiometry (DEXA) and chest CT at the same time in 20 male patients with IPF, and compared the BMD measured by DEXA with the BMD measured by chest CT. The thoracic BMD via chest CT was strongly correlated with the lumbar BMD ($r = 0.735$, $p < 0.001$) and the femoral neck BMD ($r = 0.757$, $p < 0.001$) measured by DEXA (Fig. 1).

**Statistical analysis**

All statistical analyses were performed using JMP version 10 (SAS Institute, Cary, NC, USA). Results for continuous variables are presented as mean ± standard deviation (SD). Shapiro–Wilk statistical test was used to determine whether the variable had a standard normal distribution. Unpaired *t*-tests were used for comparisons of continuous variables between the two groups, and chi-square tests were used for comparisons of results for categorical variables. Between-variable associations were analyzed with Pearson's correlation coefficient. Based on the results of univariate analysis, we performed a stepwise multiple regression analysis to identify independent contributing

factors to the thoracic vertebral BMD, entering the independent variables that yielded a p-value of <0.10 in univariate analysis. A p-value of < 0.05 was considered statistically significant.

## Results

### Characteristics of patients and control smokers

The participant characteristics are shown in Table 1. There were no significant differences between control smokers and patients with IPF in age, BMI, or pack-years of smoking. FVC was significantly lower in patients with IPF than in control smokers, while $FEV_1$/FVC was significantly higher in patients with IPF than in control smokers. Among the 55 patients with IPF, 16 (29.1%) were diagnosed with CPFE. At the time of enrollment, no patients were being treated with long-term oxygen therapy, and one patient had been treated with inhaled corticosteroids.

### Frequency of decreased BMD in patients with IPF

The thoracic vertebral BMD of patients with IPF was significantly lower than that of control smokers (139.9 ± 28.5 mg/mL vs 160.9 ± 39.5 mg/mL, $p < 0.01$, Fig.2). We also measured the thoracic vertebral BMD in 27 healthy young adults (9 females and 18 males with comparable BMD) to define standard values. The thoracic vertebral BMD in young adults was 177.3 ± 22.0 mg/mL and had a standard normal distribution; 1 SD and 2.5 SD below the mean BMD of young adults were 155.3 mg/mL and 122.4 mg/mL, respectively. Among patients with IPF, 24 (43.6%) had a BMD 1–2.5 SD below the mean BMD of young adults and 15 (27.2%) had a BMD more than 2.5 SD below the mean BMD of young adults (Fig.2).

### Comparison of lung CT indices between IPF patients and controls

Quantitative CT indices of lung density and visual emphysema score between patients with CPFE, non-CPFE IPF, and control smokers are shown in Table 2. Patients with IPF (both CPFE and non-CPFE IPF) showed lower TLV, lower FLV, and higher ILDV than control smokers. Visually assessed emphysema score in patients with CPFE was significantly higher than that in non-CPFE IPF and control smokers, while semi-automatically calculated EV% was not significantly different between patients with CPFE and control smokers.

**Relationships between quantitative CT indices and both PFT results and the visual emphysema score in patients with IPF**

We also investigated the relationships between the quantitative CT indices of lung density and both the PFT data and the visual emphysema score in patients with IPF. FLV had a good correlation with FVC ($r = 0.64$, $p < 0.01$) and $FEV_1$ ($r = 0.55$, $p < 0.01$). In addition, ILDV% had a good correlation with %FVC ($r = -0.50$, $p < 0.01$), %DLCO ($r = -0.44$, $p < 0.001$), and CPI ($r = -0.52$, $p < 0.01$), while EV had a significant negative correlation with $FEV_1$/FVC ($r = -0.38$, $p < 0.01$). Moreover, EV% had a positive correlation with the visual emphysema score ($r = 0.50$, $p < 0.01$).

**Thoracic vertebral BMD and its relationships with other variables**

Next, we evaluated the relationships of the thoracic vertebral BMD with clinical variables in the patient group (Table 3). The thoracic vertebral BMD was marginally correlated with age and BMI, but not with pack-years of smoking. In PFTs, the thoracic vertebral BMD was associated with neither %$FEV_1$, $FEV_1$/FVC, nor disease severity, including measures of %FVC, %DLCO, and CPI. Concerning the laboratory data, thoracic vertebral BMD in patients with IPF was not correlated with serum calcium, phosphorus, or 25-OH vitamin D levels. There was no significant correlation between BMD and serum MMP9 levels and other serum MMP concentrations in patients with IPF (data not shown). We also investigated the associations between thoracic vertebral BMD and quantitative CT indices of lung density. The thoracic vertebral BMD had a significantly negative correlation with EV ($r = -0.28$, $p = 0.04$, Fig. 3a) and EV% ($r = -0.39$, $p < 0.01$, Fig. 3b). ILDV and ILDV% were marginally associated with thoracic vertebral BMD, due to the result that ILDV% was negatively correlated with EV% ($r = -0.78$, $p < 0.01$). We obtained almost the same results even when we excluded one patient who was treated with inhaled corticosteroids. We also confirmed that the thoracic vertebral BMD was significantly correlated with visually assessed emphysema score ($r = -0.28$, $p = 0.04$) and the diagnosis of CPFE ($r = -0.41$, $p < 0.01$)

Finally, we performed stepwise multiple regression analysis to identify predictors of thoracic vertebral BMD, entering the variables yielding a p-value <0.10 by univariate analysis

(i.e., age, BMI, EV%, and ILDV%). This analysis identified that EV% was an independent explanatory variable for thoracic vertebral BMD (Table 3).

**Discussion**

In the present study, we showed that thoracic vertebral BMD was significantly lower in patients with IPF than in control smokers without COPD or ILD. Among 55 patients with IPF, 15 (27.2%) had BMD more than 2.5 SD below the mean BMD of young adults. Further, the extent of emphysema by quantitative CT analysis and visual assessment had a significantly negative correlation with BMD. To the best of our knowledge, this is the first study to identify a relationship between emphysema and BMD in patients with IPF.

Our study demonstrated that BMD in steroid-naïve patients with early IPF was decreased compared with that in control smokers. Previous studies have investigated BMD in patients with various diffuse lung diseases, with many recruiting patients awaiting lung transplantation. For example, Tschopp et al. reported that osteoporosis was very common in patients with end-stage pulmonary disease, independent of the underlying disease, and that BMI and corticosteroid use were independent risk factors for reduced BMD [24]. Caplan-Shaw et al. measured BMD in patients with ILD (including those with IPF) and found that low BMD was common, and that lower BMI and Hispanic ethnicity were independently associated with osteoporosis [4]. However, these studies included several different lung diseases and were therefore unable to reveal the specific relationship between bone loss and IPF. Moreover, lung transplantation candidates represent a cohort with very severe lung disease. Therefore, their physical activity is often limited and some of them will have already received oral corticosteroid therapy for acute exacerbations. We excluded patients with ILD of known etiology, women, and those with any history of oral corticosteroid use to remove the impact of sex and corticosteroid hormones. Thus, our results suggest that the pathophysiology of IPF directly affects BMD, even in patients with mild disease.

We have also demonstrated a relationship between emphysematous lesions and BMD in patients with IPF. The results of the present study suggest that low BMD is affected by the extent of

emphysema, but not the extent of fibrosis in patients with IPF. Notably, BMD was not associated with obstructive impairment ($FEV_1$) on the PFTs, but was associated with the extent of emphysema, as shown by CT. This may have been because $FEV_1$ tends to be preserved in patients with CPFE as compared to patients with COPD [25]. Preserved $FEV_1$ can be explained by the increased traction caused by pulmonary fibrosis, which prevents the expiratory airway collapse seen in emphysema [26]. Among the 16 patients with CPFE in this study, only two met the criteria of COPD. Concerning the physiological characteristic of CPFE, the existence of emphysema on HRCT, and not simply COPD, indicates greater risk of reduced BMD.

We performed quantitative CT analysis of lung density and evaluated the extent of emphysema using quantitative CT indices (EV or EV%). Consistent with previous research [21], ILDV% was significantly associated with PFT indices reflecting the disease severity of ILD, whereas EV was associated with an index of airflow limitation. In addition, EV% had a good correlation with the visual emphysema score. Thus, we confirmed that the quantitative CT indices were reliable. In the present study, control smokers and patients with non-CPFE IPF had higher EV% values than visually assessed emphysema scores. We measured EV% using a high-spatial-frequency reconstruction algorithm [21], which theoretically increases the emphysematous area compared with a standard algorithm, and with the extent identified being dependent on the CT scanner used. We consider that this explains why the visual emphysema score and semi-automatically calculated EV% were different. Moreover, there was no significant difference in EV% between patients with CPFE and control smokers. One possible reason for this is that interstitial lung abnormalities, including pulmonary fibrosis, are associated with reductions in the extent of emphysema [27]. This may also explain why EV% in non-CPFE IPF was lower than that of controls in our study. However, the visual emphysema score in patients with CPFE was also significantly higher than that in control smokers. This may be because the visual score was dependent on the levels assessed and was strongly affected by score in the upper lung area, which is smaller and contains more emphysema and less interstitial abnormalities compared with the middle and lower lung areas. Accordingly, semi-automatically calculated EV% may represent the extent of

emphysema in the total lung field more accurately than the visual emphysema score among patients with IPF. Nevertheless, it might be problematic to compare EV% between controls and IPF.

To explore a possible linking mechanism between emphysema and bone mineral metabolism in IPF, we measured and compared serum MMP concentrations among patients. MMPs are a purported cause of emphysema because of their capacity to degrade collagen and elastin, but are equally essential for skeletal development [28]. MMP-9 can degrade α1-antitrypsin, and potentiate CXCL8, which amplifies the alveolar inflammation and destruction [15, 29]. In addition, MMP-9 has a role in the maintenance of bone structure and is essential for the migration of osteoclasts and their precursors [16]. Indeed, recent studies have demonstrated that serum MMP-9 levels were associated with osteoporosis in patients with COPD [30, 31]. However, we found no significant relationship between MMP-9 or the other MMPs and BMD in patients with IPF, regardless of the presence of emphysema.

Another possible link between emphysema and bone metabolism in IPF is cellular senescence. Indeed, it has recently been reported that both IPF and emphysema are related to cellular senescence [32]. For example, telomeres are DNA-protein structures, the length of which limits the replicative capacity of tissues. Previous studies suggest that both IPF and emphysema are associated with shortened telomeres and that some telomerase mutation carriers can have both IPF and emphysema concurrently [33]. Of note, Valdes et al. showed that shorter telomere length in leukocytes was associated with decreased BMD [34], while another animal study revealed that defects in telomere maintenance molecules caused low bone mass [35]. Accelerated senescence affected by telomere length could explain the relationship between bone loss and CPFE.

As mentioned in previous studies [22, 23], the thoracic vertebral BMD was determined by chest HRCT. Although the number of patients was small, we confirmed that the thoracic BMD measured by CT had a strong correlation with the BMD measured by DEXA. Although DEXA is the gold standard for measuring BMD and diagnosing osteopenia or osteoporosis, it does have several limitations [36]. DEXA is sensitive to degenerative changes, and is affected by structures overlying the spine and by morphologic changes (i.e., aortic calcification and laminectomy). Further, when

using DEXA, superimposed soft tissue can lead to increased BMD levels in patients with a BMI over 25 kg/m$^2$. CT may be better suited because it provides trabecular bone measurement only, and previous studies have shown that quantitative CT has a better capacity to identify individuals with fragility fractures [37, 38].

There were some limitations in the present study. First, this was a cross-sectional study with a limited number of patients, so a longitudinal study with a larger cohort will be needed to confirm our results. Second, we evaluated BMD in men with IPF only, specifically excluding women to limit the impact of sex hormones on BMD. Although we think that women with IPF would have a lower BMD than men with IPF, further studies are needed to clarify the issue. Finally, we did not assess physical activity, which can significantly affect BMD. However, the participants in this study did not have end-stage IPF, and were not receiving long-term oxygen therapy at the time of enrollment, suggesting that physical activity was unlikely to be severely limited.

In conclusion, our study has demonstrated that the extent of emphysema significantly correlated with low BMD in patients with steroid-naïve IPF. Consequently, we should note that a decrease of BMD was not rare even in steroid-naïve IPF, particularly patients with CPFE. Further studies are needed to clarify the precise mechanism of BMD decrease in patients with IPF, and to determine whether treatment of decreased BMD has any impact on BMD itself or on other clinically important outcomes.

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**Figure legends**

Figure 1. The relationships between the thoracic vertebral bone mineral densities (BMDs) measured by computed tomography (CT) of the chest and the BMD of the lumbar vertebrae (a) and femoral neck (b) measured by dual energy X-ray absorptiometry (DEXA). BMD measured by CT showed a good correlation with BMD measured by DEXA. The r-value indicates the correlation coefficient. The regression line is shown.

Figure 2. Comparison of thoracic vertebral bone mineral density (BMD) between healthy young adults (177.3 ± 22.0 mg/mL), control smokers (160.9 ± 39.5 mg/mL), and patients with idiopathic pulmonary fibrosis (IPF) (139.9 ± 28.5 mg/mL). The horizontal bar indicates the mean values. The dotted line shows the mean thoracic vertebral BMD in healthy young adults (young adult mean; YAM). The broken lines show 1 SD and 2.5 SD below the mean BMD of young adults.

Figure 3. Scatter diagrams showing the correlation between thoracic vertebral BMD with emphysema volume (a) and emphysema volume% (the ratio of emphysema volume to total lung volume) in patients with idiopathic pulmonary fibrosis. The r-value indicates the correlation coefficient. The regression line is shown.

Table1. Characteristics of healthy young adults, control smokers, and patients with idiopathic pulmonary fibrosis

| | Young adults (n = 27) | Control smokers (n = 55) | IPF (n = 55) | p-value* |
|---|---|---|---|---|
| Age, years | 38.8 ± 3.6 | 65.1 ± 7.0 | 68.0 ± 9.4 | NS |
| BMI, $kg/m^2$ | 22.6 ± 3.6 | 24.7 ± 2.5 | 24.3 ± 3.1 | NS |
| Smoker/nonsmoker, n | 13/14 | 55/0 | 54/1 | NS |
| Smoking, pack-years | 17.6 ± 12.8 | 42.2 ± 32.2 | 49.0 ± 30.5 | NS |
| %FVC, % | 98.6 ± 11.5 | 100.3 ± 12.0 | 88.1 ± 21.3 | < 0.01 |
| $\%FEV_1$, % | 98.1 ± 10.9 | 97.6 ± 10.7 | 93.3 ± 23.1 | NS |
| $FEV_1/FVC$, % | 82.8 ± 5.1 | 77.4 ± 3.9 | 82.4 ± 7.0 | < 0.01 |
| %DLCO, % | NA | NA | 45.9 ± 14.9 | NA |
| CPI | NA | NA | 46.1 ± 12.8 | NA |
| $A\text{-}aDO_2$, mmHg | NA | NA | 17.1 ± 11.0 | NA |
| 6MWD, m | NA | NA | 458 ± 99 | NA |
| Minimum $SpO_2$ at 6MWT, % | NA | NA | 87.6 ± 7.8 | NA |
| Serum 25-OH vitamin D, ng/mL | NA | NA | 23.5 ± 5.4 | NA |
| Serum albumin, g/dL | NA | NA | 4.1 ± 0.3 | NA |
| Serum calcium, mg/dL | NA | NA | 9.1 ± 0.4 | NA |
| Serum phosphorus, mg/dL | NA | NA | 3.3 ± 0.5 | NA |
| Serum alkaline phosphatase, U/L | NA | NA | 231 ± 68 | NA |
| Serum creatinine, mg/dL | NA | NA | 0.92 ± 0.22 | NA |
| Serum MMP-9, ng/mL | NA | NA | 65.3 ± 47.7 | NA |
| CPFE, n | NA | NA | 16 | NA |

Data are presented as number or mean ± SD. IPF, idiopathic pulmonary fibrosis; BMI, body mass index; %FVC, percent predicted forced vital capacity; $\%FEV_1$, percent predicted forced expiratory volume in 1 second; %DLCO, percent predicted diffusing capacity of the lung for carbon monoxide; CPI, composite physiologic index; $A\text{-}aDO_2$, alveolar-arterial oxygen pressure difference; 6MWD, 6 min-walk distance; $SpO_2$, oxygen saturation; 6MWT, 6 min-walk test; MMP, matrix metalloproteinase; CPFE, combined pulmonary fibrosis and emphysema; NA; not available; NS, not significant.

* p-values are for comparisons between patients and control smokers.

Table 2. Mean values of quantitative computed tomography (CT) indices of lung density and visually assessed emphysema score between patients with combined pulmonary fibrosis and emphysema (CPFE), non-CPFE idiopathic pulmonary fibrosis, and control smokers

| | CPFE (n = 16) | Non-CPFE IPF (n = 39) | Control smokers (n = 55) |
|---|---|---|---|
| Quantitative CT indices | | | |
| TLV, $cm^3$ | 4099 ± 710* | 3698 ± 883* | 5029 ± 818 |
| EV, $cm^3$ | 705 ± 203† | 504 ± 237* | 802 ± 312 |
| EV%, % | 17.1 ± 3.6† | 13.2 ± 3.9* | 15.6 ± 4.3 |
| FLV, $cm^3$ | 2615 ± 609* | 2390 ± 786* | 3710 ± 584 |
| FLV%, % | 63.3 ± 5.0* | 65.2 ± 4.9* | 73.9 ± 3.1 |
| ILDV, $cm^3$ | 779 ± 142* | 753 ± 155* | 517 ± 92 |
| ILDV%, % | 19.7 ± 5.8* | 21.6 ± 6.9* | 10.5 ± 2.3 |
| Visual assessment of emphysema | | | |
| Emphysema score | 26.5 ± 15.7*† | 1.3 ± 2.4 | 1.8 ± 4.0 |

Data are presented as mean ± SD. CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; CT, computed tomography; TLV, total lung volume; EV, emphysema volume; FLV, functional lung volume; ILDV, interstitial lung disease volume.

*$p < 0.05$ vs control smokers, †$p < 0.05$ vs patients with non-CPFE IPF.

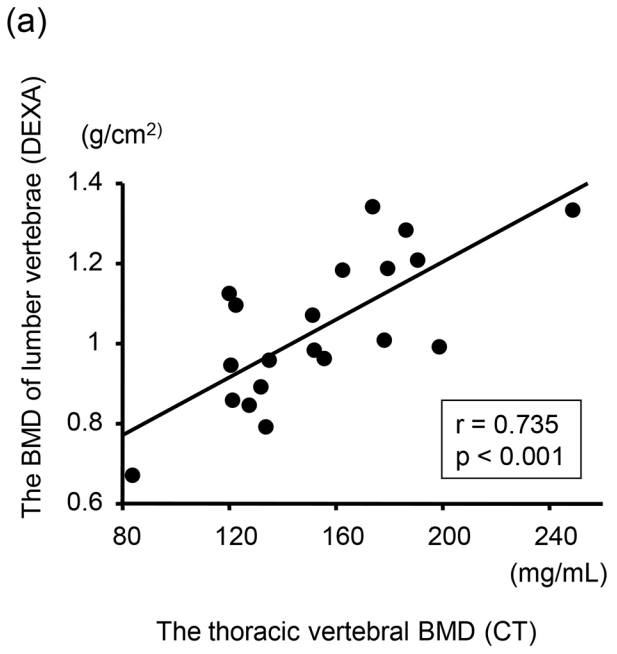
Table 3. Relationships between the bone mineral density of thoracic vertebrae and clinical variables in patients with idiopathic pulmonary fibrosis (n = 55)

| Univariate Associations | r | p-value |
|---|---|---|
| **Patient characteristics** | | |
| Age,y | −0.27 | 0.05 |
| BMI, $kg/m^2$ | 0.24 | 0.07 |
| Pack-years | −0.06 | 0.65 |
| **Pulmonary function** | | |
| %FVC, % | −0.11 | 0.40 |
| $\%FEV_1$, % | −0.18 | 0.18 |
| $FEV_1/FVC$, % | −0.07 | 0.60 |
| %DLCO, % | 0.10 | 0.46 |
| CPI | −0.09 | 0.50 |
| $A\text{-}aDO_2$, mmHg | −0.04 | 0.79 |
| 6MWD, m | 0.14 | 0.33 |
| Minimum $SpO_2$ at 6MWT, % | −0.21 | 0.16 |
| **Laboratory data** | | |
| Serum 25-OH vitamin D, ng/mL | −0.17 | 0.25 |
| Serum albumin, g/dL | −0.08 | 0.54 |
| Serum calcium, mg/dL | −0.001 | 0.99 |
| Serum phosphorus, mg/dL | −0.02 | 0.89 |
| Serum alkaline phosphatase, U/L | 0.03 | 0.84 |
| Serum creatinine, mg/dL | −0.25 | 0.07 |
| Serum MMP-9, ng/mL | −0.13 | 0.37 |
| **Quantitative indices of CT** | | |
| TLV, $cm^3$ | −0.07 | 0.59 |
| EV, $cm^3$ | −0.28 | 0.04 |
| EV%, % | −0.39 | < 0.01 |
| FLV, $cm^3$ | −0.12 | 0.37 |
| FLV%, % | 0.01 | 0.95 |
| ILDV, $cm^3$ | 0.25 | 0.07 |
| ILDV%, % | 0.24 | 0.08 |
| **Visual assessment of emphysema** | | |
| Emphysema score | −0.28 | 0.04 |

| | | | |
|---|---|---|---|
| The diagnosis of CPFE | −0.41 | < 0.01 | |
| **Stepwise multivariate regression** | **β** | **p-value** | **$R^2$** |
| EV%, % | −0.35 | < 0.01 | 0.14 |

r, correlation coefficient; BMI, body mass index; %FVC, percent predicted forced vital capacity; %$FEV_1$, percent predicted forced expiratory volume in 1 second; %DLCO, percent predicted diffusing capacity of the lung for carbon monoxide; CPI, composite physiologic index; A-a$DO_2$, alveolar-arterial oxygen pressure difference; 6MWD, 6 minute-walk distance; $SpO_2$, oxygen saturation; 6MWT, 6 minute-walk test; MMP, matrix metalloproteinase; TLV, total lung volume; EV, emphysema volume; FLV, functional lung volume; ILDV, interstitial lung disease volume; CPFE, combined pulmonary fibrosis and emphysema; β, standard regression coefficient; $R^2$, coefficient of determination.

Figure 1


(a)
The BMD of lumber vertebrae (DEXA)
(g/cm2)
1.4
1.2
1
0.8
0.6
80
120
160
200
240
(mg/mL)
r = 0.735
p < 0.001
The thoracic vertebral BMD (CT)

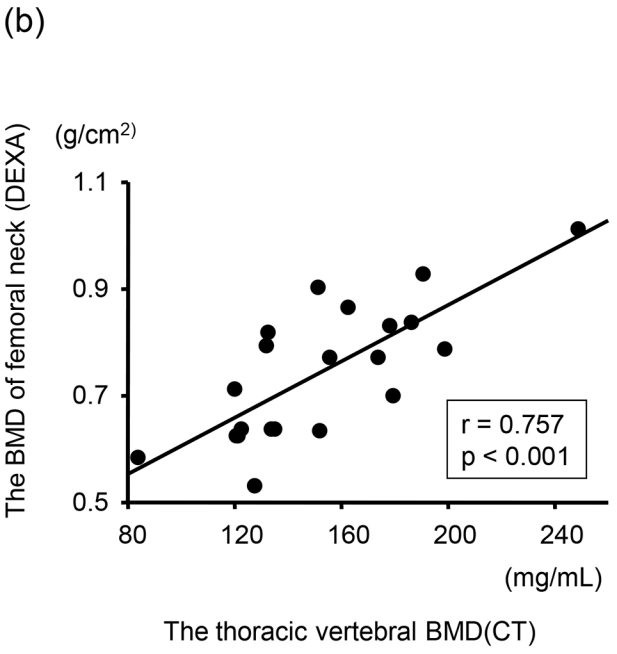

(b)
The BMD of femoral neck (DEXA)
(g/cm2)
1.1
0.9
0.7
0.5
80
120
160
200
240
(mg/mL)
r = 0.757
p < 0.001
The thoracic vertebral BMD(CT)

Figure 2

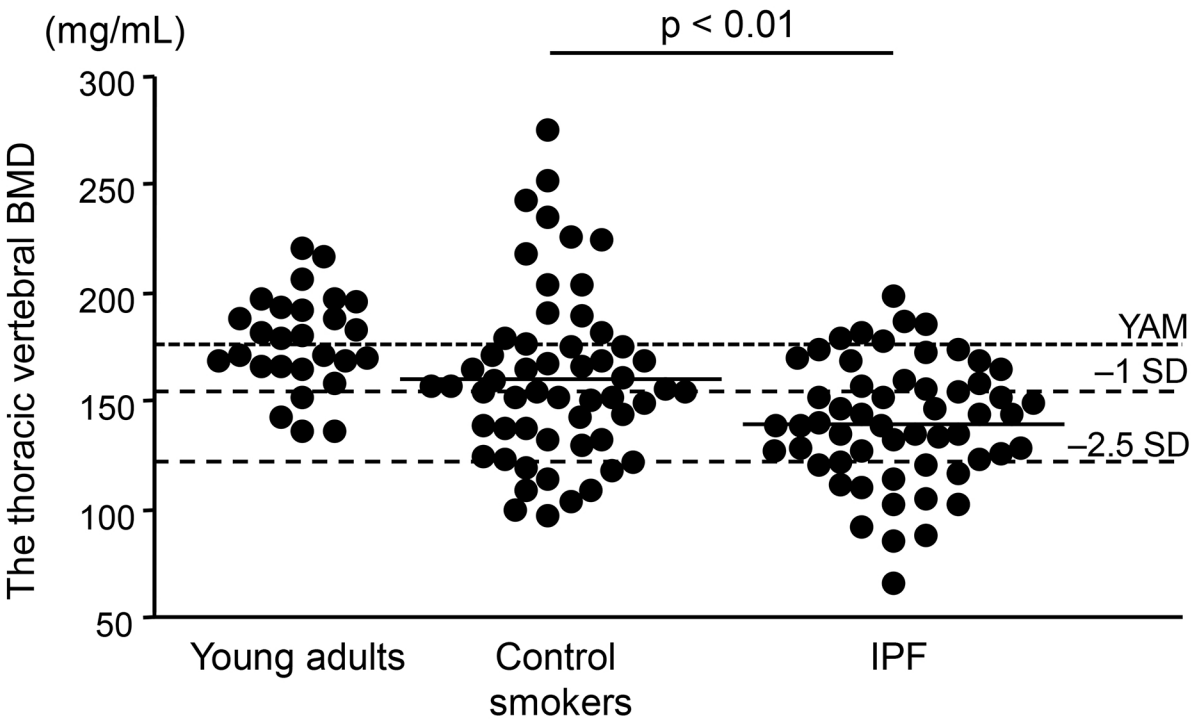
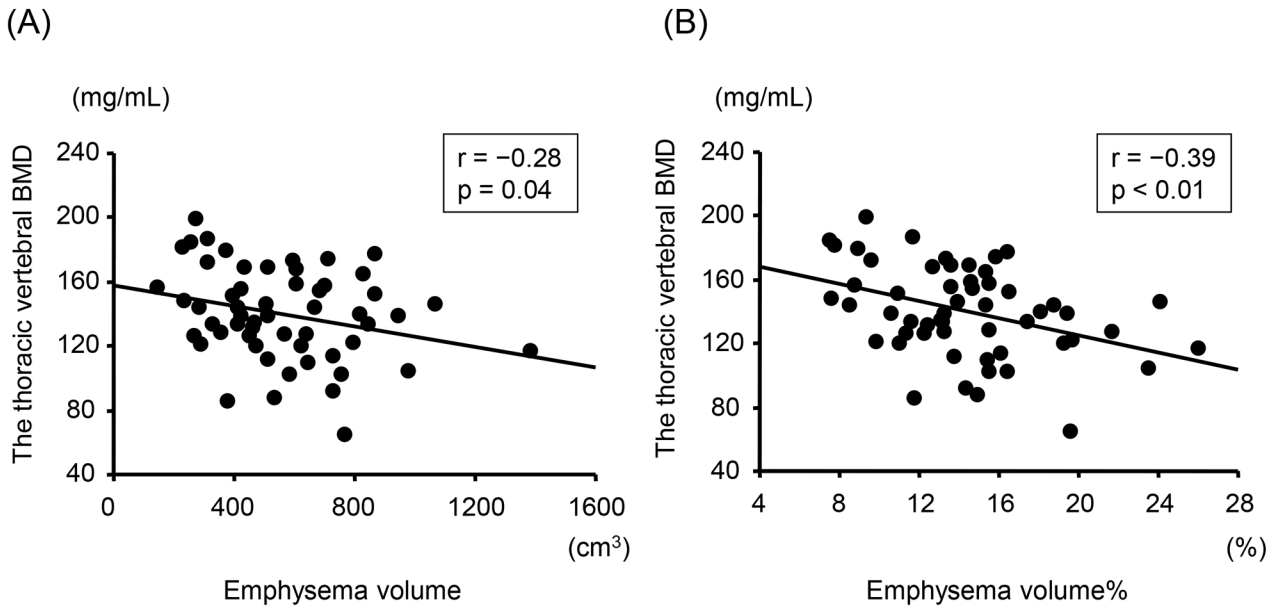

(mg/mL)
p < 0.01
300
250
200
150
100
50
The thoracic vertebral BMD
YAM
–1 SD
–2.5 SD
Young adults
Control smokers
IPF

Figure 3


(A)
(mg/mL)
The thoracic vertebral BMD
240
200
160
120
80
40
r = −0.28
p = 0.04
0
400
800
1200
1600
(cm3)
Emphysema volume
(B)
(mg/mL)
The thoracic vertebral BMD
240
200
160
120
80
40
r = −0.39
p < 0.01
4
8
12
16
20
24
28
(%)
Emphysema volume%