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Original Article

Bone Mineral Density in Lung Transplant Recipients: Experience of A Referral Lung Transplantation Center

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A B S T R A C T

Background Osteoporosis is a well-recognized and curable complication of lung transplantation. This study aimed to determine the degree of bone mineral density before transplantation and to evaluate the risk factors associated with osteoporosis in lung transplant patients.

Material and Methods The bone mineral density of 72 patients who underwent lung transplantation with the diagnosis of end-stage lung diseases between December 2016 and April 2021 was evaluated in the pre-transplant period.

Results 58 of 72 patients who underwent lung transplantation were included in the study. The age range of the cases was 14-64 (mean 48) years, and 14 (23.7%) were female. The presence of osteoporosis in the study population was 49.2% (n: 29), and osteopenia was 40.7% (n: 24). Osteoporosis was significantly more common in patients with younger age and lower body mass index ($p = 0.024$ and $p = 0.009$, respectively). And most down forced expiratory volüme 1 values were in patients with osteoporosis ($p < 0.001$ and $p = 0.008$, respectively). Steroid usage (OR: 0.06, 95% CI: 0.01-0.36, $p = 0.002$) in T score (femur neck) and 1.25 dihydroxy vitamin D (OR: 1.15, 95% CI: 1.03-1.28, $p = 0.012$) in T score (lumbal spine) were found to be independent predictors of osteoporosis according to multivariate analyzes.

Conclusions A significant proportion of patients with end-stage lung disease undergoing lung transplantation have osteoporosis and osteopenia. Interestingly, the candidates were similarly affected despite the variety of underlying conditions. Since osteoporosis is treatable, strict follow-up and treatment management are recommended before referral for transplant candidates.

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INTRODUCTION

Lung transplantation has become a life-saving treatment option that can improve survival and quality of life in selected patients with end-stage lung disease.[1] However, although it is a life-saving measure, organ transplantation is associated with a well-known complication of osteoporosis. Patients with chronic disease, including pre-and post-transplant end-stage lung disease, are exposed to several factors that, on their own, may affect bone mineral metabolism and predispose them to post-transplant bone disease. For instance, patients with a chronic illness that leads to prolonged bed rest are at risk for disuse osteodystrophy. In addition, many drug treatments administered to these patients before transplantation are also associated with bone disease.[2] Post-transplant quality of life has become increasingly important as transplant patients' surgical and medical management advances have led to long-term survival.[2,3]

Osteoporosis is one of the important causes of morbidity after lung transplantation, and fractures resulting from it can significantly affect the life expectancy of patients. Numerous studies have documented the degree of bone mass loss that occurs after kidney[4-6], heart[7,8], and liver[9-11] transplantation. Lung transplantation has been associated with a decrease in bone mass index, but there are few studies on this topic. In particular, end-stage lung disease patients on chronic glucocorticoid use are at risk for osteoporosis or osteopenia. Aris *et al.*[12] revealed that 75% of post-lung transplant patients had bone mineral densities for the spine and femur below the fracture threshold. Patients with end-stage lung disease who are candidates for lung transplantation must be directed by their primary follow-up physicians to the lung transplantation centre at the appropriate time and with the best medical support before contraindications develop because osteoporosis is a potentially manageable comorbidity. This study aimed to investigate the bone mineral density status and presence of osteoporosis in patients with lung transplantation during the initial evaluation for transplantation.

MATERIAL AND METHODS

This single-centre retrospective cohort study was conducted at the lung transplantation clinic in the tertiary hospital. The local ethics committee approved the study. The patients' files were collected from the hospital database. All patients' ID information was kept confidential.

Study population

Patients who were admitted between December 2016 and April 2021 were retrospectively evaluated. The study included 72 patients who were diagnosed with end-stage lung disease due to various underlying conditions: obstructive lung disease (OLD), interstitial lung disease (ILD), cystic fibrosis (CF), and non-CF bronchiectasis who were lung transplantation. In all, 14 patients were excluded due to insufficient data for this research.

Data collection

Demographic data were age, gender, body mass index (BMI, kg/m2), time of diagnosis, six-minute walk distance (SMWD), respiratory function tests, pulmonary artery mean pressure (PAPmean) by catheterization, steroid usage, 1,25-dihydroxy vitamin D (1,25[OH]$_2$D, pg/mL), serum calcium (mg/dL), T-score femur neck (FN), Z-score FN, T-score lumbal spine (LS), and Z-score LS were collected from patients' records.

The six-minute walk test (6MWT) was enforced according to American Thoracic Society guideline criteria by a physiotherapist with specific experience while the subjects had their usual oxygen flow. The course was performed in a 30 m (meter) corridor by a physiotherapist with a unique experience. Two traffic cones did the 6MWT, and the passage was marked every 3 m, according to the American Thoracic Society standards.13

Right heart catheterization (RHC) was regulated with a balloon-tipped and flow-directed pulmonary artery catheter. The catheter was placed through the right femoral or internal jugular vein utilizing local anaesthesia and the Seldinger technique.14

Bone mineral density (BMD) was determined by dual-energy X-ray absorptiometry (DXA) with quantitative digital radiography. The examination was performed at three skeletal locations: FN and LS L1-L4. The results of the measurements were expressed as grams per centimetre squared (g/cm^2), as T-scores and Z-scores. The Z-score utilizes age-matched reference ranges. The T-score is defined as the diversity of a standard deviation below the peak bone mass. Osteoporosis, as defined by the World health organization, is present when the T score is below -2.5. Osteopenia or low bone mass is determined by a T score between -1.0 and -2.5.15

Statistical analysis

All statistical analyses were performed with SPSS 23.0 for Windows (SPSS Inc., Chicago, IL). A descriptive analysis was used to investigate patients' demographic and clinical data retrieved from retrospectively scanned files. Descriptive statistics were shown as median, 25th and 75th percentiles as the normality assumption was not satisfied. Furthermore, three independent groups were compared with Kruskal-Wallis variance analysis for continuous variables, while categorical variables were compared with Chi-Square. The univariate logistic regression models were conducted to specify candidate variables in multiple logistic regression. The significant variables at $p < 0.25$ were chosen for multiple logistic regression. Backward elimination was performed with those variables. The results of the final logistic regression models have represented an odds ratio (OR), 95% of the confidence interval and p-value. The correlation of BMDs with collected parameters was determined using Spearman's correlation coefficient (r). The level of statistical significance was set at a p - value < 0.05. All reported p-values are 2-sided.

RESULTS

58 of 72 patients with end-stage lung disease were enrolled in the study. The age range of the study was 14-64 years (median 48), and 14 (23.7 %) were female. When the cases are grouped according to their underlying diseases, forty-four per cent of all patients (n: 26) were ILD group, which was the vast majority of the study population; OLD, CF and non-CF bronchiectasis groups (15.3%, n: 9; 13.6%, n: 8; 25.4%, n: 15; respectively). The presence of osteoporosis was 49.2% (n: 29), and osteopenia was 40.7% (n: 24) in the study population.

Patients with CF were younger and had a lower BMI than other disease groups ($p = 0.001$ and $p = 0.012$, respectively). Compared to other groups, male patients ($p = 0.001$) were significantly higher in the ILD group than in others. Laboratory parameters and bone mineral densitometry measurements were similar between groups. In addition, the waiting time until transplantation after listing in the CF group was higher ($p = 0.007$) than in other disease groups. Forced expiratory volume (FEV)1 and steroid usage were significantly higher in patients with ILD ($p < 0.001$ and $p = 0.004$; respectively). 6MWT forced vital capacity (FVC) and PAPmean were similar between both groups. The demographic characteristics of study patients were summarized in Table 1.

According to our results, 49.2% were osteoporosis, 40.7% were osteopenia, and normal BMD was 8.5%. The greatest prevalences of BMD (≤ -2.5) were seen

Table 1. Demographic and clinical characteristics of the study.

	OLD	ILD	CF	non-CF bronchiectasis	*P* - value
Number of patients	9 (15.3)	26 (44.1)	8 (13.6)	15 (25.9)	
Age (years)	55 (53-57)	52 (46-58)	24 (23-36)	31 (26-56)	0.001
Male gender	8 (88.9)	25 (96.2)	3 (37.5)	9 (60)	0.001
BMI (kg/m^2)	25 (24-26)	26.3 (22.2-28.6)	19.1 (16.5-24.6)	20 (16.9-26.8)	0.012
Waiting time (day)	96 (69-116)	82 (42-171)	214 (163-436)	115 (39-194)	0.007
6MWD (meter)	233 ± 95	231 ± 126	234 ± 115	273 ± 121	0.714
FEV_1 (%)	22 (18-28)	44 (30-50)	21 (20-40)	21 (18-26)	< 0.001
FVC (%)	38 (33-52)	39 (28-43)	32 (32-34)	25 (22-36)	0.060
PAP_{mean}*	21(17-26)	29 (21-33)	26 (24-28)	30 (24-38)	0.137
Steroid using	9 (29)	10 (32.3)	6 (19.4)	6 (19.4)	0.004
1,25[OH]$_2$D (pg/mL)	14.5 ± 9.4	12.5 ± 5.4	15.6 ± 7.9	12.8 ± 5.5	0.655
Calcium (mg/dL)	9.2 ± 0.5	9.4 ± 0.5	9.0 ± 0.5	9.1 ± 0.8	0.980
T-score femur	-2.5 ± 1.2	-1.7 ± 1.1	-2.4 ± 0.7	-2.4 ± 1.0	0.163
Z-score femur	-1.5 ± 1.3	-1.2 ± 1.3	-1.6 ± 1.6	-1.8 ± 0.9	0.551
T-score lumbal spine	-1.8 ± 2.1	-1.3 ± 1.5	-1.5 ± 1.5	-2.0 ± 1.2	0.734
Z-score lumbal spine	-1.5 ± 1.6	-1.0 ± 1.4	-1.6 ± 0.7	-1.2 ± 1.3	0.780

OLD: obstructive lung disease, ILD: interstitial lung disease, CF: cystic fibrosis, BMI: body mass index, 6MWD: six minutes walk distance, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, PAP_{mean}: mean pulmonary artery pressure, 1,25 dihydroxy vitamin D: 1,25[OH]$_2$D. *By catheterization.

The values were expressed as n (%), median (25-75% interquartile ratio) or mean±standart deviation.

Table 2. Age, gender, BMI, FEV1, FVC, 6MWD, vitamin D, calcium, waiting time of patients referred for lung transplantation with and without osteoporosis.

Variables	Osteoporosis	No osteoporosis	*P* - value
Age (years)	36 (24-55)	52 (37-58)	0.024
Male gender	16 (35.6)	29 (%35.6)	0.057
BMI (kg/m^2)	20 (17-26)	25.5 (21.7-27)	0.009
Steroid using	21 (67.7)	10 (33.3)	< 0.001
OLD	5 (17.2)	4 (13.3)	0.731
ILD	10 (34.5)	16 (50)	0.295
CF	5 (17.2)	3 (10)	0.472
non-CF bronchiectasis	9 (31)	6 (20.7)	0.550
Mortality	12 (46.2)	14 (53.8)	0.795
$FEV_{1,}$ (%)	23 (20-29)	37 (25-49)	0.008
FVC (%)	32 (23-38)	36 (28-43)	0.080
6MWD (meter)	257 ± 102	231 ± 114	0.495
$1,25[OH]_2D$ (pg/mL)	11.4 (9.1-15.2)	11.9 (9.8-14.1)	0.806
Calcium (mg/dL)	9.2 (9.0-9.7)	9.3 (8.7-9.7)	0.662
PNI	43.5 (42.0-48.0)	44.5 (41.9-52.0)	0.382
Waiting time (day)	119 (80-194)	88 (35-171)	0.135

BMI: body mass index, OLD: obstructive lung disease, ILD: interstitial lung disease, CF: cystic fibrosis, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, 6MWD: six minutes walk distance, 1,25 dihydroxy vitamin D: $1,25(OH]_2D$, PNI: prognostic nutritional index.

The values were expressed as n (%), median (25-75% interquartile ratio) or mean±standart deviation.

in CF (62.5%) and non-CF bronchiectasis (56.3%) groups; however, there was no significant difference between disease subgroups.

Table 2 showed patients' demographic and clinical parameters with and without osteoporosis. The patients with osteoporosis had a younger age and lower BMI (p = 0.024 and p = 0.009, respectively). Steroid usage and lowest FEV1 values were in patients with osteoporosis (p < 0.001 and p = 0.008, respectively). There were no significant differences in gender, waiting for time, FVC, 6MWT, calcium, and 1,25[OH]2D between the groups.

Correlation analysis of LS, FN T-score values and patients' characteristics were summarized in Table 3. Analysis of the FN T-scores revealed a moderate correlation in age, BMI, FEV1, and FVC (p = 0.018, r = 0.306; p = 0.003, r = 0.383; p = 0.001, r = 0.416 and p = 0.010, r = 0.333, respectively). LS T-score was found to have a weak correlation with BMI and a negative correlation with $1,25[OH]_2D$ (p = 0.025, r = 0.292; p = 0.012, r = -0.320, respectively). There was no correlation between baseline LS, FN T-score and gender, serum calcium, or waiting time in the transplant list.

In the logistic regression analysis of T-score (FN) and T-score (LS), univariate predictors were age, gender, BMI, FEV1, 6MWD, $1,25[OH]_2D$, steroid usage, PAPmean, FEV1, patients with ILD and COPD respectively. In multivariate analyses, steroid usage (OR: 0.06, 95% CI: 0.01-0.36, p = 0.002) in T-score (FN) and $1,25[OH]_2D$ (OR: 1.15, 95% CI: 1.03-1.28, p = 0.012) in T-score (LS) were found to be independent predictors of osteoporosis.

DISCUSSION

Our study determined that osteoporosis was common in patients who underwent lung transplantation in the initial evaluations. Almost half of the cases had osteoporosis, and 42.4% had osteopenia. Only 8.5% of patients referred for assessment for transplantation had normal BMD. Similar results have been shown in other studies, indicating that low bone mass density is widespread in end-stage lung patients who are candidates for lung transplantation.[16-18]

The patients with CF and non-CF bronchiectasis were the most affected according to the underlying

Table 3. Correlation between pre-transplant T score and demographic/clinical parameters.

Parameters	T-Score			
	Lumbal spine		Femur neck	
	r value	*P* - value	r value	*P* - value
Age	0.130	0.298	0.306	0.018
Gender	-0.100	0.407	-0.27	0.057
Body mass index	0.292	0.025	0.383	0.003
FEV_1	0.120	0.329	0.416	0.001
FVC	0.100	0.893	0.333	0.010
6MWD	-0.077	0.561	-087	0.512
$1,25(OH]_2D$	-0.320	0.012	-0.25	0.051
PNI	0.194	0.142	0.072	0.587
Serum calcium	0.079	0.573	-0.170	0.899
Waiting time	-0.560	0.673	-0.047	0.725

FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, 6MWD: six minutes walk distance, 1,25 dihydroxy vitamin D: $1,25(OH]_2D$, PNI: prognostic nutritional index.

disease groups. Higher age, female gender, and low body weight are accepted risk factors for osteoporosis in the general population.[19] Interestingly, although patients with CF and non-CF bronchiectasis are a young patient group in terms of osteoporosis development, they have a lower body mass index than other disease groups, and we thought that steroid use might also be an influential factor in the development of osteoporosis. Patients with end-stage lung diseases referred to our clinic with extensive parenchymal damage mostly had a history of chronic steroid use. Although we do not know objectively how much steroid the cases have used since the date of diagnosis, we think it is used during exacerbations of primary diseases, emergency admission, or hospitalizations. The well-known dose-dependent side effect of glucocorticoid therapy is osteoporosis.[20]

Although high age is one of the risk factors for osteoporosis, the reason why it was seen more frequently in low-age patients in our study; explained that patients with CF and non-CF bronchiectasis are younger than the others.

Physical activity is known to be important in the prevention of osteoporosis. However, we found no association with the 6MWT.[21] Regarding this result, 6MWT may not reflect physical activity in the past years. Body weight loss is probably a more stable indicator for muscle mass loss than a walking distance in lung transplantation evaluation. In contrast, lower FEV1 values were associated with lower BMD. The reason for this may be low FEV1 reflects not only airflow inhibition but also muscle mass loss.

The second main finding of this study is the positive correlation between age, BMI, FEV1, FVC and osteoporosis, as well as the negative correlation between BMI, 6MWT, and osteoporosis. Another study by Tschopp *et al.*18 showed the relationship between low BMI and low BMD. However, there needs to be more data in the literature on the BMI values of patients before lung transplantation and osteoporosis. Chaikriangkrai *et al.*[22] showed that in lung transplant recipients, pre-transplant BMI and SMWD are independent predictors of post-transplant mortality. According to this study, being thin and obese was associated with mortality. According to multivariate analysis, $1,25[OH]_2D$ and glucocorticoid use were independent risk factors for osteoporosis.

One of the crucial limitations of this study is that due to the retrospective nature of the study, the frequency of steroid treatment and the total dose of the patients could not be recorded during the period from diagnosis to transplantation evaluation. In addition, since the patient applied in different periods from the time of diagnosis, it is impossible to reach precise numbers about the number of disease exacerbations and total hospitalizations. Another limitation is that parathormone levels were not controlled in lung transplant candidates evaluated in our clinic, so we could not contribute to the relationship between the development of secondary hyperparathyroidism, low 25-hydroxy vitamin D levels, and the BMD status of the patients.

CONCLUSIONS

In conclusion, we showed that osteoporosis is a common disease in end-stage lung patients. Surprisingly, we found that lung patients with various diagnoses under the heading of lung transplant candidates are similarly affected. Therefore, clinicians who plan to refer their patients for lung transplantation should not neglect patient management in osteoporosis. In addition, high-dose steroid treatment should be avoided as much as possible in this group of patients. Osteoporosis goes along with considerable morbidity and decreased quality of life, as shown for patients with bone disease after lung transplantation.23 Therefore, our findings suggest that transplant candidates with osteoporosis should be closely monitored for pre- and post-transplant treatment and follow-up.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Kartal Koşuyolu Training and Research Hospital, İstanbul, Turkey. (Decision number: 2021114/545, date: 19.10.2021).

Authors' Contribution

Study Conception: PAG, İI; Study Design: PAG; Literature Review: İI; Critical Review: İI; Data Collection and/or Processing: ANH, PAG; Analysis and/or Data Interpretation: PAG; Manuscript preparing: PAG, İI.

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