

Association between pulmonary fibrosis and osteoporosis in the elderly people

A case–control study

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Abstract

In this case–control study, we evaluated the association between osteoporosis and pulmonary fibrosis in the elderly. Participants were divided into a test group and a control group depending on bone mineral density and grid pattern changes of pulmonary fibrosis. We measured general conditions, related risk factors, serum biochemical index, grid pattern changes of double lungs, pulmonary function, arterial oxygen pressure (PO₂), and bone mineral density of participants, and investigated the data through statistical analysis on SPSS 17.0 (SPSS Inc, Chicago, Illinois, USA). Significant differences were observed between groups in all collected indices except PO₄. The ratio of pulmonary function disorder was higher in the test group versus the control group (12.0% vs 4.3%). Logistic regression shows that pulmonary fibrosis is a risk factor of osteoporosis, independent of age, sex, body mass index, smoking status, diabetes mellitus, alkaline phosphatase, glycosylated hemoglobin, Ca, PO₄, tumor necrosis factor- α , vitamin D total, ventilation disorder, diffusive dysfunction, and hypoxemia. Senile osteoporosis is closely associated with pulmonary fibrosis, diabetes mellitus, smoking, sexuality, age, and body mass index. Pulmonary fibrosis modestly affects the incidence of osteoporosis and thus is a more promising predictor of osteoporosis.

Abbreviations: ALP = alternative liquidity pool, BMD = bone mineral density, BMI = body mass index, PF = pulmonary fibrosis, PO₂ = oxygen pressure, SD = standard deviation, TNF- α = tumor necrosis factor- α , VD = vitamin D.

Keywords: osteoporosis, pulmonary fibrosis, tumor necrosis factor, vitamin D

1. Introduction

Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD), abnormal bone architecture, and compromised bone strength that predispose the victims to an increased risk of fractures.^[1] Osteoporosis frequently attacks the middle-aged and elderly. Currently, the prevalence of osteoporosis is rising along with age, as it is affecting one third of people above age 60 and half of the elderly above age 65.^[2] As an age-related disease, the high morbidity and mortality of osteoporosis threatens senile health.^[3] The most serious consequence of

osteoporosis is the various osteoporotic fractures. The occurrence of fractures raises the risk of dying from various complications by 40% to 50% for women and 13% to 22% for men compared with other major diseases, and 50% of survivors of fractures experience lower quality of life and cannot live independently.^[4] Therefore, osteoporosis has become a common public health concern. Osteoporosis-related fractures aggravate the economic burden on health care systems, and this disease has severe and debilitating consequences if untreated.^[5]

Pulmonary fibrosis is a confusing, progressive, irreversible, and diffused interstitial lung disease characterized by rapidly progressive lung tissue damage, fibrosis, and insidious onset. These negative changes eventually permeate the whole lungs and severely damage the lung structure and function. The most common clinical symptoms of pulmonary fibrosis are progressive dyspnea, cough, progressive lung function deterioration, hypoxemia, and eventually death from end-stage respiratory failure.^[6] Pulmonary fibrosis has some similar characteristics as chronic obstructive pulmonary disease, which is a strong independent risk factor of osteoporosis.^[7–9] The existing research is mainly focused on the range of cystic fibrosis (genetic disease),^[10,11] but rarely on the relationship between osteoporosis and PF. With the research development in this field, a growing number of researchers point to a close relationship between pulmonary fibrosis and osteoporosis because of their common risk factors (e.g., age, smoking and environment)^[12,13] and similar pathogenesis and clinical treatment ways.^[14] Moreover, the bone mass loss of osteoporosis is positively correlated with the acceleration of pulmonary fibrosis.^[15,16] Drugs used for treatment and prevention of osteoporosis also can inhibit pulmonary fibrosis. Moreover, medicines to pulmonary fibrosis or osteoporosis, such

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as corticosteroids and calcitonin drugs, have combined effects. In this study, we evaluate the associations between osteoporosis and pulmonary fibrosis in the elderly through a case-control design.

2. Methods

2.1. Study population

In this case-control study, patients from No. 2 Geriatric Department, Shaanxi Provincial People's Hospital were divided into a test group (osteoporosis) and a control group (non-osteoporosis). Patients from both groups were well controlled with blood glucose and had no respiratory failure or other underlying disorders. The basic characteristics were collected through a standard questionnaire. The following indices were collected: age, sex, smoking status, history of diseases, history of medication, and occupation. A healthy examiner checked all subjects by a blinded method. Height and weight were measured to calculate body mass index (BMI). The Ethics Committee of the First Affiliated Hospital of University of South China approved the study protocol.

2.2. Inclusion criterion

The World Health Organization diagnostic criteria for osteoporosis define osteoporosis as a BMD greater than 2.5 standard deviations (SDs) below the average. Specifically, normal bone, osteopenia and severe osteoporosis (1 or more fragility fractures) are defined as BMD 1 SD or less, 1 to 2.5 SD, and more than 2.5 SD below average, respectively.^[17] The diagnosis of pulmonary fibrosis refers to *Guidance for Diagnostic and Treatment of Pulmonary Fibrosis* (Chinese Thoracic Society, 2002): occult onset or progressive dyspnea with dry cough, and above symptoms are aggravated after activity; obvious inspiratory Velcro sound; High-resolution computerized tomography shows reticular or honeycomb sign with frosted glass-like shadow and linear opacities in the lower part of bilateral lung or subpleural area; restrictive ventilatory disorder and/or diffusion dysfunction in lung function, and arterial blood gas analysis shows hypoxemia or hypoxemia after exercise; and lung biopsy shows pulmonary interstitial lesion.^[18] Diabetes was diagnosed as fasting plasma glucose of 6.1 mmol/L or more and/or 2-hour plasma glucose of 11.1 mmol/L or more.^[19]

2.3. Exclusion criterion

Patients with the one of following symptoms were excluded: movement disorders and/or history of fracture in 6 months; digestive system function disorder; history of disease about thyroid gland, parathyroid glands, and adrenal gland; use of drugs for calcium supplements, glucocorticoid, antituberculosis drug, anti-tumor, and any other drug that could affect bone metabolism and/or pulmonary fibrosis; malignant tumor, tuberculosis, and connective tissue diseases; and occupational specialties.

2.4. Biochemical examination

Blood samples were collected by venous before breakfast. Glycosylated hemoglobin (HbA1c), Ca, PO₄ and alkaline phosphatase (ALP) were examined using an automatic biochemical analyzer (UniCelDx C800, BeckMan Cou Iter). Serum vitamin D total (VD total) and tumor necrosis factor- α (TNF- α) were detected using enzyme-linked immune sorbent assay. BMDs in the areas of lumbar spine and femur were measured using dual-

energy X-ray absorptiometry. Pulmonary ventilation function and diffusion were assessed by a respiratory function instrument (COSMED, Italy) as follows: the ratio of forced expiratory volume in 1 second to forced vital capacity of more than 70% (normal), normal forced vital capacity rate of one second but forced vital capacity or total lung capacity of less than 80% (restrictive ventilator disorder); CO diffusing capacity of the lung of more than 80% (impairment of the lung diffusing function) and carbon monoxide diffusing capacity of 80% or more (normal). For some patients with airway obstruction, we assessed lung function after inhalation of bronchodilators. Arterial blood oxygen tension was detected using an automatic blood-gas analyzer (GEM Premier 3000, IL, USA).

2.5. Statistical analysis

All statistical analyses were conducted on SPSS 17.0 (SPSS Inc). Data in normal distribution were expressed as mean \pm SD. Differences were examined by Student *t* test for quantitative variables and by chi-square test for qualitative variables. Relationship between osteoporosis and pulmonary fibrosis was explored using multi-variable-adjusted logistic. The controlled factors included age, sex, smoking, BMI, diabetes mellitus, ALP, HbA1c, Ca, PO₄, TNF- α , VD total, ventilation disorder, diffusive dysfunction and hypoxemia. The significance level was set at $P < 0.05$.

3. Results

3.1. Screening of subjects

Initially, 278 subjects including cases and controls were enrolled. Fifty-five patients were excluded due to movement disorders and/or history of fracture in 6 months ($n=15$), history of disease about thyroid gland ($n=13$), use of some drugs for calcium supplements, glucocorticoid ($n=9$), bone tumor ($n=2$), 4 tuberculosis ($n=4$), or occupational special diseases ($n=12$). Finally, 223 patients were included.

3.2. General characteristics of the subjects

Statistical analysis and calculations were conducted on the 108 patients and 115 controls. As showed in Table 1, significant difference was observed between groups in all tested indices except for PO₄. Physical examination identified the test group to be/have older, smoker, lower BMI, diabetes mellitus (61.1% vs 43.5%), and female compared with the control group (all $P < 0.05$). Biochemical detection showed the test group had significantly higher ALP, HbA1c, and TNF- α levels than the control group (all $P < 0.05$). On the contrary, the control group has significantly higher serum Ca level and VD total density (both $P < 0.05$). Pulmonary ventilation function detection showed the ratios of pulmonary function disorders were higher in the test group versus the control group, including pulmonary fibrosis (12.0% vs 4.3%), ventilation disorder (50.9% vs 30.4%), diffusive dysfunction (51.9% vs 34.8%), and hypoxemia (38.9% vs 26.1%) (Fig. 1).

3.3. Multiple logistic regression

The multiple logistic regression model involves osteoporosis status as the dependent variable and other variables as covariates. Results show pulmonary fibrosis is a risk factor of osteoporosis, independent of age, sex, BMI, smoking status, diabetes mellitus, ALP, HbA1c, Ca, PO₄, TNF- α , VD total, ventilation disorder,

Table 1
General characteristics of case and control.

Parameters	Case group (n=108)	Control group (n=115)	P
Age, y	77.6±5.6	75.8±5.2	0.006
Sex (female/male)	65/43	37/78	<0.001
Smoking (yes/no)	68/40	34/81	<0.001
Body mass index, kg/m ²	19.1±1.6	22.7±1.6	<0.001
Diabetes mellitus (yes/no)	66/42	50/65	0.008
ALP, IU/L	98.6±26.4	74.2±22.8	<0.001
HbA1c, %	5.1±1.4	4.7±1.4	0.017
Ca, mmol/L	2.4±0.3	2.5±0.4	0.018
PO ₄ , mmol/L	1.3±0.4	1.3±0.4	0.175
TNF-α, pg/mL	278.5±57.4	145.4±49.8	<0.001
VD Total, ng/mL	17.7±5.7	25.4±3.3	<0.001
BMD	-3.02±0.91	-2.43±1.26	0.001
PF (yes/no)	13/95	5/110	0.035
Ventilation disorder (yes/no)	55/53	35/80	0.001
Diffusive dysfunction (yes/no)	56/52	40/75	0.010
Hypoxemia (yes/no)	42/66	30/85	0.041

ALP=alternative liquidity pool, BMD=bone mineral density, PF=pulmonary fibrosis, PO₄=phosphate, TNF-α=tumor necrosis factor-α, VD=vitamin D.

diffusive dysfunction and hypoxemia (Table 2). The risk ratio of the test group versus the control group is 1.32 (95% confidence interval CI: 1.08–1.63). Other factors in the equation are age, sex, BMI, smoking, and diabetes (Fig. 2).

4. Discussion

We find pulmonary fibrosis is associated with osteoporosis in the elderly and people with pulmonary fibrosis have a higher risk of suffering from osteoporosis. This founding is independent of some potential confounding factors. Our results provide a new clue and support regarding the pathogenesis of osteoporosis.

Osteoporosis and pulmonary diseases are common in the elderly.^[20,21] Their prevalence rates both rise with age, which seriously reduces the quality of life and life span of the elderly. Unfortunately, previous studies did not completely illustrate the mechanism of osteoporosis, especially for elderly under the status of multiple potential diseases. It is reasonable to believe that pulmonary fibrosis could be related with osteoporosis after we consider many common risk factors of the 2 diseases, such as old age, female gender, higher BMI, diabetes mellitus, and history of smoking.^[22–24]

There are several likely explanations about the relationship between osteoporosis and pulmonary fibrosis. The first one could be attributed to the presence of oxidative stress. Reactive oxygen species (ROS), which mainly include superoxide, hydrogen

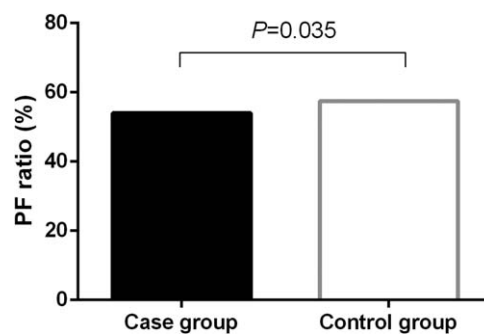


Figure 1. Ratio of pulmonary fibrosis case and control group.

peroxide (H₂O₂), and hydroxyl radical (–OH) characterized by the ability of oxidation, are constantly produced during the substance metabolism. ROS play an important role in regulation of physiological functions (cell apoptosis, genetic expression, signal transduction). However, ROS at high concentrations can easily oxidize with biomacromolecules, which would damage cellular structures and functions.^[25] It is suggested that oxidative stress could induce osteoclast death through necrosis and apoptosis while ROS could promote osteoblast differentiation.^[26] In other words, the high-level ROS could affect bone metabolism through the way of antioxidant exhaustion, osteoclast activation, inhibition of osteoblast and bone formation, and finally promotion of occurrence and development of primary osteoporosis.^[27] ROS is associated with pulmonary fibrosis since many lipid peroxides have been found in the bronchoalveolar lavage fluid.^[28] Moreover, the ROS level in the body is positively related with degree of pulmonary fibrosis, which highlights the important role of ROS during the pulmonary epithelial cell damage.^[29] Animal experiments also show that the –OH and H₂O₂ levels obviously elevate in bleomycin-induced pulmonary fibrosis rats, but drop significantly after intervention by antioxidant drug N-acetylcysteine, thus significantly relieving the damage and fibrosis of pulmonary epithelial cells.^[30] This study shows that ROS is involved in the occurrence and development of pulmonary fibrosis. Besides, the levels of antioxidants (glutathione, superoxide dismutase, and catalase) reduce notably in pulmonary fibrosis patients, suggesting that the imbalance of oxidation and oxidation resistance could be a potential factor of pulmonary fibrosis.

Another important factor could be inflammatory reaction. Many inflammatory factors are involved in the pathogeny of osteoporosis and pulmonary fibrosis. TNF-α generated by mononuclear macrophage is a bone resorption resultant. Animal

Table 2
Multiple logistic regression in patients with osteoporosis.

Variables	B	SE	Wald	P value	Odds ratio	95% CI
Constant	-7.96	3.211	7.481	0.011	-	-
Age	0.421	0.189	4.965	0.026	1.52	1.05–2.21
Sex	0.677	0.209	10.512	0.001	1.97	1.31–2.96
BMI	-1.386	0.384	6.125	0.000	0.25	0.12–0.53
Smoking	0.759	0.160	22.401	0.000	2.14	1.56–2.92
Diabetes	0.105	0.041	4.321	0.039	1.11	1.03–1.20
PF	0.279	0.105	7.128	0.008	1.32	1.08–1.63

BMI=body mass index, CI=confidence interval, PF=pulmonary fibrosis, SE=standard error.

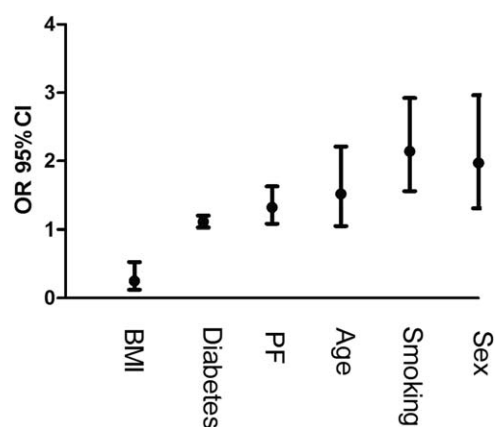


Figure 2. Risk factors of osteoporosis from multivariable analysis.

experiment shows that TNF- α could combine with the corresponding P55 receptor covered by marrow mononuclear cells and promote the growth and activity of osteoclasts, which make more bone absorption and develop into osteoporosis.^[31] TNF- α could regulate the transcription of fibrosis synthetic factors (e.g., fibronectin, collagen) in pulmonary fibrosis patients through the monocyte chemoattractant protein-1 and cell adhesion molecules. This procedure can induce inflammatory cell adsorption and collagen protein deposition and finally promote fibroblast hyperplasia.^[32] Like TNF- α , transforming growth factor- β (TGF- β) regulates diverse other cell factors in bone metabolism. TGF- β can inhibit the proliferation and differentiation of T cells, reduce interferon- γ secretion, lower the reaction of interferon- γ to the relevant transcription activation factor gene and reduce the generation of TNF- α . The whole procedure could inhibit the proliferation and differentiation of osteoclasts and prevent the occurrence of osteoporosis.³² In fact, TGF- β is the mediator most closely related with the occurrence and development of pulmonary fibrosis.^[33] As one of a set of multifunctions from the TGF- β superfamily, the bone morphogenetic protein is also involved in osteoporosis and pulmonary fibrosis,^[34,35] but relevant research is still at the stage of animal experiments and needs further investigation.

This study has several limitations. First, a case-control study determining the cause and effect between osteoporosis and pulmonary fibrosis still has some shortcomings, but still significantly supports future study. A prospective study could provide better evidence support and thus needs more investigation. Second, some patients may have received drug treatment, but we did not investigate these data, which could have some bias on the results. Considering study subjects without other serious disease and the possibility of taking the same drug, we think the bias may be little. Third, some unmeasured confounding factors (e.g., postmenopausal women, history of alcohol, unobvious renal insufficiency, and physical activity) may affect the results, especially the physical activity, because these factors could modestly affect pulmonary fibrosis, bone growth, and metabolism. Further research should pay attention on these potential factors.

5. Conclusions

Senile osteoporosis is closely associated with risk factors such as pulmonary fibrosis, diabetes mellitus, smoking, sexuality, age, and BMI. BMI as a protective factor of osteoporosis can modestly

retard bone loss of the elderly. Pulmonary fibrosis affects the incidence of osteoporosis to some extent, which is a more promising predictor of osteoporosis.

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