Original Article

A study of chronic obstructive pulmonary disease-specific causes of osteoporosis with emphasis on the emphysema phenotype

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Abstract:

BACKGROUND: Osteoporosis, the most common extra-pulmonary complication of chronic obstructive pulmonary disease (COPD), may be related to general causes or COPD-specific causes such as low forced expiratory volume in 1 s (FEV1) and hypoxia. A few studies reported that emphysema is an independent risk factor for osteoporosis. However, other workers considered the association to be confounded by low FEV1 and low body mass index (BMI) which cluster with emphysema.

AIMS: To study the association between osteoporosis and emphysema in a model that includes these potentially confounding factors.

METHODS: We studied prospectively 52 COPD patients with both high resolution computed tomography and carbon monoxide diffusion coefficient as diagnostic markers of emphysema. Dual-energy X-ray absorptiometry was used to measure the bone mass density (BMD) of lumbar vertebrae and neck of the femur. Vertebral fractures were evaluated using the Genant semiquantitative score. Multiple linear regression analysis was used to identify the following independent variables: age, BMI, FEV1% predicted, PaO_2, emphysema score, C-reactive protein (CRP), and dyspnea score as related to BMD. $P \leq 0.05$ was considered statistically significant.

RESULTS: There was no significant difference in the serum Vitamin D levels, vertebral fracture score, or BMD between the emphysematous and nonemphysematous patients. Multivariate analysis showed that (in a model including age, BMI, FEV1, PaO_2, emphysema score, CRP, and dyspnea score) only reduced BMI, FEV1, and PaO_2 were independent risk factors for low BMD.

CONCLUSIONS: The emphysematous phenotype is not a risk factor for osteoporosis independently of BMI, FEV1, and PaO_2.

Key words:

Chronic obstructive pulmonary disease, emphysema, osteoporosis

Chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality, is associated with serious extrapulmonary comorbidities. The most frequent of these is bone disease: osteoporosis has an overall prevalence of 35.1% (range: 9%–69%) as reported in a review of 13 studies on COPD patients.[1] In addition, 38.4% (range: 27%–67%) suffered from osteopenia.[1] Epidemiological studies reported a 1.5–2-fold increased risk of osteoporosis in COPD subjects compared with controls.[2,3] Vertebral fractures in osteoporotic COPD are most common in the midthoracic region, which not only worsen the quality of life but have also a negative impact on the lung physiology.[4] It was estimated that each thoracic vertebral fracture results in a 9% decline of the lung vital capacity.[5] Osteoporosis in COPD is attributed to general causes such as age, low body mass index (BMI), corticosteroid use or hypogonadism or COPD-specific causes.[6] The latter include the stage of COPD as measured by forced expiratory volume in 1 s (FEV1), respiratory failure, the severity of dyspnea, and COPD phenotype as assessed by CT scan (emphysematous versus nonemphysematous).[6-9] There is growing interest

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in phenotyping as various studies documented that emphysema is associated with lower FEV1, worse dyspnea score, and lower BMI.[10-12]

Four studies reported that emphysema was a risk factor for osteoporosis independent of age, BMI or the stage of the lung disease.[4,9,13,14] The association was called ""Holes in the lungs, holes in the bones!"[15] It was speculated that the common link between osteoporosis and emphysema was the heightened inflammatory markers in the two conditions.[16] However, other authors expressed doubts and considered low FEV1 and wasting (which cluster with emphysema) and not emphysema to be the trigger for osteoporosis.[17] It is interesting that the serum levels of C-reactive protein (CRP) (an inflammatory marker linked to both COPD and osteoporosis) was reported to be lower in the emphysema phenotype than the peribronchial thickening/bronchiectasis phenotype of COPD.[18] Although some studies documented a positive association between the inflammatory markers and osteoporosis, the longitudinal Framingham Offspring Study found no consistent association between osteoporosis and serum levels of interleukin-6, tumor necrosis factor-alpha (TNF-α), or CRP.[19]

The aim of this study is to delineate the COPD specific causes of osteoporosis and to test the hypothesis that emphysema is not a risk factor independent of low FEV1 and BMI. The differences between the various phenotypes of COPD are attracting new interest. To the best of our knowledge, no study has ever reported on the effect of emphysema on osteoporosis in a model that included together the potentially confounding factors of FEV1, BMI, and hypoxia. Vertebral fracture score and bone mass density (BMD) will be used as indicators of osteoporosis.

Methods

Patient selection and pulmonary function tests

The study was conducted at the teaching hospital of King Saud University, Riyadh, Saudi Arabia between 2011 and 2015 on all consecutive patients with COPD managed in the Pulmonology clinic. The study's protocol was approved by the Ethics Committee of the University as a prospective descriptive study and written informed consent was obtained from all patients. The criteria were age 40 or above, history of a chronic cough and dyspnea, cigarette smoking of at least ten pack years, postbronchodilator FEV1/forced vital capacity <70% and FEV1 <80% predicted.[20] Tiotropium (Spiriva Handihaler; Boehringer Ingelheim; Ingelheim, Germany) 18 μg once daily was prescribed. As long-acting β-2 agonists were not licensed for single use in Saudi Arabia, all patients were started on budesonide 320 μg/formoterol 9 μg (Symbicort Turbuhaler; AstraZeneca; London, UK) twice daily. Spirometry was performed with reversibility, carbon monoxide transfer coefficient (KCO) and arterial blood gasses. A KCO <80% predicted was considered indicative of emphysema. Arterial puncture of the radial artery (after lignocaine infiltration) was performed by a trained pulmonology function technician. The preheparinized syringe was packed in ice and analyzed in the Central Laboratory at King Khalid University Hospital. The test was performed at the time of the first pulmonary function test while the patient is breathing room air.

High resolution computed tomography scan scoring of emphysema

High-resolution computed tomography (HRCT) scanning was used (LightSpeed 16 or VCT XT; GE Medical Systems, Milwaukee, Wisconsin, USA). Full-volume acquisitions reconstructed every 2.5 mm were obtained throughout the entire thorax. Images were acquired employing a standard window setting (window level: −700 Hounsfield Units [HU]; window width 1500 HU). We used Goddard's quantitative visual scoring of emphysema (defined as areas of attenuation of the lung parenchyma).[21] Zero represented no abnormality; 0.5 score was given for 1–5% involvement; 1 was given for 6%–25% involvement; 2 for 26%–50%; 3 for 51%–75%; and 4 for 76% or more. All patients had to be free of bronchiectasis and interstitial lung disease on HRCT scan.

The same three observers (AAA, FAA-K, and a second clinician) scored three cuts at the following levels: arch of the aorta, bifurcation of the trachea, and one cut above the diaphragm. Emphysema was considered significant if the average scoring was ≥1. This was based on reports that the lowest 25% percentile for emphysema displays features of asthma.[22] Consensus was used to smooth out any inter-observer differences.

Measurement of bone mass density

BMD was measured at the lumbar spine (L2–L4) and femoral necks by dual X-ray absorptiometry (DEXA) bone scan. The average BMD of lumbar vertebrae BMD (V) and the worst of the right and left femoral neck sites BMD (N) was used for statistical analysis and designated BMD (V/N). The T-score, which represents the number of standard deviations of BMD from the reference value for healthy young adults, was the basis for diagnosing osteoporosis. According to the definition of the World Health Organization osteoporosis corresponded to a T-score of ≤−2.5 and osteopenia to a score of ≤−1 and >−2.5.[23] DEXA bone scans were performed at least 6 months after stabilizing all the patients on the same dose of budesonide (320 μcg twice daily), and none received systemic corticosteroids for the same period.

Genant scoring of vertebral fractures

Vertebral fractures were evaluated by CT scan using the Genant semiquantitative score.[24] Normal vertebrae (Grade 0) show minimal deformity with a <20% reduction in anterior, middle, and posterior vertebral height. Grade 1 is defined as a reduction of 20%–25% in vertebral height. Grade 2 and Grade 3 vertebral fractures are, respectively, defined as reductions of >25%–40% and >40% in vertebral height.[24]

Statistical methods

Data were analyzed using SPSS PC+ version 21.0 (IBM Inc., Chicago, USA) statistical software. Descriptive statistics and standard deviations were used to describe the quantitative study variables. Student's *t*-test was used to compare mean values of quantitative variables between the emphysematous and nonemphysematous groups. Multiple linear regression analysis was used to identify the independent variables (age, BMI, FEV1% predicted, PaO_2, emphysema score, CRP, and dyspnea score) related to BMD (V/N). A $P \leq 0.05$ was considered statistically significant. The 95% confidence intervals (CIs) for Beta coefficients were reported to assess

their precision. Beta is a regression coefficient which explains the linear relationship between outcomes (dependent) and independent variables.

Results

A total of 55 patients fulfilled the criteria. Only one patient was lost to follow-up, and another two did not show up for their BMD testing. There were only three female patients. The COPD was moderate (FEV1 ≥50% to <80% predicted) in 61%, severe or very severe (FEV1 <50% predicted) in 39% of cases. Two patients were on long-term home oxygen. A total of 36.5% had osteoporosis, and 34.6% had osteopenia. BMD was normal in only 28.8%.

Table 1 shows the characteristics of the patients. The emphysematous were 27 out of 52 and the nonemphysematous 25 out of 52. The emphysematous group was significantly older, with lower BMI, FEV1, and PaO_2 and higher dyspnea score compared with the nonemphysematous. However, the two groups were not significantly different with regards to CRP, Vitamin D serum level, the Genant vertebral fracture score, BMD (V), BMD (N), or BMD (V/N). The Vitamin D serum level mean ± standard deviation (range) was 49.33 ± 22.8 (21–121) and 39.3 ± 16.7 (9–66) nmol/L, respectively, with roughly symmetrical distribution on both sides of the mean. Multivariate analysis [Table 2] showed that among age, BMI, FEV1, PaO_2, emphysema score, CRP, and dyspnea score only reduced BMI, FEV1, and PaO_2 were identified as independent risk factors for low BMD. The Beta values and their 95% CIs were as follows: BMI = 0.011 (0.004–0.017), FEV1 = 0.006 (0.002–0.02), and PaO_2 = 0.006 (0.001–0.012).

Discussion

The prevalence of osteoporosis and osteopenia in our study were 36.5% and 34.6%, respectively which is in line with the bulk of previous studies.[1] In a univariate analysis, the emphysematous group was significantly older, with lower BMI, FEV1, and PaO_2 and higher dyspnea score compared with the nonemphysematous. However, there was no significant difference with regards to serum Vitamin D level, fracture score, CRP, BMD (V), BMD (N), or BMD (V/N). The multivariable regression model (incorporating age, BMI, FEV1, PaO_2, emphysema score, dyspnea score, and CRP) showed that only reduced BMI, FEV1, and PaO_2 and were identified as independent risk factors for low BMD.

COPD was reported to be the leading cause of secondary osteoporosis.[25] The various studies on COPD reported conflicting results on the effect of various variables on BMD except for BMI where there is general agreement on its significance.[1,6,8,26-28] A large meta-analysis of twelve studies found a reverse and nonlinear relationship between low BMI and osteoporotic fractures.[29] The mechanisms for such association are probably multifactorial. Low BMI is associated with muscle wasting which reduces the mechanical loading on the bones and worsens osteoporosis.[6,7] Adipose tissue produces several bone-active adipokines such as leptin which enhances the proliferation of osteoblasts while inhibiting osteoclasts.[30,31] Similarly, obesity is protective against osteoporosis even though it increases the risk of low-trauma fractures.[27]

Apart from the general causes of osteoporosis, there are factors specific to COPD.[6] These are the stage of COPD as measured by FEV1, hypoxia, dyspnea score, and emphysema.[4,8,9,13,14,26,28] Similar to our findings studies are nearly unanimous on the presence of an association between FEV1 and the severity of osteoporosis.[2,7,26,28] Although the stage of COPD was shown to be an independent risk factor for osteoporosis, it is likely that the association is further enhanced by other factors prevalent in advanced COPD such as cachexia, skeletal muscle weakness, and reduced mobility.[7,32] We are aware of only two studies which failed to detect an association between BMD and FEV1.[14,33] However, these two studies had enrolled only 30 and 19 patients with osteoporosis which may explain the lack of association.[14,33]

Hypoxia blocks the differentiation of osteoblasts while stimulating the action of osteoclasts.[34] Our literature search indicates that we are the first to report on a multivariate analysis showing PaO_2 to be an independent risk for low BMD. One study found no association between oxygen desaturation and osteoporosis.[33] However, that study had only 19 osteoporotic patients and 11 controls.[33] Similarly, the relationship between PaO_2 and oxygen saturation is not linear, and significant hypoxia may occur in the absence of desaturation.[35] Previous reports are divergent on whether the dyspnea score is a risk factor for osteoporosis.[8,25]

Table 1: Differences between the two groups expressed as mean±standard deviation

	Emphysematous group (*n*=27)	Nonemphysematous group (*n*=25)	*P*
Age (years)	67.85±8.94	59.6±9.755	0.003
BMI (kg/m²)	24.035±4.758	31.07±9.42	0.002
FEV1 (percentage predicted)	50.033±13.07	58.167±11.484	0.023
PaO_2 (mmHg)	64.893±9.114	76.783±8.034	<0.0001
CRP (mg/L)	6.695±9.103	7.226±11.198	0.851
Dyspnea score	4.41±7.752	1.28±0.678	0.05
Serum Vitamin D level (nmol/L)	49.33±22.8	39.3±16.7	0.079
Genant fracture score	0.89±0.698	0.76±0.779	0.532
BMD (V) (kg/m²)	0.9439±0.165	1.014±0.145	0.112
BMD (N) (kg/m²)	0.8915±0.228	0.9845±0.242	0.161
BMD (V/N) (kg/m²)	0.9177±0.169	0.9993±0.175	0.094

FEV1 = Forced expiratory volume in 1 s, PaO_2 = Arterial partial pressure of oxygen, CRP = C-reactive protein, BMD (V) = Bone mass density of vertebrae, BMD (N) = Bone mass density of neck of femur, BMD (V/N) = Average bone mass density of vertebrae and neck of femur, BMI = Body mass index

Table 2: Multivariate analysis of average bone mass density of vertebrae and neck of the femur

Variables	β	*t*	*P*	95% CI
Age (years)	−0.004	−1.844	0.073	−0.009-0.000
BMI (kg/m²)	0.011	3.411	0.001	0.004-0.017
FEV1 (percentage predicted)	0.006	3.068	0.004	0.002-0.02
PaO_2 (mmHg)	0.006	2.394	0.021	0.001-0.012
Emphysema score	−0.017	−0.654	0.517	−0.070-0.036
CRP (mg/L)	0.001	0.672	0.506	−0.003-0.005
Dyspnea score	0.000	−0.038	0.970	−0.007-0.007

FEV1 = Forced expiratory volume in 1 s, PaO_2 = Arterial partial pressure of oxygen, CRP = C-reactive protein, BMI = Body mass index, CI = Confidence interval

Four studies reported that emphysema is an independent risk factor for osteoporosis, also termed "holes in the lungs, holes in the bones" theory.[4,9,13-15] Ohara *et al*. used the percentage of the low-attenuation area (LAA%) on CT scan to diagnose emphysema in 65 male COPD patients.[9] They reported in 2008 that LAA% and BMI were predictive of BMD among age, BMI, smoking index, FEV1, arterial blood gasses, and LAA%.[9] The mean BMI was 21.3 ± 2.7.[9] A critical appraisal of the association suggested that low BMI and not emphysema is the cause of low BMD.[17] CT-diagnosed emphysema, hypoxemia, low BMI (in spite of high caloric intake) and muscle wasting are known to cluster.[7,8,31,36,37] Furthermore, the LAA% used in the study is not specific to emphysema but overlaps with severe asthma (even in nonsmokers) and correlates inversely with FEV1.[38] Bon *et al*. reported in 2011 that the visual score of emphysema and female sex were the only factors that increased the likelihood of osteopenia/osteoporosis in multivariate logistic regression.[13] However, they did not explore the role of BMI, and 38% of their sample did not have airway obstruction (smokers "at risk" for COPD) who would not qualify nowadays for a diagnosis of COPD.[13] Recently Jaramillo *et al*. used LAA% −950 HU as an indicator of emphysema.[4] They reported an association between emphysema and BMD after adjusting for age, race, BMI, and the use of oral corticosteroids.[4] However, their model did not include FEV1 adjustment which may have biased the results.[4] The level of attenuation of − 950 HU is known to overlap with nonemphysematous obstructive lung disease.[38] The same methodology (LAA% −950 HU) was used by Bai *et al*. who reported in 2011 that LAA% and BMI were significantly different in the group with the lowest BMD.[14] Similarly, their model did not include FEV1.[14] In our study, the multivariate regression model included age, BMI, hypoxia and FEV1, which may explain why the association between emphysema and BMD was not significant.

A review in 2012 by Bon attempted an explanation as to why radiographic emphysema increased the risk of osteoporosis.[16] The first explanation offered is that both emphysema and osteoporosis are the result of high inflammatory load.[16] TNF-α, interleukins, and metalloproteinase were the inflammatory markers highlighted as potential candidates.[16] Metalloproteinase, interleukins, and CRP were shown to rise not only in the emphysematous phenotype but also in the bronchial thickening phenotype of COPD.[18,39] Similarly, TNF-α far from being raised was shown in some studies to be significantly lower in emphysema.[39] Although some studies reported an association between osteoporosis and some inflammatory markers, the Framingham offspring longitudinal study found no consistent association in postmenopausal women between osteoporosis and serum levels of interleukin-6, TNF-α or CRP.[19] The second explanation offered in the review is that both emphysema and osteoporosis are autoimmune conditions.[16] The evidence for COPD being an autoimmune condition is tenuous and not widely endorsed. Although a third of patients with stable COPD display abnormal titers of antinuclear and anti-tissue antibodies, these were not specific to the emphysema phenotype and were considered to be the result and not the cause of tissue destruction.[40-42] More specific antibodies aimed at elastin were considered to be potential inducers of emphysema. However, several studies could not identify antielastin antibodies or their levels in plasma or bronchoalveolar lavage were not elevated compared to controls.[43-45] The review and its references cite the osteoporosis of rheumatoid arthritis, lupus, and celiac disease as conditions where auto-antibodies have been "associated" with low BMD.[16] Even in these exclusively autoimmune conditions, osteoporosis is multifactorial as there exist no antibodies directed against bone tissue. The review also failed to address the role of severity of COPD and cachexia as confounding factors for the role of emphysema.[16]

Conclusion

Our findings support the doubts expressed about emphysema being an independent risk factor for osteoporosis. Low BMI, severity of COPD and hypoxia play a dominant role. In the first reported multivariate model including these three factors (as well as age and CRP), emphysema was shown not to be an independent risk factor.

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Conflicts of interest

There are no conflicts of interest.

References

1. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: A systematic review. Eur Respir J 2009;34:209-18.
2. Chen SJ, Liao WC, Huang KH, Lin CL, Tsai WC, Kung PT, *et al*. Chronic obstructive pulmonary disease and allied conditions is a strong independent risk factor for osteoporosis and pathologic fractures: A population-based cohort study. QJM 2015;108:633-40.
3. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E; Osteoporotic Fractures in Men (MrOS) Research Group. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. Osteoporos Int 2010;21:1341-9.
4. Jaramillo JD, Wilson C, Stinson DS, Lynch DA, Bowler RP, Lutz S,

et al. Reduced bone density and vertebral fractures in smokers. Men and COPD patients at increased risk. Ann Am Thorac Soc 2015;12:648-56.
5. Harrison RA, Siminoski K, Vethanayagam D, Majumdar SR. Osteoporosis-related kyphosis and impairments in pulmonary function: A systematic review. J Bone Miner Res 2007;22:447-57.
6. Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: Links, risks, and treatment challenges. Int J Chron Obstruct Pulmon Dis 2016;11:637-48.
7. Cielen N, Maes K, Gayan-Ramirez G. Musculoskeletal disorders in chronic obstructive pulmonary disease. Biomed Res Int 2014;2014:965764.
8. Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in chronic obstructive pulmonary disease. Clin Med Insights Circ Respir Pulm Med 2015;9:5-21.
9. Ohara T, Hirai T, Muro S, Haruna A, Terada K, Kinose D, *et al.* Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. Chest 2008;134:1244-9.
10. Van Tho N, Ogawa E, Trang le TH, Ryujin Y, Kanda R, Nakagawa H, *et al.* A mixed phenotype of airway wall thickening and emphysema is associated with dyspnea and hospitalization for chronic obstructive pulmonary disease. Ann Am Thorac Soc 2015;12:988-96.
11. Tatsumi K, Kasahara Y, Kurosu K, Tanabe N, Takiguchi Y, Kuriyama T; Respiratory Failure Research Group in Japan. Clinical phenotypes of COPD: Results of a Japanese epidemiological survey. Respirology 2004;9:331-6.
12. Cerveri I, Corsico AG, Grosso A, Albicini F, Ronzoni V, Tripon B, *et al.* The rapid FEV(1) decline in chronic obstructive pulmonary disease is associated with predominant emphysema: A longitudinal study. COPD 2013;10:55-61.
13. Bon J, Fuhrman CR, Weissfeld JL, Duncan SR, Branch RA, Chang CC, *et al.* Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. Am J Respir Crit Care Med 2011;183:885-90.
14. Bai P, Sun Y, Jin J, Hou J, Li R, Zhang Q, *et al.* Disturbance of the OPG/RANK/RANKL pathway and systemic inflammation in COPD patients with emphysema and osteoporosis. Respir Res 2011;12:157.
15. Cooper CB. Do holes in the lungs beget holes in the bones? Am J Respir Crit Care Med 2011;183:835-7.
16. Bon J. Does radiographic emphysema correlate with low bone mineral density? Curr Opin Pulm Med 2012;18:125-30.
17. van den Borst B, Schols AM. Low bone mineral density in emphysema: Epiphenomenon of a wasting phenotype? Am J Respir Crit Care Med 2011;184:1087-8.
18. Tulek B, Kivrak AS, Ozbek S, Kanat F, Suerdem M. Phenotyping of chronic obstructive pulmonary disease using the modified Bhalla scoring system for high-resolution computed tomography. Can Respir J 2013;20:91-6.
19. Sponholtz TR, Zhang X, Fontes JD, Meigs JB, Cupples LA, Kiel DP, *et al.* Association between inflammatory biomarkers and bone mineral density in a community-based cohort of men and women. Arthritis Care Res (Hoboken) 2014;66:1233-40.
20. GOLD. Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2015. Available from: http://www.goldcopd.org/. [Last accessed on 2015 Nov 11].
21. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. Clin Radiol 1982;33:379-87.
22. Hersh CP, Jacobson FL, Gill R, Silverman EK. Computed tomography phenotypes in severe, early-onset chronic obstructive pulmonary disease. COPD 2007;4:331-7.
23. World Health Organization. Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis: Report of a WHO Study Group [Meeting Held in Rome from 22 to 25 June 1992]; 1994.
24. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
25. Ryan CS, Petkov VI, Adler RA. Osteoporosis in men: The value of laboratory testing. Osteoporos Int 2011;22:1845-53.
26. Lin CW, Chen YY, Chen YJ, Liang CY, Lin MS, Chen W. Prevalence, risk factors, and health-related quality of life of osteoporosis in patients with COPD at a community hospital in Taiwan. Int J Chron Obstruct Pulmon Dis 2015;10:1493-500.
27. Graat-Verboom L, Spruit MA, van den Borne BE, Smeenk FW, Martens EJ, Lunde R, *et al.* Correlates of osteoporosis in chronic obstructive pulmonary disease: An underestimated systemic component. Respir Med 2009;103:1143-51.
28. Vrieze A, de Greef MH, Wijkstra PJ, Wempe JB. Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. Osteoporos Int 2007;18:1197-202.
29. De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, *et al.* Body mass index as a predictor of fracture risk: A meta-analysis. Osteoporos Int 2005;16:1330-8.
30. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes. Endocrinology 1999;140:1630-8.
31. Cornish J, Callon KE, Bava U, Lin C, Naot D, Hill BL, *et al.* Leptin directly regulates bone cell function *in vitro* and reduces bone fragility *in vivo*. J Endocrinol 2002;175:405-15.
32. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, *et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:728-35.
33. Liu WT, Kuo HP, Liao TH, Chiang LL, Chen LF, Hsu MF, *et al.* Low bone mineral density in COPD patients with osteoporosis is related to low daily physical activity and high COPD assessment test scores. Int J Chron Obstruct Pulmon Dis 2015;10:1737-44.
34. Arnett TR. Acidosis, hypoxia and bone. Arch Biochem Biophys 2010;503:103-9.
35. Chuang ML, Lin IF, Vintch JR, Ho BS, Chao SW, Ker JJ. Significant exercise-induced hypoxaemia with equivocal desaturation in patients with chronic obstructive pulmonary disease. Intern Med J 2006;36:294-301.
36. Renvall MJ, Friedman P, Ramsdell JW. Predictors of body mass index in patients with moderate to severe emphysema. COPD 2009;6:432-6.
37. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(6 Pt 1):1791-7.
38. Biernacki W, Redpath AT, Best JJ, MacNee W. Measurement of CT lung density in patients with chronic asthma. Eur Respir J 1997;10:2455-9.
39. Bon JM, Leader JK, Weissfeld JL, Coxson HO, Zheng B, Branch RA, *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.
40. Núñez B, Sauleda J, Antó JM, Julià MR, Orozco M, Monsó E, *et al.* Anti-tissue antibodies are related to lung function in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;183:1025-31.
41. Taraseviciene-Stewart L, Voelkel NF. Oxidative stress-induced antibodies to carbonyl-modified protein correlate with severity of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:1026.
42. Sapey E, Wood AM. Auto-antibodies and inflammation. A case of the chicken and the egg? Am J Respir Crit Care Med 2011;183:959-60.
43. Rinaldi M, Lehouck A, Heulens N, Lavend'homme R, Carlier V,

Saint-Remy JM, *et al*. Antielastin B-cell and T-cell immunity in patients with chronic obstructive pulmonary disease. Thorax 2012;67:694-700.

44. Low TB, Greene CM, O'Neill SJ, McElvaney NG. Quantification and evaluation of the role of antielastin autoantibodies in the emphysematous lung. Pulm Med 2011;2011:826160.
45. Greene CM, Low TB, O'Neill SJ, McElvaney NG. Anti-proline-glycine-proline or antielastin autoantibodies are not evident in chronic inflammatory lung disease. Am J Respir Crit Care Med 2010;181:31-5.