

Association of Bone Mineral Density with Airway Obstruction and Emphysema

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Background: Airway obstruction and the extent of emphysema are reported to be responsible for reduced bone mineral density (BMD). Corresponding to different phenotypes of a pulmonary disease, different severity in extra pulmonary features may exist. We compared BMDs of subjects with or without airway obstruction and/or emphysema and investigated the relationships among BMD, the severity of airway obstruction, and the extent of emphysema.

Methods: Using a university hospital database, we reviewed patients over 40 years old who performed spirometry, computed tomography of chest, and measurement of BMD of the lumbar (L) spine. According to the presence or absence of airway obstruction and/or emphysema, four groups were classified.

Results: Among a total of 59 subjects, 33 (56%) had osteoporosis. The prevalence of osteoporosis in subjects with no airway obstruction and no emphysema, those with only emphysema, those with only airway obstruction, and those with both airway obstruction and emphysema were 42%, 57%, 64%, and 73%, respectively ($p=0.047$ by linear-by-linear association). The mean T-scores of BMD of L1 ($p=0.032$) and L1-4 spines were different among the four groups ($p=0.034$). Although the T-score of L1 BMD negatively correlated with the extent of emphysema ($r=-0.275$, $p=0.035$) and positively with each of body mass index (BMI) ($r=0.520$, $p<0.001$), forced expiratory volume in one second (FEV_1) ($r=0.330$, $p=0.011$), FEV_1 /forced vital capacity ($r=0.409$, $p=0.001$), and forced expiratory flow at 25~75% of FVC ($FEF_{25-75\%}$) ($r=0.438$, $p=0.0001$), respectively, multiple linear regression analysis indicated that BMI ($p<0.001$) and $FEF_{25-75\%}$ were predictive of BMD ($p=0.012$).

Conclusion: Low BMI and airway obstruction were strongly associated with reduced bone density rather than the extent of emphysema.

Key Words: Airway Obstruction; Bone Density; Pulmonary Emphysema; Osteoporosis; Body Mass Index

Introduction

Osteoporotic fractures decrease an individual quality of life and increase a socioeconomic burden. To predict the risk of osteoporotic fractures, measurements of bone mineral density (BMD) have been widely used. It has

been reported that BMD is lower in patients with chronic obstructive pulmonary disease (COPD) than in healthy subjects^{1,2}. COPD is currently understood to be associated with systemic inflammation as well as pulmonary inflammation³. Several factors such as the severity of airway obstruction and the extent of emphysema have been reported to be responsible for the reduced bone density in patients with COPD^{1,2,4-10}. Recently, the extent of pulmonary emphysema was suggested to correlate with reduced bone density better than forced expiratory volume in one second (FEV_1)⁹. However, there has been little study to investigate differences in BMDs or the prevalence of osteoporosis according to phenotypes of COPD, such as emphysema and airway ob-

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struction, as well as control subjects. Our aims were to compare prevalence and BMDs among subjects in the presence or absence of airway obstruction and/or emphysema and investigate the relationships among BMD, the degree of airway obstruction, and the extent of emphysema.

Materials and Methods

1. Subjects

From medical record database of the Ewha Womans University Hospital from September 2003 through May 2009, we selected patients over 40 years who performed all three of spirometry, computed tomography (CT) of chest, and BMDs of lumbar spine within one-year period. Among them, we excluded those with significant lesions, such as interstitial lung disease, active pulmonary tuberculosis, tuberculous destroyed lung, pneumonia, lung cancer, and bronchiectasis, except emphysema, to affect lung volume measured by using CT images. Finally, 59 patients were retrospectively evaluated. The Institutional Review Board approved the analyses of the data.

2. Pulmonary function tests

Spirometry was performed as recommended by the American Thoracic Society using the Vmax 22 (Sensor Medics, Yorba Linda, CA, USA)¹¹. The following values were evaluated: FEV₁, forced vital capacity (FVC), the ratio of FEV₁ to FVC (FEV₁/FVC), forced expiratory flow at 25~75% of FVC (FEF_{25-75%}). Airway obstruction is defined as a FEV₁/FVC less than the lower limits of the normal range (LLN) for FEV₁/FVC^{12,13}.

3. Chest CT scans

Chest CT scans were performed on all patients at full inspiration using a 16-multi detector CT scanner (Somatom Sensation; Siemens Medical System, Forchheim, Germany). Images of the whole lung were extracted automatically and the attenuation coefficient of each pixel was calculated. The cutoff level between normal lung density and low-attenuation areas (LAA) was defined as

−950 Hounsfield Units¹⁴. To evaluate pulmonary emphysema quantitatively, the total lung volume and the volume of LAA were automatically measured using a volume data set on a computer workstation (Rapidia 3D version 2.8; Infinitt Health Care, Seoul, Korea), and the percentage volume of LAA (%) was calculated as (volume of LAA)/(total lung volume)×100 (%). Emphysema is defined as having LAA% of more than 10%.

4. Measurements of BMD in vertebral bone

Bone mineral parameters were measured by using a Dual energy X-ray absorptiometry (Prodigy; GE-lunar, Houston, TX, USA) at the lumbar spine (vertebrae L1~4). Parameters were expressed in standard globally accepted terms: BMD (g/cm²). Standardized T-score analyses were used to compare individual bone density determinations for study subjects to those of a young normal control population of the same gender. This was done to standardize the BMD measurements to peak bone mass, which occurs at 30 years of age. The BMD measured is therefore correlated to the peak bone mass and is expressed as a T-score which is the number of standard deviations below or above peak bone mass for the relevant gender. T-score values between −1.0 and −2.5 are definable for osteopenia and T-scores below −2.5 are definable for osteoporosis¹⁵.

5. Statistical analysis

Statistical analysis was performed using SPSS-PC for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive data are expressed as median value with interquartile range and frequencies are expressed as number (%). According to the presence or absence of airway obstruction and/or emphysema, four groups were classified. Differences between four groups were tested using the Kruskal-Wallis test. Prevalence of osteoporosis or osteopenia of four groups was compared by linear-by-linear association. To know relationship between a parameter of BMD and each variable, we used Pearson correlation analysis. To find out independent correlates of BMD, multiple linear regression analysis was used. Statistical significance was accepted at the

p-values of <0.05 level.

Results

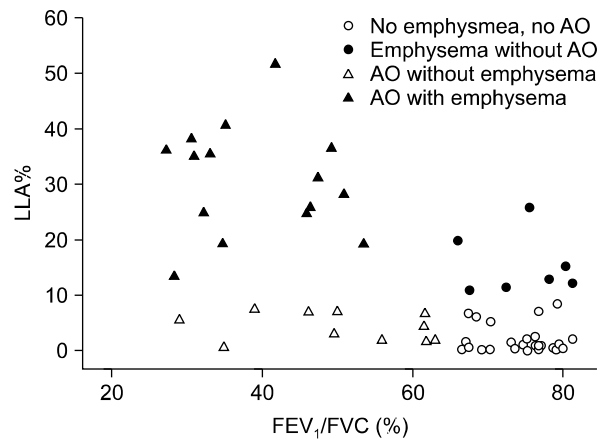


Figure 1. Four groups of patients disclosed by the presence or absence of airway obstruction and/or emphysema. Group 1 (n=26) with no airway obstruction (AO) and no emphysema are presented as hollow circles; group 2 (n=7) with emphysema and no AO, full circles; group 3 (n=11) with AO and no emphysema, hollow triangles; and group 4 (n=15) with both AO and emphysema, full triangles.

The mean age of our study subjects was 73 (interquartile range, 65~79) years and 33 patients (56%) were male. Among total 59 subjects, 47 had osteopenia or osteoporosis, and the prevalence of osteoporosis and osteopenia were 56% and 25%, respectively. Twenty-six patients (44%) had airway obstruction, and 22 (37%) had emphysema.

According to the presence or absence of airway obstruction and/or emphysema, four groups were classified (Figure 1). Group 1 consisting of 26 patients (44%) is characterized by no airway obstruction and no emphysema. Group 2 consisting of 7 patients (12%) is characterized by emphysema without airway obstruction. Group 3 includes 11 patients (19%) with airway obstruction without emphysema. Group 4 consists of 15 patients (25%) with both airway obstruction and emphysema. Table 1 shows the characteristics of four groups.

The prevalence of reduced BMD, including osteopenia and osteoporosis, and osteoporosis in group 1, 2, 3, and 4 were: 65%, 86%, 91%, and 93% (p=0.021 line-

Table 1. Anthropometric, lung function, and CT measurements of four groups

| Group | 1 (n=26) | 2 (n=7) | 3 (n=11) | 4 (n=15) | |
|-----------------------------------|------------------|------------------|------------------|------------------|---------|
| Airway obstruction | — | — | + | + | p-value |
| Emphysema | — | + | — | + | |
| Age, yr | 73 (60~78) | 70 (60~79) | 75 (71~79) | 71 (66~81) | 0.841 |
| Gender, male, n (%) | 10 (39) | 2 (29) | 6 (55) | 15 (100) | <0.001 |
| Height, cm | 158 (149~165) | 155 (151~163) | 160 (145~163) | 162 (158~165) | 0.393 |
| Weight, kg | 57 (50~66) | 61 (45~67) | 48 (45~52) | 45 (40~58) | 0.011 |
| BMI, kg/m ² | 23 (20~26) | 24 (19~25) | 20 (17~23) | 18 (15~22) | 0.006 |
| FEV ₁ % predicted | 90 (81~113) | 79 (66~104) | 53 (38~91) | 40 (32~45) | <0.001 |
| FVC% predicted | 88 (79~106) | 72 (54~83) | 69 (53~105) | 67 (58~88) | 0.202 |
| FEV ₁ /FVC, % | 75 (70~79) | 76 (68~80) | 50 (39~62) | 35 (30~47) | <0.001 |
| FEF _{25-75%} % predicted | 66 (54~81) | 48 (44~72) | 22 (15~27) | 14 (11~18) | <0.001 |
| Lung volume, L | 3.16 (1.99~3.63) | 3.06 (1.92~3.47) | 3.48 (2.18~4.48) | 5.27 (4.61~6.14) | <0.001 |
| LAA% | 1.0 (0.3~2.2) | 12.9 (11.4~19.8) | 4.1 (1.6~6.8) | 31 (25~36) | <0.001 |

The data are presented as median (interquartile range) or number (%).

BMI: body mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; FEF_{25-75%}: forced expiratory flow at 25~75% of FVC; LAA%: computed tomography (CT) measurement of the percentage of low attenuation area less than -950 Hounsfield Units.

ar-by-linear association) and 42%, 57%, 64%, and 73% ($p=0.047$ linear-by-linear association), respectively (Table 2, Figure 2). T-scores of L1 ($p=0.032$) and L1~4 were different among four groups ($p=0.034$) (Table 2, Figure 3).

BMI ($p<0.001$, $p=0.001$, $p<0.001$, and $p<0.001$) and FEF_{25-75%} predicted positively correlated with BMD of L1 and L1~4 and T-scores of L1 and L1~4, respectively ($p=0.001$, $p=0.010$, $p=0.001$, and $p=0.007$). A

ratio of FEV₁/FVC correlated with each of three BMD parameters except BMD of L1~4. FEV₁% predicted correlated with BMD ($p=0.030$) and T-score of L1 ($p=0.011$). LAA%, the extent of emphysema, negatively correlated with only L1 T-score ($p=0.035$) (Table 3). However, by multiple linear regression analysis, body mass index (BMI) ($p<0.001$, $p=0.001$, $p=0.001$, and $p=0.001$) and FEF_{25-75%} remained significantly associated with BMD of L1 and L1~4 and T-scores of L1 and L1~4 ($p=0.012$, $p=0.026$, $p=0.019$, and $p=0.031$).

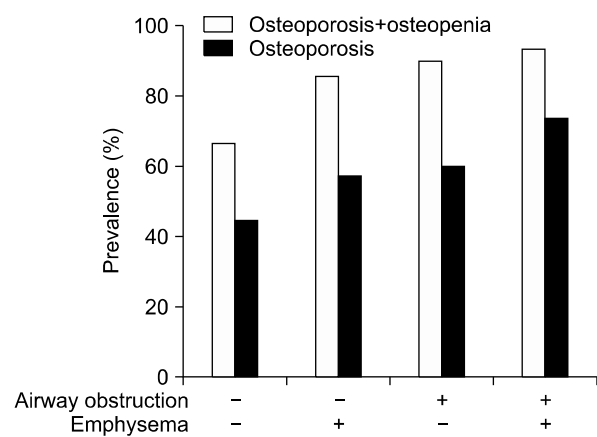


Figure 2. Association between the presence of reduced bone mineral density (BMD) and four groups. The prevalence of reduced BMD, including osteopenia and osteoporosis, and osteoporosis in the four groups were: 65%, 86%, 91%, and 93% ($p=0.021$ linear-by-linear association) and 42%, 57%, 64%, and 73% ($p=0.047$ linear-by-linear association), respectively.

Discussion

Cigarette smoking elicits airway inflammation in all of those who smoke, but in those who develop airflow obstruction there is persistent inflammation, even after smoking cessation¹⁶. This has led to the concept that an abnormal inflammatory response to cigarette smoke leads to the development of COPD in the susceptible individual. The spectrum of COPD is vast, with airway narrowing at one end and emphysema on the other, with the majority of patients existing somewhere in the middle. The reasons for the development of different phenotypes with the same exposure to cigarette smoke have not been elucidated. Possibly these phenotypes may exhibit a variety of spectrum or severity in extrapulmonary features. Even though not exactly, three of our four groups (Figure 1) could correspond to these

Table 2. Prevalence of osteoporosis and parameters of BMD of four groups

| Group | 1 (n=26) | 2 (n=7) | 3 (n=11) | 4 (n=15) | p-value |
|-----------------------------|------------------|--------------------|------------------|------------------|---------|
| Airway obstruction | - | - | + | + | |
| Emphysema | - | + | - | + | |
| Reduced BMD, n (%) | 17 (65) | 6 (86) | 10 (91) | 14 (93) | 0.021 |
| Osteoporosis, n (%) | 11 (42) | 4 (57) | 7 (64) | 11 (73) | 0.047 |
| Osteopenia, n (%) | 6 (23) | 2 (29) | 3 (27) | 3 (20) | 0.893 |
| L1 BMD, g/cm ² | 0.82 (0.77~1.02) | 0.74 (0.55~0.97) | 0.60 (0.51~0.82) | 0.72 (0.61~0.85) | 0.091 |
| L1 T-score | -2.3 (-2.7~-0.6) | -2.7 (-4.30~-0.90) | -2.7 (-4.7~-2.1) | -2.9 (-4.1~-2.2) | 0.032 |
| L1~4 BMD, g/cm ² | 0.90 (0.85~1.07) | 0.89 (0.54~1.23) | 0.72 (0.60~0.95) | 0.82 (0.75~0.88) | 0.081 |
| L1~4 T-score | -2.1 (-2.7~-0.8) | -2.7 (-5.1~-0.5) | -3.6 (-4.5~-1.9) | -3.0 (-3.6~-2.5) | 0.034 |

The data are presented as median (interquartile range) or number (%). BMD: bone mineral density; L: lumbar spine.

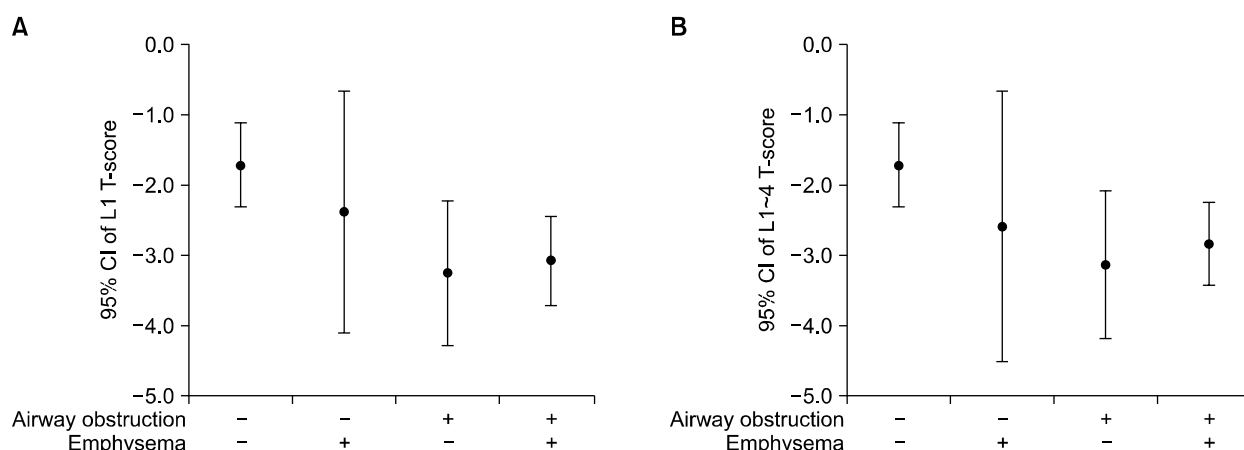


Figure 3. (A, B) T-scores of L1 and L1~4 in four groups. CI: confidence interval.

Table 3. Parameters of demography, lung function, and CT and correlation with BMD (n=59)

| Variables | Median | IQR | L1 (g/cm ²) | | L1~4 (g/cm ²) | | L1 T-score | | L1~4 T-score | |
|-----------------------------------|--------|--------|-------------------------|--------|---------------------------|-------|------------|--------|--------------|--------|
| | | | r* | p | r | p | r | p | r | p |
| Age, yr | 73 | 65~79 | -0.170 | 0.198 | -0.182 | 0.167 | -0.159 | 0.229 | -0.185 | 0.160 |
| BMI, kg/m ² | 21 | 18~24 | 0.471 | <0.001 | 0.431 | 0.001 | 0.520 | <0.001 | 0.466 | <0.001 |
| FVC% predicted | 83 | 62~99 | 0.188 | 0.154 | 0.195 | 0.140 | 0.208 | 0.113 | 0.207 | 0.116 |
| FEV ₁ % predicted | 76 | 45~104 | 0.282 | 0.030 | 0.225 | 0.087 | 0.330 | 0.011 | 0.254 | 0.052 |
| FEV ₁ /FVC, % | 67 | 46~76 | 0.356 | 0.006 | 0.249 | 0.057 | 0.409 | 0.001 | 0.284 | 0.030 |
| FEF _{25-75%} % predicted | 44 | 17~68 | 0.414 | 0.001 | 0.332 | 0.010 | 0.438 | 0.001 | 0.345 | 0.007 |
| LAA% | 6.2 | 1.1~19 | -0.222 | 0.091 | -0.172 | 0.194 | -0.275 | 0.035 | -0.221 | 0.092 |

*Pearson's correlation coefficient.

BMD: bone mineral density; IQR: interquartile range; BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; FEF_{25-75%}: forced expiratory flow at 25~75% of FVC; LAA%: computed tomography (CT) measurement of the percentage of low attenuation area less than -950 Hounsfield Units.

phenotypes, emphysema, airway obstruction, and a mixture of these. Since emphysema patients without airway obstruction had markedly variable level of BMD shown in Figure 3 and the number of those was too small, we need further data. Patients with airway obstruction, even without emphysema, could have higher risk of reduced bone density than those with only emphysema. Similarly, while the prevalence of osteoporosis was the highest among subjects with both of airway obstruction and emphysema, it was higher among subjects with only airway obstruction than those with only emphysema. We assume that airway inflammation contributing to airway obstruction may closely related to systemic inflammation, which affects decrease in

bone density.

In the present study, BMI is the most important factor associated with BMD. It is consistent with the results of previous studies^{1,2,4,6,7,9,10}. In the general population, low BMI has also been identified as a risk factor for osteoporosis¹⁷. The link between low BMI and low BMD in COPD could be increased inflammation, decreased physical activity and/or other mechanisms leading to proteolysis¹⁸⁻²⁰. If osteoporosis is a result of systemic inflammation of COPD, BMI rather than airway obstruction or emphysema is likely to reflect systemic inflammation and more important predictor of osteoporosis. Another explanation for more osteoporosis in patients with lower BMI could be that bone formation

is decreased because there is relatively low mechanical loading on these bones. Indeed, astronauts lose as much bone mass in a 1-month spaceflight as postmenopausal females in 1 year²¹. In addition, COPD patients have been shown to be physically inactive compared with age-matched healthy subjects²².

Even though each of FEV₁, FEV₁/FVC, and the extent of emphysema was related to BMD, FEF_{25-75%} showed significant association with BMD in our population. FEF_{25-75%} is known to be a good indicator of small airway obstruction. It was reported to be lower in asymptomatic male smoker compared to male non-smokers and correlated with eosinophilic inflammation in childhood asthma^{23,24}. Thus, it seems to be a marker of early airway inflammation induced by smoking or allergy. Our study design including subjects without airway obstruction may let FEF_{25-75%} be more associated with BMD than FEV₁. On the other hand, the extent of emphysema lost statistical significance when using multiple linear regression analysis. It is different from the study of Ohara et al.⁹. They showed that the extent of emphysema and BMI were predictive of BMD rather than FEV₁. The discordance may be due to different study population. While our study included not only COPD patients but also subjects without COPD and female, they studied only male COPD patients. A lower FEV₁ has been shown to be correlated with a low BMD^{7,10}. Also, in subjects without COPD, significant correlations between FEV₁ and BMD have been found²⁵⁻²⁷. These relationships between lung function parameters and BMD are complex and not yet clear. Again, in COPD patients, systemic inflammation can be a key factor, as reduced lung function has been found to be associated with increased inflammatory markers, which is a risk factor for osteoporosis²⁸. However, emphysema is not correlated with functional impairment as much as spirometric parameters and expected to lesser reflect process of systemic inflammation. It is also possible that there is no causal relationship between lung function and BMD. Perhaps reduced physical activity because of impaired lung function is the reason for reduced BMD²⁹.

There are several limitations in this study. The most

important limitation was a small number of subjects. However, even with the relatively small population, we were able to demonstrate the strong correlations between the several parameters and BMD. Second, this study might have selection bias because of small sample size and controls being hospital user. However, results of this study are not different from previous study that BMD was related to more function of patients including disability of exercise due to dyspnea from airway obstruction than anatomical structure as emphysema. Third, we retrospectively selected subjects who had performed all three of BMD, spirometry, and CT. This might make selection bias and result in insufficient data collection of history of smoking, medication, and associated diseases. We did not have any data of osteoporosis-related biomarkers. Fourth, our classification not exactly corresponds to traditional phenotypes of COPD. However, in clinical practice, we often meet patients with emphysema and no airway obstruction. Fifth, we used FEV₁/FVC rather than FEV₁/VC recommended by American Thoracic Society/European Respiratory Society (ATS/ERS) guideline³⁰. Even LLN for the FEV₁/FVC ratio is enough to reduce the possibility of over-diagnosis of airway obstruction in our subjects over 40 years particularly compared to a fixed ratio of FEV₁/FVC < 0.7^{12,13}. Finally, postbronchodilator response was not measured. This study might include some subjects with reversible obstruction. Large randomized-controlled study should be required, later.

Our study suggested that BMI is the most important factor associated with reduced bone density in adults over 40 years regardless of airway obstruction and/or emphysema. Osteoporosis is more prevalent in patients with airway obstruction and emphysema. Airway obstruction seems to be more associated with bone density rather than does the extent of emphysema possibly due to physical inactivity and systemic inflammation.

Acknowledgements

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