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ORIGINAL RESEARCH

Exploring the Association Between Emphysema Phenotypes and Low Bone Mineral Density in Smokers with and without COPD

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Rationale: Emphysema and osteoporosis are tobacco-related diseases. Many studies have shown that emphysema is a strong and independent predictor of low bone mineral density (BMD) in smokers; however, none of them explored its association with different emphysema subtypes.

Objective: To explore the association between the different emphysema subtypes and the presence of low bone mineral density in a population of active or former smokers with and without chronic obstructive pulmonary disease (COPD).

Methods: One hundred and fifty-three active and former smokers from a pulmonary clinic completed clinical questionnaires, pulmonary function tests, a low-dose chest computed tomography (LDCT) and a dual-energy absorptiometry (DXA) scans. Subjects were classified as having normal BMD or low BMD (osteopenia or osteoporosis). Emphysema was classified visually for its subtype and severity. Logistic regression analysis explored the relationship between the different emphysema subtypes and the presence of low BMD adjusting for other important factors.

Results: Seventy-five percent of the patients had low BMD (78 had osteopenia and 37 had osteoporosis). Emphysema was more frequent (66.1 vs 26.3%, p=<0.001) and severe in those with low BMD. Multivariable analysis adjusting for other significant cofactors (age, sex, FEV_1, and severity of emphysema) showed that BMI (OR=0.91, 95% CI: 0.76–0.92) and centrilobular emphysema (OR=26.19, 95% CI: 1.71 to 399.44) were associated with low BMD.

Conclusion: Low BMD is highly prevalent in current and former smokers. BMI and centrilobular emphysema are strong and independent predictors of its presence, which suggests that they should be considered when evaluating smokers at risk for low BMD.

Keywords: emphysema, COPD, low bone mineral density, osteopenia, osteoporosis; smokers

Introduction

Tobacco smoking has long been identified as a risk factor for osteoporosis. Many studies have shown that smokers have decreased bone mineral density (BMD) with increased risk fracture compared to nonsmokers, particularly at the hip.[1] Additionally, a recent study demonstrates that current smokers show a more rapid BMD decline over time compared to former smokers.[2]

It is well known that chronic obstructive pulmonary disease (COPD) is one of the most common diseases related to cigarette smoke, and several and large epidemiologic studies have demonstrated an increased prevalence of osteopenia

and osteoporosis in these patients.[3] The prevalence of low BMD in the absence of steroid use in patients with mild airflow limitation[4,5] suggests a pathogenic link between the lung and the skeleton different from traditional osteoporosis risk factors.

Smokers with and without COPD also have the destruction of lung parenchyma called emphysema. In fact, two recent studies suggest that emphysema could be an independent marker of low BMD in smokers; one performed in patients with COPD[6] and the other also including patients without COPD.[7] The similarities between emphysema and osteoporosis, with potential mechanisms linking the two processes (loss of extracellular matrix and the association with inflammatory mediators, such as tumor necrosis factor-α)[8,9] support this hypothesis. Interestingly, both studies showed in the multivariate analysis that emphysema remained a significant predictor of low BMD, whereas airflow obstruction severity did not. These findings were later replicated in other studies.[10,11]

However, none of these studies have explored the association of different emphysema subtypes (centrilobular, panlobular and paraseptal) and the presence of low BMD. Centrilobular emphysema (CLE) is associated with a higher smoking history,[12,13] a unique systemic chronic inflammation[12] and a protease-antiprotease misbalance,[14] that is also associated with osteoporosis.[15,16] Therefore, we hypothesized that it is likely that CLE emphysema is associated with low BMD. The main objective of our study is to describe the association of different emphysema subtypes with the presence of low BMD.

Methods

Participants

One hundred and fifty-three consecutive active and former smokers from the pulmonary department of the Clínica Universidad de Navarra were invited to participate between August 2014 and March 2016. Study subjects were men 50 years of age or older and postmenopausal women, with a smoking history of ≥10 pack-years. Those who had a previous diagnosis of osteoporosis and/or were using preventive treatment for osteoporosis were excluded. None of the subjects were under oral corticosteroid treatment. All subjects signed an informed consent prior to enrollment and the protocol was approved by the Institution's ethics committee (Comité de Ética Clínica Universidad de Navarra, number151/2014). The study was conducted in accordance with the Declaration of Helsinki.

Patients were evaluated during their initial visit and each subject underwent a medical history and physical examination, including a questionnaire administered by the same investigator that registered their age, race, body mass index (BMI), menopause information, fracture history (including family history), tobacco and alcohol intake history, medication use in the past and present, and number of respiratory exacerbations in those with a previous diagnosis of COPD. These exacerbations were defined following the global initiative for chronic obstructive lung disease (GOLD) guidelines[17] as an acute worsening of respiratory symptoms that result in the use of additional therapy.[18] Patients underwent pulmonary function tests (PFTs), 6-minute walking distance (6MWD), bone densitometry (BMD measurement) and a low-dose chest-computed tomography (LDCT).

Figure 1 shows the Flowchart of the included individuals. One hundred and sixty-four patients were initially evaluated but 11 patients were excluded because they met the exclusion criteria. One hundred and fifty-three patients were finally included in the analysis (69 females and 84 males), 104 patients with COPD and 49 without.

Pulmonary Function Tests (PFTs)

Airway function (spirometry, lung volumes and diffusing capacity) was measured in all participants using a flow spirometer (Vmax22; SensorMedics, Yorba Linda, CA) according to guidelines of the American Thoracic Society.[19] Results were expressed as a percentage of the predicted value according to the European Community Lung Health Survey.[20] All post-bronchodilation measurements were determined 15 minutes after the inhalation of

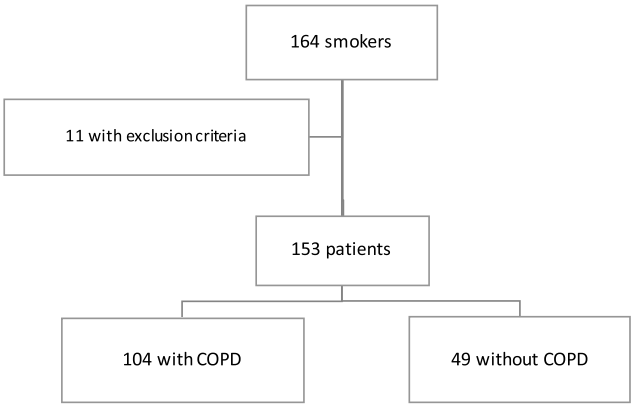

Figure 1 Flowchart showing the inclusion of the participant.

400 µg of salbutamol. The presence and severity of airflow obstruction was determined using criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD; post bronchodilation forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio <70%).[17] The 6MWD was performed following the current American Thoracic Society guidelines.[21]

Bone Density by Dual X-Ray Absorptiometry

A dual X-ray absorptiometry (DEXA) technique with a Lunar iDXA scan (General Electric Co) was used to measure the bone mineral density of the lumbar spine (L1 to L4), femoral neck, total hip and in some cases non-dominant forearm (33%). Diagnosis of osteoporosis was based on the lowest T-score of these locations and defined according to the world health organization (WHO) criteria (osteoporosis: T-score≤-2.5; osteopenia or low bone mass: T-score <-1.0 and >-2.5; and normal bone mass: T-score ≥ −1.0).[22]

All DXA scans were interpreted by a physician certified by ISCD and following standard quality control procedures, including daily phantom scanning. Coefficient of variation was 1% for L1-L4 BMD and 1.1% for total hip BMD.

Low-Dose Chest CT (LDCT)

Patients were scanned using a sixty-four slice multidetector CT scanner (Somatom Sensation 64, Somatom Definition, Siemens Healthcare, Erlangen, Germany) at a low-dose setting (120 kV tube voltage, 40 mAs tube current, 64x0.6 mm slice collimation, 0.5 s gantry rotation time, 1.4 pitch, 1 mm slice thickness, 1 mm reconstruction interval). Examinations were acquired with patients in the supine position, in cranio-caudal direction and at end-inspiration. Resulting images were reconstructed with a high convolution reconstruction algorithm (B60) and lung window.[23]

Assessment of Emphysema on LDCT

A pulmonologist (JG) visually assessed the emphysema presence, type and severity, using validated criteria established by the Fleischner Society.[24] Following these guidelines, pulmonary emphysema was classified into three subtypes: centrilobular (CLE), panlobular (PLE) and paraseptal (PSE). To determine the emphysema severity, a five-level semiquantitative scale based on criteria used in the National Emphysema Treatment Trial was used.[25] However, no division of the lung into different zones was undertaken. Therefore, severity was assessed using this scoring system throughout the whole lung.

Statistical Analysis

Statistical analysis was performed using STATA. Normal distribution of samples was assessed by the Shapiro–Wilks tests. Quantitative data are represented as mean ± SD or median (interquartile range), depending on the data distribution; relative frequencies were used for qualitative data. Differences between study groups were evaluated by the Student's t test for normally distributed variables, the Mann–Whitney U-test for non-normally distributed variables, and χ^2 statistics for categorical variables. Uni- and multivariable logistic regression analyses were performed to study the potential independent association between low BMD and the studied parameters. The multivariable analysis included age, sex, BMI, FEV_1, severity and subtype of emphysema.

Results

According to the results of the DXA scan, 38 patients (24.8%) had normal BMD and 115 (75.2%) low BMD, including 78 (50.9%) subjects with osteopenia and 37 (24.2%) with osteoporosis. Subjects with low BMD tended to be women (50.9% vs 26.3%; p=0.008) with lower BMI (26.4 vs 29.7 Kg/m2; p=<0.001) (Table 1). No significant differences were found in the smoking history or in the use of inhaled steroids. No differences were found in the proportion of COPD patients in both groups. However, emphysema was more frequently found in the group with low BMD (66.1% vs 26.3%; p=<0.001). There were also differences between the emphysema subtypes (p=<0.001) with CLE, alone (31.3% vs 7.9%) or in combination with PSE (30.4% vs 13.2%), being most frequent in the low BMD group. Furthermore, emphysema was more severe in this group of patients. Regarding the lung function, FEV_1 and DLCO were lower in the group with low BMD that walked fewer meters in the 6MWD.

In the univariate analysis, the presence and severity of emphysema was associated with the presence of low BMD (OR=5.45; CI: 2.40–12.37; p=<0.001; OR=1.83; CI: 1.19–2.81 p=0.006, respectively) (Table 2). Interestingly, CLE subtype showed a greater risk of having a low BMD (OR=8.61; CI: 2.40–30.79; p=0.001), that decreased when its presence is combined with PSE (OR=5.02; CI: 1.74–14.43; p=0.003). However, PSE alone does not seem to have an effect on the presence of low BMD (OR=1.79; CI: 0.32–9.92; p=0.503). Other predictive factors for low BMD were male sex (OR=0.34; CI: 0.15–0.77; p=0.010), BMI (OR=0.84; CI:

Table 1 Baseline Clinical, Radiographic and Densitometric Characteristics of Patients with and without Low Bone Mineral Density (Osteopenia and Osteoporosis)

Characteristics	Normal Bone Density (n=38)	Low Bone Mineral Density (n=115)	p value
Demographic			
Age years-old, Mean (SD)	61.4 (9.3)	63.5 (7.6)	0.175
Male, N_o (%)	28 (73.7)	56 (49.1)	0.008
BMI Kg/m^2, Mean (SD)	29.7 (4.3)	26.4 (4.5)	<0.001
Clinical			
Active smoker, N_o (%)	15 (39.4)	59 (51.3)	0.206
Pack-years of smoking, Median (IQR)	43.9 (28.5)	47.6 (28.9)	0.491
COPD, No (%)	22 (59.5)	82 (71.9)	0.155
Inhaled steroids, No (%)	7 (19.4)	32 (28.1)	0.304
Radiographic			
Emphysema, N_o (%)	10 (26.3)	76 (66.1)	<0.001
Type of emphysema, No (%)			<0.001
Centrilobular alone	3 (7.9)	36 (31.3)	
Centrilobular and paraseptal	5 (13.2)	35 (30.4)	
Paraseptal alone	2 (5.3)	5 (4.3)	
Severity of emphysema, by NETT (0–4), Median (IQR)	0.5 (1)	1.1 (1)	0.004
Pulmonary function tests			
FVC-L, Mean (SD)	4.1 (0.9)	3.5 (1.2)	0.052
FVC-%, Mean (SD)	114.5 (20.6)	114.9 (24.6)	0.952
FEV_1-L, Mean (SD)	2.5 (0.7)	2 (0.8)	0.007
FEV_1-%, Mean (SD)	88.8 (19.2)	81.1 (25.6)	0.161
FEV_1/FVC, Median (IQR)	62.6 (12.4)	56.9 (14)	0.077
DLCO-mL/min/mmHg, Mean (SD)	20.7 (5.7)	18.8 (6.2)	0.008
DLCO-%, Mean (SD)	80.3 (18.9)	69.2 (21.1)	0.026
6MWT-meters, Median (IQR)	534.2 (103.5)	479 (109.2)	0.031

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartil range (25–75 percentile); NETT, national emphysema treatment trial; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BODE, Body-mass index, airflow Obstruction, Dyspnea, and Exercise; FVC, forced vital capacity; FEV1, forced expiratory volume-one second; DLCO, diffusing capacity for carbon monoxide; 6WMT, six minutes walking test.

0.76–0.92; p=<0.001), FEV_1 (OR=0.43; CI: 0.24–0.80; p=0.008) DLCO (OR=0.90; CI: 0.83–0.97; p=0.012) and the 6MWD (OR=0.99; CI: 0.98–0.99; p=0.034). A spirometric diagnosis of COPD did not show any relationship with the presence of low BMD (OR=1.74; CI: 0.80–3.78; p=0.157).

Multivariable logistic regression analysis was constructed based on a model of risk factors that included those that either reached a statistically significant difference in the univariable analysis or are well-known factors associated with low BMD.

Table 2 Predictors of Low Bone Mineral Density (Osteopenia/ Osteoporosis) in Current and Former Smokers, Univariate Analysis

Variables	OR	IC 95%	P value
Age years-old	1.03	0.98–1.08	0.176
Male	0.34	0.15–0.77	0.010
BMI Kg/m^2	0.84	0.76–0.92	<0.001
Active smoker	1.61	0.76–3.40	0.208
Pack-years	1	0.99–1.01	0.490
Inhaled steroids	1.61	0.64–4.06	0.307
COPD	1.74	0.80–3.78	0.157
BODE	1.51	0.92–2.47	0.099
Post-bronchodilator FEV_1 (L)	0.43	0.24–0.80	0.008
DLCO (mL/min/mmHg)	0.90	0.83–0.97	0.012
6MWT meters	0.99	0.98–0.99	0.034
Emphysema	5.45	2.40–12.37	<0.001
Severity of emphysema, by NETT (0–4)	1.83	1.19–2.81	0.006
Type of emphysema			
Centrilobular alone	8.61	2.40–30.79	0.001
Centrilobular and paraseptal	5.02	1.74–14.43	0.003
Paraseptal alone	1.79	0.32–9.92	0.503

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; BMI, body mass index; NETT, national emphysema treatment trial; FEV1, forced expiratory volume-one second; DLCO, diffusing capacity for carbon monoxide; 6WMT, six minutes walking test.

The model included age, sex, BMI, FEV_1, severity and type of emphysema. Only BMI and the presence of CLE were significantly associated with low BMD (Table 3). The relationship between the different emphysema subtypes and the risk of low BMD, was only with those that had CLE alone or in combination with PSE while those patients with PSE alone were not associated with the presence of low BMD.

Table 3 Predictors of Low Bone Mineral Density (Osteopenia/ Osteoporosis) in Current and Former Smokers, Multivariate Analysis

Variables	OR	IC 95%	P value
Age years-old	1.02	0.94–1.10	0.577
Male	0.39	0.09–1.61	0.194
BMI Kg/m^2	0.91	0.76–0.92	<0.001
Post-bronchodilator FEV_1 (L)	0.54	0.23–1.27	0.161
Severity of emphysema, by NETT (0–4)	0.46	0.17–1.19	0.112
Type of emphysema			
Centrilobular alone	26.19	1.71–399.44	0.019
Centrilobular and paraseptal	23.53	2.03–272.62	0.011
Paraseptal alone	4.23	0.31–57.68	0.278

Abbreviations: BMI, body mass index; NETT, national emphysema treatment trial; FEV1, forced expiratory volume-one second.

Discussion

The most important and novel finding of the present study in a population of active or former smokers is that the presence of a specific emphysema phenotype (CLE) and a low BMI were the best predictors of the presence of a low BMD in the bone densitometry. But most importantly, this association was independent of the most common risk factors for low BMD and of the presence and degree of airflow obstruction.

Evidence shows that BMI is one of the modifiable factors affecting BMD,[26] being protective in older subjects if high[27–30] and considered a high-risk factor for osteoporosis if low.[31,32] Moreover, many studies corroborate that low BMI is associated with low BMD and fractures.[33,34] Even more, a study showed that voluntary weight loss in overweight elderly women increases bone loss suggesting their tight relationship.[35] Interestingly, the fundamental basis of emphysema is loss of lung tissue and recent data from the literature shows that emphysema is often associated with less tissue in other body compartments such as BMI, muscle wasting measured as a lower fat-free mass index (FFMI)[36,37] as well as low BMD.[6,7,10] Likewise, a recent study shows that at baseline, patients with more severe emphysema had lower BMI, lower FFMI and a higher prevalence of self-reported osteoporosis.[38] The results of our study are in accordance with this groundswell of literature and support the hypothesis of tissue wasting associated with those smokers that developed emphysema.

The independent association of radiographic emphysema and low BMD observed in several studies and in ours suggest a common pathogenic link between lung parenchymal destruction and bone loss. There is a growing body of literature promoting a central pathophysiologic role of chronic inflammation in emphysema to explain this link. Accelerated bone loss and osteoporosis are explained by the imbalance between bone formation by osteoblasts and bone resorption by osteoclasts, which are managed by a complex network of inflammatory cells and cytokines.[39,40] For example, interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6 and IL-17, all stimulators of osteoclastic bone resorption, have been implicated in emphysema in both human and animal models.[8,9,41–45] Moreover, it has been shown a correlation between plasma TNF-α levels with plasma collagen type I cross-linked C-telopeptide (CTX) levels, a marker of bone resorption in patients with severe obstructive lung disease,[46] indicating an increased bone turnover in these patients. This inflammatory theory could result in protease-antiprotease imbalance leading to tissue destruction in both lungs and bone, being these certain inflammatory proteins markers of bone turnover or bone mineral density. In this regard, Bolton et al[16] reported higher levels of metalloproteinase 9 (MMP-9) in patients with COPD and osteoporosis compared with a control group of COPD without osteoporosis. Furthermore, the relationship between MMP-9 and bone density was independent of lung function. Interestingly, these inflammatory proteins such as TNF-α and MMP-9 have been also implicated in emphysema.[9,43,47] This is just a proposed explanation for the potential link between emphysema and low BMD, because unfortunately none of these inflammatory makers were measured in the present study. Further, well-designed studies should explore this pathogenically link to explain our findings.

The finding that CLE is the phenotype specifically associated with low BMD independently of the most important risk factor is novel and important. This emphysema subtype is the one usually associated with tobacco smoking,[12,13] with a higher chronic systemic inflammation response and a specific lung repair mechanism unique to the exposure and probably due to a different genetic predisposition, although this has not been shown yet. Patients with CLE have higher white blood cells counts[12] and a unique protease-antiprotease balance, characterized by a higher expression of matrix metalloproteinase 9 (MMP9) and transforming growth beta 1 (TGB1),[14] which could explain the potential link with osteoporosis.[15,16] In contrast, patients with paraseptal emphysema (PSE) usually have less respiratory symptoms and do not affect the lung function decline typically seen in patients with CLE.[12] Furthermore, PSE occurs even in the absence of tobacco exposure and may depend on age and genetic susceptibility, but again this needs to be shown.

The main strength of the present study is that all major risk factors for low BMD in smokers were considered, including lung function and COPD diagnosis, presence of radiological emphysema and its types, usually not explored in other groups. Another strength is that an equal number of men and women were included in our sample. The present study also had several limitations. Firstly, it is a relatively small sample size with a low number of patients with osteoporosis, but they were very well characterized and studied. Secondly, the findings of the present work should be replicated in another cohort

with more cases of PLE and PSE alone to externally validate its most important messages.

In summary, the present study shows that in active or former adult smokers, the specific subtype of CLE associates with low BMD and low BMI. These findings if reproduced in other cohorts could have important clinical implications for the management of these patients.

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Disclosure

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