Radiographic Emphysema, Circulating Bone Biomarkers, and Progressive Bone Mineral Density Loss in Smokers

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Abstract

Rationale: Osteoporosis is common in individuals with chronic obstructive pulmonary disease. Lung-specific factors, including radiographic emphysema, independently associate with low bone mineral density in cross-sectional smoking cohorts. However, factors associated with progressive bone loss in smokers are understudied and largely unknown.

Objectives: To determine the relationship between radiographic emphysema, circulating bone metabolism markers, and pulmonary function and accelerated bone mineral density loss in smokers.

Methods: Two hundred and forty male and female current and former smokers, 40 years of age or older, underwent baseline and 2-year assessments of pulmonary function, computed tomography–assessed emphysema, dual X-ray absorptiometry–measured bone mineral density, and circulating bone metabolism biomarker levels (type I collagen C-telopeptide [CTX], amino-terminal propeptide of type I procollagen [PINP]). The association of radiographic emphysema, bone metabolism biomarker levels, and pulmonary function with accelerated hip bone mineral density loss, defined by the 75th percentile of annual hip bone mineral density decline, was determined by logistic regression modeling with adjustment for age, sex, inhaled and intermittent steroid use, active smoking, body mass index, and the presence of baseline low hip bone mineral density.

Results: Of those participants with accelerated hip bone mineral density loss, 22% had moderate or severe visually assessed emphysema compared with 7.2% of smokers without accelerated bone mineral density decline. Moderate to severe visually assessed emphysema (odds ratio, 2.84; 95% confidence interval, 1.01–7.98 compared with trace/mild or no visually assessed emphysema) and the 75th percentile of CTX levels (odds ratio, 2.38; 95% confidence interval, 1.20–4.72 compared with CTX levels below the 75th percentile), a marker of bone resorption, were associated with accelerated hip bone mineral density decline after adjustment for covariates and the presence of baseline low hip bone mineral density. FEV₁% predicted was not associated with accelerated bone mineral density decline after adjustment for covariates. Multivariate modeling showed moderate to severe visually assessed emphysema, and the 75th percentiles of CTX were independently associated with accelerated hip bone mineral density decline after adjustment for covariates.

Conclusions: Emphysema and elevated markers of bone resorption are independently associated with progressive bone mineral density loss in smokers. These clinical markers may guide targeted bone mineral density screening and monitoring in smokers at highest risk.

Keywords: chronic obstructive pulmonary disease; osteoporosis; biomarkers

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The prevalence of comorbidities, including osteoporosis, is increased in chronic obstructive pulmonary disease (COPD) across the spectrum of airflow obstruction severity. Vertebral and hip fractures resulting from low bone mineral density (BMD) in patients with COPD have been associated with impaired lung function, worse quality of life, and increased mortality (1–4). Notably, the increased occurrence of osteoporosis in COPD cannot be explained solely by osteoporosis risk factors frequently present in individuals with severe lung disease (i.e., the use of systemic steroids or low body mass index), as established by cross-sectional studies showing an increased prevalence of low BMD in individuals with mild spirometric airflow obstruction (5–9). In cross-sectional cohorts, our group (9) and others (10, 11) have shown that both visually assessed and quantitative emphysema on computed tomographic (CT) scan of the chest are associated with low BMD and fractures independent of airflow obstruction or the presence of traditional osteoporosis risk factors. These studies have speculated that common inflammatory pathways may link emphysema and BMD, although mechanistic studies investigating the causative relationship between lung parenchymal destruction and bone loss are lacking. As the acquisition of low-dose chest CT scans becomes routine in smokers at high risk for lung cancer, emphysema data will be available in a larger proportion of current and former smokers. Markers of bone metabolism, which can be measured by most clinical laboratories, have likewise been shown to be associated with cross-sectional measurements of BMD (12). Whether these easily assessed clinical factors are associated with rapid BMD decline is unknown.

Over the past decade, a number of smoking cohorts have been established with the goal of refining clinical COPD phenotypes and to study the association of these phenotypes with genotypes, patterns of inflammation, and disease outcomes (13, 14). Although these large cohorts have been used in attempts to study osteoporosis in smokers with and without airflow obstruction, they are limited by the lack of systematic, “gold standard” BMD assessments and biased by the inherent inaccuracy of patient-reported osteoporosis diagnosis. Studies that do obtain BMD assessments are most often cross-sectional

in nature and provide no information regarding factors associated with progressive BMD loss, an important risk factor for osteoporotic fracture distinct from absolute BMD (15). We have established a longitudinal cohort of current and former smokers with serial measurements of BMD to determine clinical factors associated with accelerated BMD decline. We hypothesize that radiographic emphysema (the primary exposure of interest) and markers of bone metabolism (the secondary exposures of interest) are independently associated with rapid BMD decline, particularly in early disease where risk factors such as frailty and steroid use are rare. We further hypothesize, based on our cross-sectional investigations (9), that the presence and severity of airflow obstruction are not independently associated with accelerated BMD loss in current and former smokers. Some of this work has been previously included in the master’s thesis of one of the authors (J.B.) at the University of Pittsburgh (16).

Methods

Participants

The study sample consisted of 240 male and female consecutive participants in the single-center, COPD Specialized Center of Clinically Oriented Research (SCCOR) cohort at the University of Pittsburgh, recruited over a 2-year period beginning in July 2008. All SCCOR participants were current or former smokers, 40 years of age or older, with a minimum 10-pack-year tobacco history at enrollment. SCCOR participants were recruited primarily from the larger Pittsburgh Lung Screening study (PLuSS) cohort, a single-center, tobacco-exposed cohort at the University of Pittsburgh. Only a subset of PLuSS cohort participants had spirometrically confirmed airflow obstruction (FEV_1/FVC less than 0.70). SCCOR participants were selected from the PLuSS cohort to enhance the extremes of visually assessed emphysema and airflow obstruction without *a priori* knowledge of BMD. Exclusion criteria for the SCCOR cohort included chronic, daily prednisone use, clinical or radiographic evidence of another pulmonary diagnosis (e.g., interstitial lung disease), history of lung cancer or a new, suspicious nodule on CT scan, and body mass index (BMI)

greater than 34. Participants were further excluded from the current analysis if they were being actively treated with bone-modifying or hormone replacement therapy during the 2-year study interval. Female participants were postmenopausal at the time of study entry. All eligible participants were ambulatory. Participants underwent study procedures at baseline and at a 2-year follow-up study visit. The study protocol was approved by the University of Pittsburgh Institutional Review Board. Written informed consent was obtained for each participant.

Measures

Each participant completed a chest CT scan, pre- and post-bronchodilator spirometry, measurement of lung diffusion capacity, demographic and medical history questionnaires, and dual X-ray absorptiometry (DXA) measurements of hip and lumbar spine BMD at baseline and at 2 years. Physical activity levels were quantified at baseline and 2-year follow-up, using the Stanford Brief Activity Survey, a validated, five-point activity questionnaire that addressed both on-the-job and leisure activity levels (17). The Stanford Brief Activity Survey asks participants to rate their on-the-job and leisure physical activity levels, each on a five-point scale, a value of 1 being most sedentary and a value of 5 corresponding with hard physical labor or regular, vigorous leisure activities. An average of these two scores was taken for this analysis. Symptoms were assessed with the Saint George’s Respiratory Questionnaire (SGRQ) at baseline and at 2 years, and the results are reported as the total SGRQ score. The SGRQ total score has a range of 0 to 100, with a difference of 4 being the minimal clinically important difference. BMI was assessed at each study visit. Blood specimens were collected on the morning of the baseline and 2-year study visit, with the patient in a semifasting state.

Dual X-Ray Absorptiometry

A Discovery bone densitometer (Hologic Inc.) was used to measure absolute BMD (g/cm^2) of the total hip and total lumbar spine, which included lumbar vertebral bodies 1 through 4, at baseline and at 2 years. Absolute BMD was converted to a *T*-score, which represents the number of SDs the measured BMD deviates from the mean BMD of a sex- and ethnicity-matched reference population at peak bone mass.

The NHANES (National Health and Nutrition Examination Survey) III database reference population was used to convert hip BMD measurements to *T*-scores (18) and the Hologic database reference population was used to convert lumbar spine BMD measurements to *T*-scores. We further classified participants into the following three groups based on their hip and lumbar spine *T*-scores: normal BMD (*T*-score ≥ -1.0), osteopenia ($-2.5 < T\text{-score} < -1.0$), or osteoporosis (*T*-score ≤ -2.5).

CT Scans

Radiographic emphysema was the primary exposure of interest. Noncontrast CT examinations were performed at baseline and at 2-year follow-up with a GE Healthcare LightSpeed VCT (64-detector) scanner. A chest radiologist, blinded to participant identities and characteristics, visually assessed the presence and severity of emphysema using a previously validated (19), six-point semiquantitative scoring system to define emphysema severity (0, none; 1, trace; 2, mild; 3, moderate; 4, severe; 5, very severe) corresponding to 0, less than 10, 10–25, 26–50, 51–75, and greater than 75% visually assessed emphysema. Visually assessed emphysema was then further categorized into none (visual score, 0), trace/mild (visual score, 1 or 2), or moderate/severe (visual score, 3, 4, or 5) to define three categories of visually assessed emphysema severity. To provide a quantitative emphysema measurement, the percentage of low attenuation areas (LAA%) was defined as the fraction of voxels less than –950 Hounsfield units as a percentage of total voxels, similar to the traditional density mask (20).

Biomarker Measurements

Circulating markers of bone metabolism, the secondary exposure of interest, were measured at baseline and at 2-year follow-up. Type I collagen C-telopeptide (CTX), released into the bloodstream during bone resorption and serving as a marker of mature type I collagen degradation (12), was measured by a commercially available electrochemiluminescence-based immunoassay (Roche Diagnostics). Amino-terminal propeptide of type I procollagen (P1NP), a marker of bone formation whose concentration reflects the synthesis of type I collagen (12), was measured with a commercial radioimmunoassay kit (Immunodiagnostic Systems Inc). Vitamin D levels were measured by ELISA in

duplicate. All samples were above the detection level for each measured biomarker.

Statistical Analysis

Absolute and percent change in hip and lumbar spine BMD over 2 years was calculated for each participant. Those participants falling within the 75th percentile of absolute BMD decline for the hip or lumbar spine were classified as having accelerated BMD loss at that anatomical site. The primary outcome of interest was the association of radiographic emphysema with accelerated BMD loss. The secondary outcomes of interest were the association of both markers of bone metabolism and FEV₁% predicted with accelerated BMD loss. Logistic regression analyses were performed to assess the association of primary and secondary exposures of interest with accelerated BMD loss.

Radiographic emphysema was included in models as either a categorical, visually assessed emphysema score (none, trace/mild, moderate/severe) or a quantitative, continuous variable (LAA%). Bone biomarkers were included in the models as continuous, binary (above or below median), and quartile-based categorical variables. Airflow obstruction was included in models as a continuous (FEV₁% predicted) or binary variable (airflow obstruction present, yes/no). The association of LAA%, serum levels of bone metabolism markers, and FEV₁% predicted with absolute and percent annual change in BMD was also assessed by generalized linear modeling. All models were adjusted for potential covariates either firmly established as risk factors for BMD loss in the literature (i.e., age, sex, intermittent systemic steroid use, active smoking, BMI) or associated with accelerated BMD loss in our cohort data (inhaled steroid use). Models were also adjusted for the presence of baseline low BMD at the respective anatomic site. A multivariate logistic regression model was built that included those primary and secondary exposures of interest that were independently associated with accelerated hip BMD loss adjusted for covariates. Likelihood ratio testing was used to determine whether the combination of primary and secondary exposures of interest in one model versus separate models for each exposure of interest significantly improved model fit. A sensitivity analysis, using a threshold

determined by the top 10th percentile of annual absolute hip BMD decline in smokers without lung disease to define accelerated hip BMD for the entire cohort, was also performed. Because DXA scans were added to the SCCOR protocol 1 year after cohort enrollment commenced, analyses were limited to those SCCOR participants with complete 2-year longitudinal radiographic, BMD, pulmonary function, and biomarker data. A sensitivity analysis using imputations assuming best-case (risk factor absent) and worst-case (risk factor present) scenarios was performed to address missing covariate data. A sample size of 240 participants was calculated to provide greater than 80% power to detect an odds ratio of 1.5 or higher of accelerated BMD loss in current and former smokers with visually assessed emphysema, assuming a 30% prevalence of low BMD in current and former smokers without visually assessed emphysema based on our prior published cross-sectional data (9). All statistical analyses were performed with SAS 9.2 (SAS Institute), Stata 13.1 (StataCorp LP), and PASS 14 (NCSS, LLC).

Results

Participant Characteristics

The mean age of the cohort was 64.3 years, with an equal sex distribution. One hundred and fifteen participants had visually assessed emphysema on baseline chest CT scan. The remaining 125 participants had no evidence of emphysema on visual assessment of their CT scan despite significant tobacco exposure (mean pack-years, 42.1 $\pm$ 23.1). Participants with visually assessed emphysema had greater pack-year smoking histories, lower BMI, more symptoms, greater inhaled corticosteroid use, lower physical activity levels, and lower vitamin D levels (Table 1). Nonetheless, of those with visually assessed emphysema, only 5% had low BMI ($<21.0 \text{ kg/m}^2$), only 18.4% used inhaled corticosteroids, and the median activity level was identical to those of participants without visually assessed emphysema, reflecting the overall mild disease severity within the cohort. Furthermore, physical activity levels, pack-year smoking histories, symptom scores, and vitamin D levels were similar between participants with and without accelerated BMD decline (Table 2). Only 29.2% of the cohort had moderate or severe airflow

Table 1. Participant characteristics

	All (N = 240)	No Emphysema (n = 125)	Emphysema (n = 115)
Age, mean (SD), yr	64.3 (5.6)	64.2 (5.7)	64.4 (5.6)
Sex, n (%), male	126 (52.5)	71 (56.8)	55 (47.8)
BMI, mean (SD)	28.4 (4.1)	29.5 (3.8)	27.1 (4.1)
Pack-years, mean (SD)	48.1 (25.2)	42.1 (23.0)	54.7 (25.9)
Current smoker, n (%)	102 (42.5)	50 (40.0)	52 (45.2)
Airflow obstruction, n (%)	100 (41.5)	23 (18.4)	76 (66.1)
LAA%, median (IQR)	0.6 (1.0)	0.4 (0.4)	1.1 (3.3)
FEV ₁ %, mean (SD)	85.2 (19.5)	93.0 (14.4)	76.7 (20.7)
Bone mineral density, n (%)			
Normal	97 (40.4)	64 (51.2)	33 (28.7)
Osteopenia	125 (52.1)	55 (44.0)	70 (60.9)
Osteoporosis	18 (7.5)	6 (4.8)	12 (10.4)
ICS use, n (%)	27 (11.3)	6 (4.8)	21 (18.4)
Oral steroid use,* n (%)	8 (3.3)	2 (1.6)	6 (5.3)
Activity score, median (IQR)	2 (1)	2 (0.5)	2 (1.0)
SGRQ total score, median (IQR)	13.95 (22.4)	9.8 (16.5)	20.8 (24.5)
Vitamin D, median (IQR), ng/ml	33.0 (27.4)	37.7 (28.5)	27.3 (23.0)
CTX, median (IQR), pg/ml	266.5 (203.5)	261 (214)	279 (190)
P1NP, median (IQR), pg/ml	28.4 (15.3)	28.1 (14.2)	30.3 (15.6)

Definition of abbreviations: BMI = body mass index; CTX = type I collagen C-telopeptide; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IQR = interquartile range; LAA% = low attenuation areas, tissue voxels with Hounsfield unit attenuation values < -950; P1NP = amino-terminal propeptide of type I collagen; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire. *Oral steroid use, temporary short-term use within the past 6 months.

obstruction, and one-third (32.9%) of participants with visually assessed emphysema on CT scan had no spirometric evidence of COPD. Data for primary and secondary exposures of interest were complete for all 240 participants. With the exception of one participant who was missing information regarding inhaled and oral steroid use, all covariate data were also complete.

Baseline Low Bone Mineral Density and Accelerated Bone Mineral Density Loss

The prevalence of baseline low BMD was high, with approximately 60% of the entire cohort having low BMD at either the hip or lumbar spine on baseline DXA assessment. Osteopenia and osteoporosis were significantly more common in cohort participants with visually assessed emphysema compared with unaffected smokers (71.3 vs. 48.8%; Table 1). Females had an annual median decrease in BMD at the hip of 0.005 g/cm², corresponding to a 0.47% annual median decrease, whereas males had an annual median decrease in hip BMD of 0.002 g/cm², corresponding to a 0.17% annual median decrease. Females and males within the 75th percentile of hip BMD loss had an annual 1.5 and 0.7% BMD decline, respectively. Lumbar spine

BMD increased by a median of 0.004 g/cm² annually in females and a median of 0.005 g/cm² annually in males, corresponding to an annual median percent increase in lumbar spine BMD of 0.41% and 0.46%, respectively. Only 31% of those participants with low BMD and 47% of those participants with accelerated BMD loss met current osteoporosis screening criteria.

Participants within the 75th percentile for annual decrease in hip or lumbar spine BMD showed an annual median loss of 0.013 g/cm² BMD per year (1.5% per year) at the hip and minimal change in BMD at the lumbar spine (0.56% decline). The remainder of the analyses focused on factors associated with accelerated BMD loss at the hip as there was not a significant decrease in lumbar spine BMD over 2 years, even in participants within the 75th percentile for lumbar spine BMD decline.

The Association of Radiographic Emphysema with Accelerated Hip BMD Decline

A greater proportion of cohort participants with moderate or severe visually assessed emphysema had accelerated BMD loss at the hip compared with those participants with no or only mild visually assessed emphysema (22 vs. 7.2%; $P = 0.001$). Moderate or severe visually assessed

emphysema was associated with accelerated hip BMD decline (odds ratio [OR], 3.65; 95% confidence interval [CI], 1.58–8.42 compared with trace/mild or no visually assessed emphysema), as was LAA% (OR, 1.26; 95% CI, 1.03–1.54 for every 5% increase in LAA%). The association between visually assessed emphysema, but not LAA%, remained significant (OR, 2.84; 95% CI, 1.01–7.98 compared with trace/mild or no visually assessed emphysema) after adjustment for age, sex, smoking status, inhaled and intermittent oral steroid use, BMI, and the presence of low hip BMD at baseline (Figure 1). LAA% was not associated with annual absolute or percent change in hip BMD in either unadjusted or adjusted linear regression modeling.

The Association of Circulating Markers of Bone Metabolism and Airflow Obstruction with Accelerated Hip BMD Decline

The circulating levels of CTX, a marker of bone resorption, were 312 (interquartile range [IQR], 241) pg/ml among those cohort participants with accelerated hip BMD decline and 261 (176) pg/ml in participants without rapid BMD decline. Circulating levels of P1NP, a marker of bone formation, were 28.1 (IQR, 19.4) pg/ml versus 28.4 (IQR, 14.0) pg/ml in participants with and without accelerated BMD loss, respectively. CTX levels in the 75th percentile were associated with accelerated hip BMD loss (OR, 2.78; 95% CI, 1.49–5.18 compared with CTX levels below the 75th percentile). Adjustment for age, sex, smoking status, intermittent steroid use, inhaled steroid use, BMI, and the presence of low baseline hip BMD did not impact the significance of these findings (OR, 2.38; 95% CI, 1.20–4.72 compared with CTX levels below the 75th percentile) (Figure 1). Circulating levels of CTX and P1NP were not associated with annual absolute or percent change in hip BMD in either unadjusted or adjusted linear regression modeling.

FEV₁% predicted was associated with accelerated hip BMD decline (OR, 0.16; 95% CI, 0.03–0.71 for every 1% increase in FEV₁% predicted) in unadjusted analysis but not when adjusted for age, sex, smoking status, intermittent oral steroid use, inhaled steroid use, BMI, and the presence of low baseline hip BMD (OR, 0.67; 95% CI, 0.09–5.13 for every 1% increase in FEV₁% predicted) (Figure 1). Likewise, the presence of airflow obstruction was not

Table 2. Participant characteristics stratified by the absence or presence of accelerated bone mineral density loss at the hip

	No Accelerated Loss (n = 181)	Accelerated Loss (n = 59)
Age, mean (SD), yr*	63.7 (5.4)	66.2 (6.0)
Sex, n (%),* male	109 (60.2)	17 (28.8)
BMI, mean (SD)*	28.8 (3.8)	27.2 (4.8)
Pack-years, mean (SD)	47.5 (25.4)	49.9 (24.5)
Current smoker, n (%)	79 (43.6)	23 (39.0)
Moderate or severe emphysema present, n (%)*	13 (7.2)	13 (22.0)
LAA%, median (IQR)	0.6 (0.8)	0.6 (3.4)
FEV ₁ %, mean (SD)*	86.9 (18.2)	79.8 (22.0)
GOLD, n (%)		
At risk	111 (61.3)	30 (50.8)
I (mild)	23 (12.7)	6 (10.2)
II (moderate)	41 (22.7)	18 (30.5)
III/IV (severe/very severe)	6 (3.3)	5 (8.5)
Bone mineral density, n (%)*		
Normal	75 (41.4)	22 (37.3)
Osteopenia	99 (54.7)	26 (44.1)
Osteoporosis	7 (3.9)	11 (18.6)
ICS use, n (%)*	14 (7.7)	13 (22.0)
Intermittent oral steroid use, [†] n (%)	5 (2.8)	3 (1.1)
Activity score, median (IQR)	2 (1)	2 (1.25)
Symptom score, median (IQR)	12.9 (22)	20.8 (23.9)
Vitamin D, median (IQR), ng/ml	32.8 (25.2)	34.2 (37.9)
CTX, median (IQR), pg/ml	261 (176)	312 (241)
P1NP, median (IQR), pg/ml	28.4 (14.0)	28.1 (19.2)

Definition of abbreviations: BMI = body mass index; CTX = type I collagen C-telopeptide; FEV₁ = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; IQR = interquartile range; LAA% = low attenuation areas, tissue voxels with Hounsfield unit attenuation values < -950; P1NP = amino-terminal propeptide of type I collagen; SD = standard deviation.

**P* < 0.05.

[†]Oral steroid use, temporary short-term use within the past 6 months.

associated with accelerated hip BMD loss (OR, 1.53; 95% CI, 0.85–2.77 compared with the absence of airflow obstruction).

A multivariable model including the level of visually assessed emphysema severity and CTX levels showed that both moderate and severe visually assessed emphysema (OR, 3.10; 95% CI, 1.09–8.80 compared with trace/mild or no visually assessed emphysema) and the 75th percentile of circulating CTX levels (OR, 2.50; 95% CI, 1.25–5.0 compared with CTX levels below the 75th percentile) are independently associated with accelerated BMD loss when age, sex, inhaled and intermittent oral steroid use, BMI, smoking status, and the presence of low hip BMD at baseline are accounted for in the model (Figure 1). Likelihood ratio testing, comparing adjusted models that included visually assessed emphysema severity with and without CTX levels and adjusted models that included CTX levels with and without visually assessed emphysema severity, showed that combining visually

assessed emphysema and CTX levels in one model improved model fit (*P* = 0.013 and *P* = 0.03, respectively). A sensitivity analysis using the top 10th percentile of absolute annual hip BMD decline for males and females without lung disease to define accelerated hip BMD for the entire cohort yielded similar results for visually assessed emphysema and CTX as predictors of hip BMD loss (see Table E1 in the online supplement). Further sensitivity analyses imputing the presence of inhaled and oral steroid use or the absence of inhaled or oral steroid use for the participant missing these covariate data showed that the missing data had no impact on the effect estimates for the primary or secondary exposures of interest in univariate as well as multivariate modeling (data not shown).

Discussion

We have shown that two clinical markers, visually assessed emphysema and serum

CTX levels, independently associate with accelerated BMD decline at the hip over a short follow-up interval. These findings validate the cross-sectional association between both visually assessed and quantitative emphysema and BMD described by our group (9) and others (10, 11) and provide potential clinical biomarkers to identify individuals at high risk of rapid BMD decline and who may benefit from early BMD assessment and intervention. Females had greater annual median bone loss than males at both the hip and lumbar spine, although adjustment for sex did not alter the association between radiographic emphysema, serum CTX, and accelerated BMD decline. Interestingly, osteoporosis risk factors often present in patients with significant lung disease, including active smoking, inhaled and intermittent systemic steroid use, and low BMI, did not alter the association of visually assessed emphysema and CTX levels with accelerated hip BMD decline. Further, FEV₁% predicted, although associated with accelerated hip BMD loss in univariate analysis, was not associated with accelerated BMD loss after adjustment for other known osteoporosis risk factors, suggesting that lung function *per se* may be a less useful marker of bone loss risk.

The impact of osteoporotic fractures on morbidity and mortality in individuals with COPD, combined with the high prevalence of COPD in the United States and worldwide, emphasizes the significance of this public health problem. Osteoporotic vertebral fractures lead to a reduced quality of life and diminished lung function in individuals already functionally limited by their underlying obstructive lung disease (3). Mortality rates related to hip fractures in individuals with COPD are 60–70% higher than rates following hip fracture in nonobstructed individuals, and the presence of obstructive lung disease itself can increase 1-year mortality rates up to fivefold that of the 1-year mortality rates of patients with COPD not sustaining a hip fracture (1). Primary prevention relies on appropriate osteoporosis screening, BMD assessment with DXA being the gold standard, and therapeutic intervention in high-risk individuals. Yet, little guidance exists regarding when to screen patients with COPD, as COPD-specific guidelines do not exist. Findings from our study, where only one-third of participants with low BMD and only one-half of participants

Figure 1. Forest plot depicting the association of primary and secondary exposures of interest with accelerated hip bone mineral density loss in individual models adjusted for age, sex, inhaled and intermittent oral steroid use, active smoking, body mass index, and the presence of baseline low hip bone mineral density (Individual Models, Adjusted) and primary and secondary exposures of interest independently associated with accelerated hip bone mineral density loss in a combined model adjusted for covariates (Combined Model, Adjusted). CTX = type I collagen C-telopeptide; FEV₁% = forced expiratory volume in 1 second.

with accelerated BMD loss met osteoporosis screening criteria (21, 22), would further suggest that general osteoporosis screening guidelines are not adequate for this population and that lung disease-specific factors should be considered when making osteoporosis screening decisions in COPD. Not only is recognizing the presence of low BMD crucial, but the recognition of individuals at risk for both short-term and long-term progressive BMD loss is particularly important as rapid bone turnover is an independent risk factor for fracture regardless of absolute BMD (15).

As a first step to refining osteoporosis screening strategies in smokers affected by lung disease, we aimed to focus on clinical factors associated with bone loss that can be easily assessed by practitioners without the use of specialized radiology software or laboratory assays. Under the current guidelines for lung cancer screening with chest CT imaging (23), data regarding the presence and severity of visually assessed emphysema are often clinically accessible in patients with a significant smoking history. Most clinical laboratories can also measure CTX levels. Given the accessibility of visually assessed emphysema and serum CTX levels, as well as previous studies showing that both factors are associated with cross-sectional measurements of BMD (9–12), we selected these factors as our primary and secondary exposures of interest, respectively, and found that both are likewise associated with rapid BMD

decline, an independent determinant of fracture risk (15). Furthermore, these two unrelated factors appear to complement one another and together improve the fit of our multivariate models. Whether a screening approach that includes these risk factors in addition to traditional risk factors (21) versus universal early osteoporosis screening in all smokers with lung disease is ultimately a cost-effective approach remains to be determined.

Our study has several advantages over larger epidemiologic studies examining the impact of lung disease on bone health in smokers. Studies assessing the prevalence of either low BMD using gold standard DXA assessments or osteoporotic fractures in smokers with lung disease rarely include detailed assessments of lung function or radiographic emphysema (4, 5). Those cohorts that aim to carefully phenotype smokers through pulmonary function testing and chest CT imaging often do not use gold standard assessments of BMD to define osteopenia or osteoporosis (11, 24–26), but rather rely on patient-reported osteoporosis or nonstandard BMD assessments. Unlike these studies, we combine gold standard DXA assessments of BMD with detailed physiologic and radiographic data in our longitudinal, albeit smaller, smoking cohort. The severity of lung disease in our cohort is skewed toward mild airflow obstruction with a mean FEV₁% predicted of 85.2%. Although our findings may not be generalizable to smokers with more severe airflow

limitation, we were able to study the association between our exposures of interest and BMD loss with few competing osteoporosis risk factors in smokers with early lung disease who still demonstrated significant hip BMD loss over a 2-year time interval. We are currently investigating factors impacting longer-term BMD decline, which we anticipate will be greater and may occur in a nonlinear fashion given that systemic inflammation may vary with lung disease activity (27–29). Nonetheless, the identification of factors associated with 2-year, short-term loss is clinically relevant as rapid bone turnover has been shown to be an independent risk factor for fracture (15) and early intervention in this high-risk group in particular may prevent future fracture.

We encountered several limitations during the analysis of our cohort data. To define accelerated BMD loss, an appropriate control population needs to be defined. Although population-based studies of healthy individuals are available (30–33) and have used either absolute percent loss or SD thresholds to define rapid BMD decline, these populations may not be appropriate for comparison in our cohort of current and former smokers with nonnormally distributed BMD change data. A definition of accelerated BMD loss derived from a smoking control population, although ideal, is not readily available in the published literature. To our knowledge, longitudinal cohorts of smokers in which BMD is systematically measured by DXA scan and pulmonary function and chest imaging data are available to rule out subclinical lung disease do not exist. We therefore selected an absolute 75th percentile threshold of hip BMD loss to define rapid BMD decline. Our results were further validated through a sensitivity analysis using alternative thresholds to define accelerated BMD decline. The lack of longitudinal cohorts of smokers with detailed physiologic, radiographic, and BMD assessments likewise limits our ability to validate our findings. Although we adjusted for sex in our multivariate analyses, an analysis stratified by sex may uncover differential risk factors for accelerated BMD decline. However, our sample size was too small to provide adequate power to detect sex-dependent risk factors. A final limitation of our study is the interpretation of visually assessed CT emphysema by a single radiologist. Although the evidence is compelling, additional work to define thresholds in larger populations, to

validate our findings, and to explore sex differences in BMD loss, is necessary.

In conclusion, we are the first to show that radiographic emphysema, along with serum markers of bone metabolism, associate with short-term, progressive

BMD decline in smokers. Our study is the first step in developing a precision medicine-based approach to osteoporosis screening that incorporates lung disease-specific biomarker measures associated with BMD loss to guide selection of the

most appropriate patients with COPD for osteoporosis screening and monitoring. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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