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Osteoporosis in Patients Referred for Lung Transplantation

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Abstract

Objective: Osteoporosis may significantly impair the final result of lung transplantation. The purpose of study is to determine the prevalence of osteoporosis with the regard to risk factors for osteoporosis in patients awaiting lung transplantation.

Material and methods: We determined bone mineral density (BMD) in 48 patients (12 with idiopathic pulmonary fibrosis (IPF), 15 with other form idiopathic interstitial pneumonia (IIP), 5 with sarcoidosis and 16 with COPD) referred for lung transplantation (LT). BMD was performed on lumbar spine (LS), total hip (TH), and femoral neck (FN). Osteoporosis risk factors were analyzed with the consideration to principal diagnosis, lung function tests (FVC, FEV1) and mobility (6 MWT; six minute walking test).

Results: In osteoporosis group (50% of study population) the most affected was LS (mean T-score -3 ±1), with higher steroid consumption (cumulative steroid dose 40 ±28), lower FVC, FEV1 and mobility (6 MWT: 285 m) than in patients without osteoporosis. COPD patients presented the lowest BMD with the highest cumulative steroid dose (csd/kg: 0.6 ±0.6), lowest FEV1 (21 ±15% pred.) and 6 MWT (279 m). In patients with the lowest steroid consumption (IPF) the best results of BMD and FVC, FEV1 and 6 MWT were observed. No relation was found between BMD and sex and age in study group.

Conclusions: Osteoporosis is very common in patients referred for lung transplantation, especially among COPD candidates. Steroid consumption is the mean risk factor. Therefore, early diagnosis and prevention of osteoporosis in lung transplant candidates should receive high priority.

Key words: osteoporosis, lung transplantation, referral

Introduction

In 2003 in Poland, there was the first successful lung transplantation performed. Due to lung transplantation program, which started in 2006 in Silesian Center of Heart Diseases in Zabrze, there are about 10 lung transplantations a year performed in Poland. It is the only medical centre in Poland which performs such procedures. Success of lung transplantation, expressed in life expectancy increase and quality of life improvement, depends on many factors and osteoporosis seems to be a significant one [1]. Bone mass decrease is significant and well known side effect of immunosuppressive therapy (steroids and cyclosporine). However, only few papers referring to this problem were published and even those were describing this issue in patients with COPD and cystic fibrosis- and those diseases are acknowledged osteoporosis risk factors.

The aim of study is to evaluate osteoporosis risk in potential lung receivers, not only in group of patients with COPD and to determine impact of widely acknowledged osteoporosis risk factors (age, sex, weight, steroid therapy) on presence of this symptom in end-stage lung disease patients awaiting lung transplantation.

Material and Methods

The study was performed in accordance with the Declaration of Helsinki for Human Research and the study protocol was approved by an institutional Ethics Committee.

Study Population

Among 54 patients evaluated for lung transplantation in the Department of Lung Diseases and Tuberculosis Silesian Medical University in 2006 - 2009, osteoporosis data were collected prospectively in 48 of them. The study group consisted of 35 men and 13 women aged 50.5 ±10.4 (range: 30 – 69 years). Patients presented end-stage respiratory failure due to idiopathic pulmonary fibrosis (IPF) (n = 12), other than IPF forms of idiopathic interstitial pneumonia (IIP) (n = 15), COPD (n = 16), and sarcoidosis (n=5). We performed an analysis of the various osteoporosis risk factors as follows: patient's age, weight, height, BMI, steroid consumption, time of diagnosis, and type of diagnosis, lung function tests and mobility (6 MWT).

Bone Mineral Density (BMD)

BMD was determined by a dual energy X-ray absorptiometry (DEXA) with quantitative digital radiography. Examination was performed at three skeletal locations: (1) femoral neck (FN), (2) total hip (TH), and (3) lumbar spine L1-L4 (LS). The results of the measurements were expressed as grams per centimeter squared (g/cm^2), as T-scores and Z-scores. The Z-score uti-

lizes age-matched reference ranges. The T-score is defined as the multiplicity of standard deviation below the peak bone mass. Osteoporosis, as defined by the World Health Organization, is present when T score is below -2.5. Osteopenia or low bone mass is defined by T score between -1.0 and -2.5 [1].

Steroid Consumption

Steroid consumption was presented as an actual steroid dose, cumulative steroid dose, and cumulative steroid dose related to body weight. A history of cumulative steroid dose was determined by reviewing a comprehensive shadow file and the medical record. The cumulative dose of steroid was calculated by adding the cumulative prednisone dose and the cumulative methyl prednisone dose multiplied by 1.25.

Lung Function Tests and Mobility

Spirometry was performed using Jaeger-Masterlab (Erich Jaeger GmbH, Wurtzburg, Germany).Two lung function parameters were measured: forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), and were normalized to the reference values proposed by the European Community for Coal and Steel and presented as percentage of predicted (%pred). Mobility was presented as a distance in 6 minute walking tests (6 MWT). Test was performed according to the guidelines with modified Bruce protocol [3].

Statistical Analysis

Results are expressed as means ±SD. The U Mann-Whitney test was used to compare BMD between groups with regard to the diagnosis, gender, age, body weight, and time of diagnosis, use of glucocorticosteroids, 6 MWT, FEV1, FVC, PaO_2, and $PaCO_2$. The level of significance was defined as $P< 0.05$.

Results

Prevalence

Osteoporosis (50%) and osteopenia (39.5%) were very common findings in the study population; only 5 patients (10.4%) had normal values of BMD. The mean BMD (expressed in g/cm^2) and T-score were the lowest at LS (-2.0 ±1.3) and Z-score at LS (-1.4 ±1.3) as well (Table 1). The osteoporosis groups consisted mainly of patients with COPD (42%). The patients without osteoporosis in our study populations were mainly those with different forms of idiopathic interstitial pneumonias (IPF 42%, IIP 29%) and sarcoidosis (12.5%). We observed no significant differences in age, BMI, and the mean treatment time between the

Table 1. Diagnosis, age, weight, BMI, steroid consumption, FVC, FEV1, 6 MWT, PaO_2, $PaCO_2$, T- scores, and Z-scores of patients referred for lung transplantation.

	Total (n=48)	IPF (n=12)	ILD (n=15)	Sarcoidosis (n=5)	COPD (n=16)
Age	50.5 ±10.4	55.1 ±8.9	47.7 ±12.2	43.8 ±6.6	51.8 ±9.5
Body mass (kg)	67.9 ±16.8	78.3 ±15.3	66.6 ±17.8.	68.0 ±17.5	60.1 ±13.7
BMI (kg/m^2)	23.2 ±4.8	27.1 ±4.3	22.7 ±4.9	22.8 ±5.2	20.8 ±3.1
Mean treatment time (yr)	10.2 ±7.1	5.3 ±2.3	10.4 ±5.5	18.4 ±12.9	11.1 ±6.1
Daily steroid consumption (mg)	9.0 ±6.3	9.4 ±7.3	10.3 ±6.4	9.3 ±10.3	5.3 ±8.7
Cumulative steroid dose (g)	33.0 ±30.9	17.0 ±11.1	40.3 ±28.6	48.9 ±57.2	33.2 ±30.6
Cumulative steroid dose (g/kg body wt)	0.51 ±0.5	0.2 ±0.2	0.6 ±0.4	0.6 ±0.6	0.6 ±0.6
FVC (% pred)	40.4 ±16.7	42.2 ±14.7	42.3 ±16.8	35.6 ±12.6	38.7 ±20.0
FEV1 (% pred)	31.6 ±17.3	44.0 ±15.9	36.1 ±16.1	23.4 ±8.5	21.0 ±15.2
6 MWT (m)	305 ±112	332 ±66	298 ±116	342 ±131	280 ±131
PaO_2 (mmHg)	47.3 ±10.3	46.7 ±8.8	45.7 ±9.6	52.3 ±9.8	48.1 ±12.4
$PaCO_2$ (mmHg)	44.4 ±10.7	39.5 ±6.1	43.3 ±8.6	41.5 ±8.5	50.0 ±13.9
T score FN	-1.8 ±0.9	-1.5 ±0.6	-1.5 ±0.8	-1.4 ±1.0	-2.5 ±0.7
T score FN (% pred)	77.1 ±11.1	81.7 ±7.3	81.1 ±9.8	82.0 ±13.9	67.8 ±8.2
Z score FN	-0.9 ±0.8	-0.8 ±0.9	-0.7 ±0.5	-0.5 ±0.5	-1.5 ±0.7
Z score FN (% pred)	86.6 ±10.8	90.9 ±12.5	89.9 ±6.9	91.0 ±8.8	78.2 ±9.8
T score TH	-1.4 ±1.1	-0.7 ±0.9	-1.1 ±0.8	-1.4 ±1.4	-2.3 ±0.7
T score TH (% pred)	81.1 ±13.0	88.9 ±10.2	85.7 ±9.7	82.4 ±17.3	70.3 ±9.8
Z score TH	-0.9 ±0.9	-0.3 ±1.0	-0.7 ±0.7	-0.8 ±0.9	-1.6 ±0.8
Z score TH (% pred)	87.2 ±13.0	94.2 ±14.5	91.1 ±9.3	88.6 ±13.3	77.7 ±10.9
T score LS	-2.0 ±1.3	-1.2 ±1.4	-2.0 ±1.0	-2.0 ±1.5	-2.8 ±1.1
T score LS (% pred)	79.9 ±12.9	87.8 ±15.7	81.2 ±9.7	80.0 ±15.0	72.3 ±10.2
Z score LS	-1.4 ±1.3	-0.8 ±1.7	-1.5 ±1.3	-1.4 ±0.7	-1.8 ±1.0
Z score LS (% pred)	85.2 ±13.8	91.1 ±20.4	85.9 ±12.8	84.4 ±9.0	80.0 ±9.0

Table 2. Age, weight, BMI, steroid consumption, FVC, FEV1, 6 MWT, PaO_2, $PaCO_2$ of patients referred for lung transplantation with and without osteoporosis.

	Total (n=48)	Osteoporosis (n=24)	No osteoporosis (n=24)	P value (osteoporosis vs. no osteoporosis)
Age (yr)	50.5 ±10.4	49.4 ±9.8	51.6 ±11.2	0.368
Body mass (kg)	67.9 ±16.8	63.3 ±16.7	72.8 ±15.7	0.027
BMI (kg/m^2)	23.2 ±4,8	22.1 ±4.5	24.5 ±4.8	0.187
Mean treatment time (yr)	10.2 ±7.1	10.4 ±5.2	10.0 ±8.7	0.899
Daily steroid consumption (mg)	9.0 ±6.3	7.2 ±7.6	9.4 ±5.7	0.290
Cumulative steroid dose (g)	33.0 ±30.9	40.5 ±28.7	25.6 ±31.9	0.003
Cumulative steroid dose (g/kg body wt)	0.51 ±0.5	0.7 ±0.5	0.3 ±0.4	0.002
FVC (% pred)	40.4 ±16.7	35.9 ±12.1	45.4 ±19.6	0.055
FEV1 (% pred)	31.6 ±17.3	25.2 ±10.6	39.0 ±20.3	0.012
6 MWT (m)	305 ±112	285 ±121	325 ±101	0.217
PaO_2 (mmHg)	47.3 ±10.3	47.7 ±10.8	46.9 ±9.9	0.543
$PaCO_2$ (mmHg)	44.4 ±10.7	48.4 ±11.7	39.8 ±7.2	0.001

groups with and without osteoporosis (Table 2). Significant differences were observed in weight, FVC, FEV1, and $PaCO_2$ between these groups.

Age

Females and males' age was comparable (48 ±11 and 51 ±12 yr, respectively). The oldest were patients with IPF (55 ±9 yr) and COPD (52 ±9 yr). The youngest were patients with sarcoidosis (44 ±7 yr). No correlation was found between age and sex, on the one side, and BMD, BMI, and weight, on the other side. Nor were there differences in BMI and weight between males and females. The patients with osteoporosis had a lower body mass ($P<0.05$) than those without it; but BMI was similar in both groups (Table 1). The largest body mass and BMI were observed in the patients with IPF (78 ±15 kg and 27 ±4 kg/m^2, respectively). In the patients with IPF, the relatively best results of BMD were observed. In the patients with COPD, the lowest values of BMI and body mass were observed (20 ±3 kg/m^2 and 60 ±13 kg, respectively). In these groups, the greatest decreases of BMD in all parameters measured (T-score and Z-score at FN, TH, and LS) were observed. Differences between weight, BMI, and BMD between the groups with IPF and COPD were significant. In the patients with ILD and sarcoidosis similar values of weight, BMI, and BMD were observed.

Steroid Consumption and Treatment Time

The mean treatment time was similar in the groups with and without osteoporosis (≈10 yr). The cumulative steroid dose was significantly higher ($P<0.001$) in the group with osteoporosis than in that without it. This dose, expressed in relation do body weight, was also more than two times higher in the group with osteoporosis ($P<0.001$) (Table 1). The mean treatment time was lowest in the patients with IPF (5 ±2 yr) and highest in the sarcoidosis group (18 ±13 yr). The patients with COPD presented a two times higher mean treatment time than those with IPF (11 ±6 vs. 5 ±2 yr). The actual, daily steroid consumption was the lowest in the COPD group (5 ±9 mg), the highest in IIP (10 ±6 mg). The patients with IPF presented the lowest cumulative steroid dose (17 ±11 g) and the cumulative dose in relation to body weight (0.2 ±0.2 g/kg) as well. The latter dose was three times higher in the patients with COPD than in those with IPF. In COPD patients, decreases in all BMD parameters were most expressed (Table 1).

Lung Function Tests and Mobility

FVC and FEV1 were strongly reduced in the study population (Table 2). The lowest values were in the patients with osteoporosis, where the difference in FEV1 was significant ($P<0.05$) compared with the patients without it. The osteoporosis group presented also a lower mobility; 285 vs. 324 m in the walking test, respectively), although this difference did not reach statistical significance. No significant differences were observed in FVC in relation to the diagnosis. The patients with COPD presented two times lower values of FEV1 compared with the IPF group (21 ±15 vs. 44 ±15 % pred, $P<0.001$) (Table 1). The COPD patients demonstrated the lowest mobility (6 MWT: 279 ±131 m). In this group, the highest values of $PaCO_2$ compared with the IPF, IIP, and sarcoidosis groups were also observed ($P<0.05$).

Discussion

In our study, osteoporosis was found to be very common in patients with different end-stage lung diseases awaiting lung transplantation. Overall, osteoporosis was present in half the study population, and osteopenia in approximately 40%. Only 10% of our lung transplant candidates presented normal bone mass density. Other studies showed similar results; a decreased bone mass is a widespread condition in lung

transplant candidates [4, 5]. In our study population the most affected was lumbar spine, whereas other authors showed that the femoral neck bone mass density is most decreased [5, 6]. This disparity may stem from the patients' age, which was higher in our population. It is well known that patients with cystic fibrosis or COPD have significantly decreased bone mass. In our study, patients with different forms of lung fibrosis presented a strong risk factor for developing a decrease in bone mass density. But the highest decrease was observed in COPD population, which is also described in other studies [4-6]. In the general population, higher age, female gender, and low body weight are accepted risk factors for osteoporosis. That was also seen in our study, where patients with COPD and the lowest weight and BMI had the highest decrease in BMD.

Patients with COPD and pulmonary fibrosis have a history of glucocrticoid therapy. Osteoporosis is a well known, dose -dependent side effect of glucocrticoid therapy [2, 6]. Glucocrticoids exert adverse effects on BMD be several mechanisms, where decreased bone formation is the most common [1]. In our study, BMD was significantly lower in patients with a history of chronic use of glucocorticoids. That effect was apparent in our patients after counting the cumulative steroid dose on body weight. The patients with COPD had the most decreased BMD; they presented three times higher steroid consumption compared with the IPF patients who had relatively best results of BMD. Likewise, the lowest FEV1 and mobility observed in the COPD group could be connected not only with airflow obstruction, but also with the loss of muscle mass due to steroid consumption.

In conclusion, our study demonstrates that osteoporosis is a common condition in advanced lung diseases and COPD patients are the most affected. Therefore, early diagnosis, prevention, and treatment of osteoporosis in patients with advanced lung disease should receive high priority. An early evaluation of bone mass and avoiding high steroid therapy should also be considered in all patients undergoing lung transplantation.

Conflicts of interest: No conflicts of interests were declared by the authors in relation to this article.

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