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EDITORIAL

# It's the Fracture that Matters – Bone Disease in COPD Patients

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Bone loss or "osteoporosis" in the context of COPD should be a critical issue for physicians providing clinical care to COPD patients, and the occurrence of bone loss in association with emphysema predominant COPD (1) is a potential tool for understanding the pathogenesis of tissue wasting disease. Four years ago we reviewed the issue of bone loss and COPD (2). Since that time a number of interesting manuscripts have been published that expand this area. In this issue of COPD: Journal of Chronic Obstructive Pulmonary Disease, a group of researchers from Japan studied a small, predominantly male COPD cohort to probe what factors predict vertebral fractures in COPD subjects (3). The paper highlights the reason that we screen for osteoporosis or bone loss: What is the future fracture risk? Their findings provide a perspective on how risk prediction may change between groups with different underlying conditions. If a prediction model applicable to the general population fails to predict fractures in patients with COPD, it may be because the factors used are not appropriate predictors in the COPD population. This may be because the usual risk prediction factors such as advancing age and female gender have less impact on the development of bone loss compared to the impact of chronic inflammation.

For clinicians and patients, bone loss is silent until it results in fracture. Fractures are associated with profoundly negative impacts on quality of life and increased mortality in the general population, and may have more severe implications for COPD patients given that studies show mortality is higher for COPD patients after hip fracture (4). Since fractures can be decreased by treatment, the effort to test for reduced bone density as a surrogate for fracture risk is important in the care of patients with COPD. Like many screening tests, however, bone density measurements do not correlate perfectly either with mechanical strength of the bone nor with the prediction of fracture risk. Algorithms such as the Fracture Risk Assessment Tool (FRAX) (http://www.shef.ac.uk/FRAX/) have been developed to improve risk prediction for fractures and can be used with or without bone mineral density (BMD) data (5). These prediction models, however, are known to have significant limitations, especially in specific populations (6,7).

Ogura-Tomomatsu *et al* found that a FRAX developed for a general Japanese population failed to predict vertebral fractures in their COPD patients. They found that age, oral corticosteroid use, long term oxygen use and severity of obstruction measured by spirometry were predictors of vertebral fracture rather than BMD derived assessment of osteoporosis or FRAX. These results suggest that COPD patients may have more fracture risk derived from the severity of their lung disease and corticosteroid use, than from the factors used in deriving the general population fracture risk. Thus, COPD patients could benefit from an alternative set of fracture risk factors based on the degree of airflow obstruction, use of glucocorticoids and frequency of exacerbations. The results from Oguro-Tomomatsu *et al* urgently imply that current recommendations for when to screen for bone loss based on

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risk factors in the general population (female, northern European, low body mass) may be ineffective in predicting risk for COPD and may lead to large numbers of COPD patients not being diagnosed or treated to prevent fractures. Although formal recommendations are lacking for COPD patients, testing for bone density and evaluating the spine for prevalent vertebral fractures in all COPD patients would be prudent.

The relationship of bone loss with COPD is supported by other recent publications. Nuti et al looked at 3,030 COPD patients from Italy and assessed vertebral fractures and bone status by ultrasound (8). They found that age, previous fracture, body mass index (BMI), severity of COPD and oral corticosteroid use were strong predictors of fractures, especially in men. Interestingly they found fracture rates in their population were similar in men and women and that 40% of their subjects had vertebral fractures.

A study from China explored the potential role of chronic, systemic inflammation relating bone loss and lung disease (9). They studied 672 subjects with mostly moderate COPD and classified them as normal, osteopenic and osteoporotic based on BMD measured by DXA. They found that three systemic markers of inflammation (C reactive Protein (CRP), TNF-α and IL-6) were each significantly higher in osteopenic and osteoporotic COPD subjects than COPD subjects with normal BMD. The severity of lung disease as measured by FEV1% and FEV1/FVC was significantly worse in each of these three groups, making a direct association between systemic inflammation, severity of lung disease and severity of bone loss.

The relationship of bone loss to emphysema severity is another tantalizing association that may give clues to common disease pathways. The initial association reported by Ohara (1) was supported by another recent publication by Bon et al (10). They studied 200 smokers with and without COPD who had both DXA bone density and chest CT scans finding that the severity of emphysema associated with BMD.

Muscle loss or cachexia has been described as another important association to bone loss. Researchers from the Netherlands used bioimpedance to measure fat free mass in 554 COPD subjects in addition to BMD by dual-energy X-ray Absorptiometry (DXA) (11). They found a strong association of cachexia to bone loss and found protective effects from obesity or increased BMI. In their population, however, CRP as a marker of systemic inflammation was not predictive of osteoporosis. They also did not find female gender to be differentially predictive of bone loss in COPD suggesting that men may be equally vulnerable to bone loss in association with COPD.

Detection of vertebral fractures and measurement of volumetric bone density on chest CT scans could be an important step forward for COPD patients. Several studies have been published demonstrating effective use of CT scans for quantitative CT (QCT) bone measurements both with (12) and without (13,14) calcium calibration phantoms. Asymptomatic vertebral fractures are important predictors of future fractures and can identify at-risk individuals for whom treatment should be considered. Two recent studies demonstrate opportunities to improve fracture detection using saggital reconstructed images from chest CT scans (15,16). Although these methodologies for bone density assessment and fracture detection might not be appropriate for the general population, in COPD patients who may have a chest CT scan done for other diagnostic purposes, there is the additional opportunity to obtain important data about future fracture risk.

Given the strong associations reported between COPD and bone loss; aggressive testing for bone loss, evaluating the spine for existing vertebral fractures and minimizing the use of corticosteroids are all appropriate in COPD subjects - regardless of prediction algorithms established for the general population. Men, in particular, should be considered at risk, and a prior vertebral fracture should be recognized as meeting the diagnostic criteria for both bone disease and future fracture risk. Specific trials to assess the effectiveness of bisphosphonates and anabolic treatments for bone loss in COPD patients still are lacking. Progress has been made, but much remains to be done in this area.

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