Radiographic Emphysema Predicts Low Bone Mineral Density in a Tobacco-exposed Cohort

Jessica Bon¹, Carl R. Fuhrman², Joel L. Weissfeld³, Steven R. Duncan¹, Robert A. Branch⁴, Chung-Chou H. Chang⁵, Yingze Zhang¹, Joseph K. Leader², David Gur², Susan L. Greenspan⁶, and Frank C. Sciruba¹

¹Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, ²Department of Radiology, ³Department of Epidemiology, ⁴Department of Clinical Pharmacology, ⁵Department of Biostatistics, and ⁶Division of Endocrinology, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

Rationale: Studies demonstrating an association between chronic obstructive pulmonary disease and low bone mineral density (BMD) implicate factors distinct from treatments and severity of lung disease in the pathogenesis of osteoporosis. Whereas emphysema has been independently associated with vascular disease and other comorbidities, its association with BMD has not been well studied.

Objectives: We explored the associations of BMD with computed tomography (CT) measures of emphysema and other risk factors in current and former smokers.

Methods: One hundred ninety subjects completed a CT scan, pulmonary function testing, questionnaires, and dual x-ray absorptiometry measurements of hip and lumbar spine BMD. Subjects were classified as having normal BMD, osteopenia, or osteoporosis. Demographic, physiologic, and radiographic characteristics were compared and the association of BMD with radiographic emphysema, airflow obstruction, and osteoporosis risk factors was assessed.

Measurements and Main Results: No difference existed in age, tobacco exposure, oral steroid use, or physical activity across BMD categories. Both osteopenia and osteoporosis were associated with the presence of airflow obstruction, inhaled corticosteroid use, and female sex, and demonstrated a significant relationship with the presence of visual emphysema ($P = 0.0003$). Quantitative emphysema, but not CT-measured indices of airway wall thickness, was inversely associated with BMD. Visual emphysema alone was a significant predictor of osteopenia/osteoporosis (odds ratio = 2.55; 95% confidence interval, 1.24–5.25) in a model including obstruction severity, age, sex, and inhaled and oral steroid use.

Conclusions: Radiographic emphysema is a strong, independent predictor of low BMD in current and former smokers. This relationship suggests a common mechanistic link between emphysema and osteopenia/osteoporosis.

Keywords: pulmonary disease, chronic obstructive; emphysema; osteoporosis

The systemic consequences of chronic obstructive pulmonary disease (COPD) significantly contribute to disease morbidity with a detrimental impact on quality of life (1–3). The increased prevalence of osteoporosis in patients with COPD can be particularly problematic, because subclinical disease may co-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Studies have established an association between chronic obstructive pulmonary disease and osteoporosis, but limited information exists about the factors linking these two disease processes.

What This Study Adds to the Field

We have demonstrated an association between radiographic emphysema and low bone mineral density independent of airflow obstruction and other osteoporosis risk factors. This finding suggests a common mechanistic link between emphysema and osteoporosis.

exist unrecognized until a debilitating fracture occurs. Although overlapping risk factors complicate the relationship between COPD and osteoporosis, the increased prevalence of low bone mineral density (BMD) in the absence of steroid use, and in those with milder airflow limitation (4, 5), implicates pathogenic associations between the two processes distinct from traditional osteoporosis risk factors.

Several studies have identified relationships between radiographic emphysema and other associated comorbidities (6–8) independent of traditional physiologic measures of airflow obstruction. In fact, the interindividual variation of the systemic inflammatory response in patients with COPD, as illustrated by our group (9, 10) and others (11–13), supports the potential for specific lung disease subtype comorbidity linkages. Indeed, similarities between parenchymal emphysema and osteoporosis, including the loss of extracellular matrix and common association with inflammatory mediators, such as tumor necrosis factor- α (14–17), alludes to a potential mechanistic link between the two processes. Despite this biologic plausibility, studies evaluating the relationship between parenchymal emphysema and low BMD have been limited to date, with only one small study demonstrating a relationship between a quantitative CT measure of emphysema and absolute BMD measured by quantitative CT in patients with airflow obstruction (18). Therefore, we conducted a cross-sectional observational study to identify radiographic, physiologic, and demographic factors predictive of low BMD, measured using dual x-ray absorptiometry (DXA), in a group of current and former smokers with and without airflow obstruction. Some of the results of this study have been previously reported in the form of an abstract (19).

METHODS

See the online supplement for an extended version of the METHODS.

(Received in original form April 28, 2010; accepted in final form October 8, 2010)

Supported by the NHLBI (K23HL095909), by the National Institutes of Health through the University of Pittsburgh SCCOR in COPD (NHLBI 1P50 HL084948 and P50-CA90440), and by the Snee-Reinhardt Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or the National Institutes of Health.

Correspondence and requests for reprints should be addressed to Frank C. Sciruba, M.D., Kaufmann Building, Suite 1211, 3471 Fifth Avenue, Pittsburgh, PA 15213. E-mail: sciruba@c.upmc.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183, pp 885–890, 2011

Originally Published in Press as DOI: 10.1164/rccm.201004-0666OC on October 8, 2010
Internet address: www.atsjournals.org

Subject Selection

The study population consisted of 201 subjects participating in the COPD Specialized Center for Clinically Oriented Research (SCCOR) at the University of Pittsburgh, Pittsburgh, Pennsylvania. SCCOR subjects were primarily recruited from the Pittsburgh Lung Screening Study cohort, a tobacco-exposed cohort with only a subset of subjects having spirometrically confirmed obstructive lung disease. The mean FEV₁ percent predicted of the Pittsburgh Lung Screening Study cohort is 81.8 ± 19.2 and mean body mass index (BMI) is 28.9 ± 5.5 . Participants were current or former smokers ages 40–79 with a 10 pack-year minimum tobacco history selected to enhance the extremes of visual radiographic emphysema and obstruction severity. Subject selection was made without any *a priori* knowledge of BMD. Subjects with a BMI greater than 35 were excluded. Each subject completed a chest CT scan, prebronchodilator and post-bronchodilator spirometry and plethysmography, measurement of lung diffusion capacity, demographic and medical history questionnaires, and DXA measurements of BMD at the hip and lumbar spine. Physical activity levels were quantified using a validated, five-point activity questionnaire that addressed both leisure and on-the-job activity levels (20). The study protocol was approved by the University of Pittsburgh Institutional Review Board and written informed consent was obtained for each subject.

CT Examination

Noncontrast CT examinations were performed with a General Electric (GE) LightSpeed VCT (64-detector) (Buckinghamshire, UK) scanner at a radiation exposure of 100 mA. A single chest radiologist, masked to subject identities and other characteristics, interpreted the CT images using a 6-point semiquantitative visual scoring system to define emphysema severity (0 = none; 1 = trace; 2 = mild; 3 = moderate; 4 = severe; and 5 = very severe), which corresponded to 0%, less than 10%, 10–25%, 26–50%, 51–75%, and greater than 75% visual emphysema. This methodology has been validated by our group in a previous publication (8). The percentage of low-attenuation units was defined as the fraction of voxels less than -910 HU as a percent of total voxels identified as lung regions similar to the traditional density mask (21). Airway wall thickness, internal perimeter, and wall area of all, small, and large airways were determined using methods described previously (22). The mean number of airway sections detected among the subjects was $524 (\pm 150)$.

Dual X-Ray Absorptiometry

BMD at the hip (total and femoral neck) and lumbar spine were determined using a Hologic 4500A Discovery bone densitometer (Bedford, MA). BMD is reported as an absolute value (gram per square centimeter) and a T score, the number of standard deviations from a young, sex- and ethnic-specific reference mean, using the NHANES III database reference population for hip BMD measurements (23) and the Hologic database reference population for spine BMD measurements. T scores were used to classify subjects as having normal BMD, osteopenia, or osteoporosis.

Statistical Analysis

Demographic, physiologic, and radiographic data were compared among subjects with normal BMD, osteopenia, and osteoporosis using an analysis of variance for continuous variables and chi-square test for trends analyses of categorical variables. Univariate logistic regression analyses were performed to assess the impact of emphysema or airflow obstruction, age, pack-years, sex, and inhaled and oral steroid use on the likelihood of having osteopenia/osteoporosis (T score less than or equal to -1). Multivariate logistic regression analyses were then performed to evaluate the relationship between both the presence of any airflow obstruction and emphysema and the severity of airflow obstruction and emphysema and osteopenia/osteoporosis. Established osteoporosis risk factors and those factors with a significance level of less than or equal to 0.20 in univariate analysis were included in the multivariate model. SAS version 9.2 (Cary, NC) was used to perform all statistical analyses.

RESULTS

Subject Characteristics

Of the 201 consecutive subjects who had DXA scans, 11 were excluded from further analysis because of a pattern of re-

striction on post-bronchodilator spirometry. The overall cohort was equally distributed among sexes (Table 1). A total of 38.4% did not have airflow obstruction (GOLD, at risk), and of these 38.3% had visual emphysema. The remaining subjects had airflow obstruction, of which 79.5% had visual emphysema. Sixty-seven percent of subjects had low BMD (T score less than or equal to -1). Very few of the subjects were underweight (BMI <21), whereas most were either overweight (BMI 25–30) or obese (BMI >30). A minority of subjects used inhaled steroids and very few were taking oral steroids or bisphosphonate therapy.

Characteristics of Subjects with Normal BMD, Osteopenia, and Osteoporosis

Subjects with osteoporosis were significantly older than those with either normal BMD or osteopenia (*see* Table E1 in the online supplement). More females than males had low BMD ($P < 0.05$; chi-square test for trends) and a greater prevalence of low BMD existed in those using inhaled steroids when not adjusted for the degree of airflow obstruction. The average BMI decreased as BMD decreased, but the mean BMI was normal even for those with osteoporosis. Physical activity levels, both leisure and on-the-job, were similar among BMD groups. Furthermore, although BMD was lower in females, there were no significant differences in both on-the-job activity levels ($P = 0.14$) and leisure activity levels ($P = 0.87$) between sexes. No difference existed in pack-years, oral steroid use, or bisphosphonate use among BMD groups, although very few subjects used either systemic steroids or bisphosphonate therapy.

Relationship of BMD with Emphysema and Lung Function

The presence of any visual emphysema was strongly associated with low BMD ($P = 0.0003$) (Table 2) and a highly significant relationship existed between the extent of emphysema and the decrement of low BMD ($P = 0.0001$) (Table 2). Furthermore, the percentage of low-attenuation units on quantitative chest CT increased with decreasing BMD, whereas no relationship

TABLE 1. SUBJECT DEMOGRAPHICS (N = 190)

Age	66 $\pm$ 6.6 (40–83)
Sex, female	92 (48.4%)
Pack-years	54.4 $\pm$ 26.8 (10–138)
Body mass index	27.9 $\pm$ 4.1 (18.8–36.4)
<21	6 (3.2%)
21–25	45 (23.7%)
25.1–30	76 (40%)
>30	63 (33.2%)
FEV ₁ %	80.7 $\pm$ 21.9 (32.7–126.1)
GOLD	
At risk	73 (38.4%)
1	35 (18.4%)
2	63 (33.2%)
3	19 (10%)
4	0 (0%)
Inhaled steroid use	34 (17.9%)
Oral steroids use	9 (4.7%)
Bisphosphonate use	11 (5.8%)
Normal bone mineral density*	63 (33.2%)
Osteopenia*	110 (57.9%)
Osteoporosis*	17 (8.9%)
Emphysema	
None	69 (36.3%)
Trace/mild	85 (44.7%)
Moderate/severe	36 (19%)

* Normal bone mineral density: T score greater than -1 at both sites (hip and spine). Osteopenia: T score less than or equal to -1 but greater than -2.5 at either site. Osteoporosis: T score less than or equal to -2.5 at either site.

existed between BMD and quantitative CT indices of airway disease (Table E2). In contrast, a weaker trend existed between airflow obstruction and the presence of low BMD ($P = 0.04$) (Table 2), with 69.2% of individuals with obstruction versus 63% of individuals without obstruction demonstrating decreased BMD. Thus, although an association did exist between obstruction severity and BMD, the severity of emphysema measured both visually and quantitatively, but not CT indices of airway inflammation and fibrosis, was more strongly associated with osteopenia and osteoporosis. No difference existed in residual volume, total lung capacity, or residual volume/total lung capacity ratio among BMD groups. However, diffusion capacity decreased significantly ($P = 0.03$) as BMD decreased across groups, consistent with the finding of increased emphysema in those with lower BMD.

Predictors of Osteopenia/Osteoporosis

Because the complex relationship between COPD and osteoporosis is confounded by the overlap of common risk factors, we performed a univariate logistic regression analysis to examine the relationship between potential risk factors and the likelihood of having osteopenia/osteoporosis (T score less than or equal to -1 at either the hip or lumbar spine) (Table 3). In agreement with our previous analyses, the presence of anatomic emphysema was associated with a greater likelihood of osteopenia/osteoporosis (odds ratio [OR], 2.51; confidence interval [CI], 1.34–4.69). However, the presence of any airflow obstruction was not related to a statistically significant increased likelihood of osteopenia/osteoporosis. Similarly, the severity of emphysema was strongly associated with the likelihood of osteopenia/osteoporosis (OR, 3.58 moderate/severe emphysema and 2.20 trace/mild emphysema, referent group no emphysema), whereas only a trend existed for the severity of airflow obstruction (OR, 2.20 for FEV₁% <50 and 1.21 for FEV₁% ≥ 50 , referent group no obstruction), but did not reach statistical significance. Women were more likely to have osteopenia/osteoporosis compared with men (OR, 2.07; CI, 1.11–3.85) and a statistically nonsignificant trend toward lower BMD was associated with inhaled steroid use (OR, 2.16; CI, 0.88–5.28).

Multivariate logistic regression analyses were performed based on a model of risk factors that either reached a significance threshold of 0.20 in univariate analyses or that have been established as having a potential impact on BMD. In a model that included the severity of airflow obstruction and emphysema, age, sex, and inhaled and oral steroid use, only sex and the extent of visual emphysema significantly increased the likelihood of having osteopenia/osteoporosis (OR, 3.68 moderate/severe emphysema and 2.33 trace/mild emphysema, referent group no emphysema) (Table E3, Figure 1), whereas no association was observed for obstruction severity or other pertinent risk factors. Similar findings were seen in a model examining the

presence of any emphysema or obstruction as risk factors for osteopenia/osteoporosis (Table 4). Additional adjustment for bisphosphonate use did not alter these results. Thus, emphysema alone seems to be a strong, independent predictor of osteopenia/osteoporosis with even trace or mild visual emphysema significantly increasing the likelihood of clinically important decrements in BMD.

DISCUSSION

We found radiographic emphysema alone to be the strongest predictor of low BMD in smokers with varying degrees of airflow obstruction and limited confounding risk factors. COPD has heterogeneous manifestations with variable contributions of parenchymal emphysema admixed with small airway inflammation and fibrosis (24–26). As greater focus is placed on the study of COPD-related comorbidities, at least some studies suggest that the presence of emphysema alone may be an independent marker of certain systemic manifestations in obstructive lung disease. McAllister and colleagues (6) demonstrated a strong, independent relationship between the extent of emphysema on quantitative CT analysis and arterial stiffness measured by pulse wave velocity. Likewise, Wilson and coworkers (8) demonstrated an independent relationship between the presence of any emphysema and lung cancer risk. A linear correlation between emphysema and absolute BMD of the thoracic and L1 vertebrae measured by quantitative CT (18) has been previously reported in a study of male smokers with obstruction. In contrast, we have demonstrated a strong association between the presence of emphysema and osteopenia/osteoporosis, defined by the gold standard DXA measurement of hip and lumbar spine BMD, in a large, highly characterized cohort. The growing evidence that emphysema is an independent correlate for many systemic manifestations of COPD not only provides an easily measurable risk factor to identify higher-risk patients, but also serves as a foundation for studies investigating the mechanistic link between chronic lung disease and its systemic manifestations.

The independent association of radiographic emphysema and low BMD is suggestive of a common pathogenesis linking parenchymal destruction and bone loss. The mechanisms underlying this relationship are speculative and may be related to local inflammatory factors acting synchronously on lung and bone matrix versus the serial effects of lung inflammation spilling over into the systemic circulation. Associations have been described linking systemic inflammatory patterns and other COPD-related comorbidities (12, 27–30). In fact, we have demonstrated an association between distinct serum inflammatory mediators and quantitative CT measurements of emphysema and airway wall thickness (10), most notably showing a positive correlation between serum levels of IL-6, a well-

TABLE 2. RELATIONSHIP OF BONE MINERAL DENSITY WITH OBSTRUCTION AND EMPHYSEMA SEVERITY

	Normal Bone Mineral Density (<i>n</i> = 63) (33.2%)	Osteopenia (<i>n</i> = 110) (57.9%)	Osteoporosis (<i>n</i> = 17) (8.9%)	<i>P</i> Value
Obstruction present, %	57.1 (36)	59.1 (65)	94.1 (16)	0.04
Obstruction severity, %				
None	42.9 (27)	40.9 (45)	5.9 (1)	0.005
FEV ₁ $\geq 50\%$	50.8 (32)	50.9 (56)	58.8 (10)	
FEV ₁ $<50\%$	6.3 (4)	8.2 (9)	35.3 (6)	
Emphysema present, %	49.2 (31)	67.3 (74)	94.1 (16)	0.0003
Emphysema severity, %				
None	50.8 (32)	32.7 (36)	5.9 (1)	0.0001
Trace/mild	38.1 (24)	47.3 (52)	52.9 (9)	
Moderate/severe	11.1 (7)	20 (22)	41.2 (7)	

TABLE 3. PREDICTORS OF OSTEOPENIA/OSTEOPOROSIS (T SCORE LESS THAN OR EQUAL TO -1) IN CURRENT AND FORMER SMOKERS, UNIVARIATE ANALYSIS*

	Odds Ratio (95% CI)	P Value
Age		0.072
≥70 vs. <60	0.30 (0.08–1.14)	
60–70 vs. <60	0.23 (0.065–0.82)	
Sex		
Female vs. male	2.07 (1.11–3.85)	0.022
Inhaled steroids	2.16 (0.88–5.28)	0.091
Oral steroids	0.60 (0.16–2.33)	0.47
Tobacco burden†		0.83
>60 vs. 10–30	0.75 (0.30–1.88)	
31–60 vs. 10–30	0.83 (0.34–2.04)	
Obstruction		
Present vs. none	1.32 (0.71–2.45)	0.38
FEV ₁ % <50 vs. none	2.20 (0.66–7.32)	0.43
FEV ₁ % ≥50 vs. none	1.21 (0.64–2.29)	
Emphysema		
Present vs. none	2.51 (1.34–4.69)	0.0039
Moderate/severe vs. none	3.58 (1.38–9.28)	0.012
Trace/mild vs. none	2.20 (1.13–4.29)	

* Unadjusted univariate logistic regression analysis.

† Measured in pack-years.

established osteoclastogenic cytokine, and the percentage of low-attenuation lung units measured by quantitative CT. As the characterization of the systemic inflammatory response in COPD (31–35) evolves, similarities emerge between the inflammatory mediators involved in both bone resorption and obstructive lung disease, including IL-6 and tumor necrosis factor- α (36–38). However, although the literature frequently implicates systemic inflammation in the pathogenesis of COPD-related osteoporosis (3, 39), this concept has never been carefully studied.

Whereas large, epidemiologic studies have demonstrated a definitive link between obstructive lung disease and osteoporosis (4, 40, 41), studies evaluating the pathophysiologic mechanisms underlying this relationship are limited. Smaller reports (42, 43) with detailed patient characterizations have focused primarily on subjects with more severe airflow obstruction and have attributed established osteoporosis risk factors, including systemic steroid use (44), older age, and low body weight (43), to the increased prevalence of osteoporosis in COPD. The etiology of COPD-related osteoporosis is almost certainly

TABLE 4. PRESENCE OF AIRFLOW OBSTRUCTION AND EMPHYSEMA AND RISK OF OSTEOPENIA/OSTEOPOROSIS (T SCORE LESS THAN OR EQUAL TO -1) IN CURRENT AND FORMER SMOKERS, MULTIVARIATE ANALYSIS*

	Odds Ratio (95% CI)	P Value
Obstruction		
Present vs. none	0.82 (0.38–1.78)	0.61
Emphysema		
Present vs. none	2.55 (1.24–5.25)	0.011
Age		0.065
≥70 vs. <60	0.23 (0.057–0.94)	
60–70 vs. <60	0.21 (0.057–0.78)	
Sex		
Female vs. male	1.99 (1.04–3.83)	0.048
Inhaled steroids	1.82 (0.68–4.87)	0.23
Oral steroids	0.52 (0.13–2.16)	0.37

* Multivariate logistic regression analysis with adjustment for bisphosphonate use.

multifactorial, particularly in patients with the most severe airflow obstruction, because they often have limited physical activity, a greater likelihood of systemic steroid use, and derangements of body composition that can predispose to decreased BMD (45, 46). However, our finding of an independent relationship between anatomic emphysema and decreased BMD, in conjunction with the finding of an increased prevalence of osteopenia/osteoporosis in those with absent or mild obstruction (5), suggests that other factors may play a more prominent role.

Our study had several limitations warranting further investigation. We found no difference in the reported activity level, an osteoporosis risk factor and potential confounder, among subjects with normal BMD, osteopenia, and osteoporosis. Because our cohort has relatively mild obstruction, physical activity levels would not be expected to differ among groups. Also, we did not find a difference in activity levels between men and women, although a greater proportion of women had low BMD. We used a validated, five-point activity questionnaire (20) to quantify on-the-job and leisure activity, a clinical tool that may not have adequate sensitivity to detect small, but clinically important, differences in activity. Future studies using more precise methods to quantify physical activity levels, such as accelerometry or multisensor activity monitoring (47), would better quantify differences in activity among individuals. The cross-sectional design of our study limits applicability of these findings to the identification of individuals who are likely to have already developed decreased BMD. However, a longitudinal analysis now in progress may potentially identify those characteristics inherent to the COPD patient at risk for accelerated loss of BMD over time, thus facilitating earlier screening and prevention and providing further insight into the mechanisms underlying low BMD in COPD.

CONCLUSIONS

Despite increasing recognition of the prevalence of low BMD in obstructive lung disease, COPD-related osteoporosis remains an underdiagnosed and understudied comorbidity. Our findings suggest that radiographic emphysema, independent of previously established risk factors or severity of obstruction, should be considered in studies examining the mechanisms underlying COPD-related bone loss. Exploration of the relationship between emphysema and low BMD could provide mechanistic insights and ultimately lead to the development of novel therapies to halt progression of both disease processes.

Author Disclosure: J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.R.F. does not have

Figure 1. Forrest plot showing risk of osteopenia/osteoporosis related to various risk factors including severity of airflow obstruction, severity of radiographic emphysema, age, sex, and inhaled and oral steroid use. The odds ratios (diamonds) and 95% confidence intervals (whiskers) are derived from a multivariate logistic regression analysis.

a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.L.W. received more than \$100,001 from the National Cancer Institute in research grants and contracts. S.R.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.A.B. received \$5,001–\$10,000 in legal consulting for a medicolegal physician defense and \$5,001–\$10,000 in legal consulting for pharmaceutical patent infringement; holds a patent from the University of Pittsburgh on the entromics concept for genetic analysis; and received \$50,001–\$100,000 from the NHLBI as a SCCOR in COPD grant as co-investigator. C.-C.H.C. received \$10,001–\$50,000 from the NIH in sponsored grants for serving as a co-investigator or statistician. Y.Z. received \$5,001–\$10,000 from the NHLBI in sponsored grants. J.K.L. received \$1,001–\$5,000 from GlaxoSmithKline in consultancy fees. D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.L.G. received \$5,001–\$10,000 from Merck and \$5,001–\$10,000 from Amgen in advisory board fees and more than \$100,001 from Eli Lilly and more than \$100,001 from Warner Chilcott in industry-sponsored grants. F.C.S. received \$1,001–\$5,000 from Pfizer in consultancy fees; \$1,001–\$5,000 from GlaxoSmithKline, \$1,001–\$5,000 from AstraZeneca, \$1,001–\$5,000 from Merck, and \$1,001–\$5,000 from PenumRx in advisory board fees; more than \$100,001 from GlaxoSmithKline, and more than \$100,001 from Pfizer, and more than \$100,001 from Boehringer Ingelheim in industry-sponsored grants.

References

- Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008;5:549–555.
- Agusti AGN. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005;2:367–370.
- Decramer M, Rennard S, Troosters T, Mapel DW, Giardino N, Mannino D, Wouters E, Sethi S, Cooper CB. COPD as a lung disease with systemic consequences: clinical impact, mechanisms, and potential for early intervention. *COPD* 2008;5:235–256.
- de Vries F, van Staa TP, Bracke MSGM, Cooper C, Leufkens HGM, Lammers JWJ. Severity of obstructive airway disease and risk of osteoporotic fracture. *Eur Respir J* 2005;25:879–884.
- Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD, Nixon LS, Evans WD, Griffiths TL, Shale DJ. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:1286–1293.
- McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D, Newby DE, Murchison JT, Macnee W. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:1208–1214.
- Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD, McEniery CM, Wilkinson IB, Cockcroft JR, Shale DJ. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:1259–1265.
- Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, Wilson J, Leader JK, Siegfried JM, Shapiro SD, *et al.* Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008;178:738–744.
- Lee JS, Rosengart MR, Kondragunta V, Zhang Y, McMurray J, Branch RA, Choi AM, Sciruba FC. Inverse association of plasma IL-13 and inflammatory chemokines with lung function impairment in stable COPD: a cross-sectional cohort study. *Respir Res* 2007;8:64.
- Bon JM, Leader JK, Weissfeld JL, Coxson HO, Zheng B, Branch RA, Kondragunta V, Lee JS, Zhang Y, Choi AM, *et al.* The influence of radiographic phenotype and smoking status on peripheral blood biomarker patterns in chronic obstructive pulmonary disease. *PLoS ONE* 2009;4:e6865.
- Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:819–824.
- Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, Shale DJ. Inflammatory response and body composition in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1414–1418.
- Pinto-Plata V, Toso J, Lee K, Park D, Bilello J, Mullerova H, De Souza MM, Vessey R, Celli B. Profiling serum biomarkers in patients with COPD: associations with clinical parameters. *Thorax* 2007;62:595–601.
- Kimble RB, Matayoshi AB, Vannice JL, Kung VT, Williams C, Pacifici R. Simultaneous block of interleukin-1 and tumor necrosis factor is required to completely prevent bone loss in the early postovariectomy period. *Endocrinology* 1995;136:3054–3061.
- Churg A, Dai J, Tai H, Xie C, Wright JL. Tumor necrosis factor- α is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. *Am J Respir Crit Care Med* 2002;166:849–854.
- Churg A, Wang RD, Tai H, Wang X, Xie C, Wright JL. Tumor necrosis factor- α drives 70% of cigarette smoke-induced emphysema in the mouse. *Am J Respir Crit Care Med* 2004;170:492–498.
- D'Hulst AI, Bracke KR, Maes T, De Bleecker JL, Pauwels RA, Joos GF, Brusselle GG. Role of tumour necrosis factor- α receptor p75 in cigarette smoke-induced pulmonary inflammation and emphysema. *Eur Respir J* 2006;28:102–112.
- Ohara T, Hirai T, Muro S, Haruna A, Terada K, Kinose D, Marumo S, Ogawa E, Hoshino Y, Niimi A, *et al.* Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. *Chest* 2008;134:1244–1249.
- Bon J, Fuhrman CR, Weissfeld JL, Duncan SR, Branch RA, Chang JHC, Leader JK, Gur D, Greenspan SL, Sciruba FC. Radiographic emphysema independently predicts low bone mineral density in chronic obstructive pulmonary disease [abstract]. *Am J Respir Crit Care Med* 2010;181:A2379.
- Taylor-Piliae RE, Norton LC, Haskell WL, Mahbouda MH, Fair JM, Iribarren C, Hlatky MA, Go AS, Fortmann SP. Validation of a new brief physical activity survey among men and women aged 60–69 years. *Am J Epidemiol* 2006;164:598–606.
- Muller N, Staples C, Miller R, Abboud R. Density mask: an objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–787.
- Zheng B, Leader J, McMurray J, Park S, Fuhrman C, Gur D, Sciruba F. Automated detection and quantitative assessment of pulmonary airways depicted on CT images. *Med Phys* 2007;34:2844–2852.
- Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC Jr, Lindsay R. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int* 1998;8:468–489.
- Gelb AF, Hogg JC, Muller NL, Schein MJ, Kuei J, Tashkin DP, Epstein JD, Kollin J, Green RH, Zamel N, *et al.* Contribution of emphysema and small airways in COPD. *Chest* 1996;109:353–359.
- Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Pare PD, Hogg JC, *et al.* Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102–1108.
- Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciruba FC, Coxson HO, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
- Engstrom G, Lind P, Hedblad B, Wollmer P, Stavenow L, Janzon L, Lindgarde F. Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins. *Circulation* 2002;106:2555–2560.
- Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514–1519.
- Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. *Chest* 2006;130:326–333.
- Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, Jensen R, Crapo R, Rubin S, Nevitt M, *et al.* Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax* 2006;61:10–16.
- Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the third national health and nutrition examination. *Am J Med* 2003;114:758–762.
- Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004;59:574–580.
- Hurst JR, Perera WR, Wilkinson TMA, Donaldson GC, Wedzicha JA. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:71–78.
- Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:250–255.
- Zhu X, Gadgil AS, Givelber R, George MP, Stoner MW, Sciruba FC, Duncan SR. Peripheral T cell functions correlate with the severity of chronic obstructive pulmonary disease. *J Immunol* 2009;182:3270–3277.

36. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. *N Engl J Med* 1995;332:305–311.
37. Cenci S, Weitzmann MN, Roggia C, Namba N, Novack D, Woodring J, Pacifici R. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. *J Clin Invest* 2000;106:1229–1237.
38. Kudo O, Sabokbar A, Pocock A, Itonaga I, Fujikawa Y, Athanasou NA. Interleukin-6 and interleukin-11 support human osteoclast formation by a rankl-independent mechanism. *Bone* 2003;32:1–7.
39. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:347–360.
40. Sin DD, Man JP, Man SF. The risk of osteoporosis in caucasian men and women with obstructive airways disease. *Am J Med* 2003;114:10–14.
41. Ferguson GT, Calverley PM, Anderson JA, Jenkins CR, Jones PW, Willits LR, Yates JC, Vestbo J, Celli B. Prevalence and progression of osteoporosis in patients with COPD. Results from TORCH. *Chest* 2009;136:1448–1449.
42. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 2007;101:177–185.
43. Graat-Verboom L, Spruit MA, van den Borne BE, Smeenk FW, Martens EJ, Lunde R, Wouters EF. Correlates of osteoporosis in chronic obstructive pulmonary disease: an underestimated systemic component. *Respir Med* 2009;103:1143–1151.
44. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, Niewoehner DE. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:704–709.
45. Biskobing DM. COPD and osteoporosis. *Chest* 2002;121:609–620.
46. Ionescu AA, Schoon E. Osteoporosis in chronic obstructive pulmonary disease. *Eur Respir J* 2003;22:64S–75S.
47. Patel SA, Benzo RP, Slivka WA, Sciruba FC. Activity monitoring and energy expenditure in COPD patients: a validation study. *COPD* 2007;4:107–112.