COPD-Related Musculoskeletal Disease

Jessica Bon Field, MD, MS
2017 Update in Internal Medicine
October 20, 2017
A 60-year old man with COPD comes into your office for a routine office visit. He is a former smoker of ½ pack per day for 30 years. He reports that his exertional tolerance is stable and that he continues to walk slower than in his friends. He rarely needs to use his albuterol inhaler and has not had any acute exacerbations over the past year. FEV1 measured at the time of his last visit six months ago was 2.2 L (66% predicted). Which of the following tests is recommended in the management of this COPD patient?

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B. Low-dose CT scan  
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C. Bone densitometry  
D. Pneumococcal antibody panel testing
Learning Objectives

1) To review the epidemiology of COPD-related osteoporosis

2) To recognize both lung-specific and traditional osteoporosis risk factors associated with bone loss in COPD

3) To understand osteoporosis screening guidelines for individuals with COPD

4) To determine appropriate therapy for osteopenia and osteoporosis in individuals with COPD
COPD-Related Osteoporosis Epidemiology
Problem: Can anyone read why this sticky note was put here?

Answer: No.
## Prevalence of Low BMD in NHANES III

### Severity of Airflow Obstruction

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### Prevalence of Low BMD in TORCH*

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<tr>
<th>Baseline BMD Values</th>
<th>Total (N=658)</th>
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<tr>
<td>Osteoporosis, BMD T score &lt; -2.5 hip or spine</td>
<td>147 (23%)</td>
</tr>
<tr>
<td>Male</td>
<td>66 (18%)</td>
</tr>
<tr>
<td>Female</td>
<td>81 (30%)</td>
</tr>
<tr>
<td>Osteopenia, T score &lt; -1.0 and &gt; -2.5 hip or spine</td>
<td>272 (42%)</td>
</tr>
<tr>
<td>Male</td>
<td>160 (42%)</td>
</tr>
<tr>
<td>Female</td>
<td>112 (41%)</td>
</tr>
<tr>
<td>Osteoporosis or osteopenia T score &lt; -1.0 hip or spine</td>
<td>419 (65%)</td>
</tr>
<tr>
<td>Male</td>
<td>226 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>193 (71%)</td>
</tr>
</tbody>
</table>

*Mean age 65
*Mean FEV1 44% predicted

Prevalence Low Bone Mineral Density University of Pittsburgh Smoking Cohort (N=388)

![Bar chart showing prevalence rates for normal, osteopenia, and osteoporosis. The chart indicates that the prevalence increases from normal to osteoporosis, with a statistical significance level of P(trend) = 0.002.](image)
Prevalence of Low Bone Mineral Density and Vertebral Fractures on Chest CT - COPDGene

3317 CT scans
37% with fractures

Odds of Vertebral Fracture by Diagnosis

- COPD
- Known osteoporosis
- Age >= 75
- Previous fractures
- Drugs "inducing" osteoporosis
- ALP bone out of range
- Diabetes
- Overweight/obese
- Female sex
- Calcemia <8.5
- Heart failure
- GFR <60
- Sedentary vs active
- Hepatic disease

Log odds ratio

Odds of Vertebral Fracture by Diagnosis

Log odds ratio

- Known osteoporosis: 2.31 [1.58-3.38]
- Age >= 75: 1.98 [1.26-3.11]
- Previous fractures: 1.87 [1.31-2.67]
- Drugs "inducing" osteoporosis: 1.53 [0.95-2.47]
- ALP bone out of range: 1.17 [0.83-1.65]
- Diabetes: 1.17 [0.75-1.83]
- Overweight/obese: 1.16 [0.81-1.65]
- Female sex: 1.07 [0.77-1.50]
- Calcemia <8.5: 1.07 [0.76-1.49]
- Heart failure: 1.05 [0.73-1.50]
- GFR <60: 1.04 [0.71-1.52]
- Sedentary vs active: 0.99 [0.69-1.41]
- Hepatic disease: 0.96 [0.55-1.66]
Impact of Fractures in COPD

• 60-70% higher risk of death after hip fracture in COPD patients compared to those without COPD

• High fracture rate with rare BMD assessments (4.4%) and osteoporosis treatment (2.8%) in male veterans with COPD

• Osteoporotic fractures lead to reduced vital capacity and FEV1

Risk Factors for COPD-Related Low Bone Mineral Density
Mechanisms of COPD-related Bone Mineral Density Loss

- Smoking
- Vitamin D Levels
- Low BMI
- Low Muscle Mass
- Hypogonadism
- Corticosteroids
- Decreased Activity

COPD → Smoking → Vitamin D Levels → Low BMI → Low Muscle Mass → Hypogonadism → Corticosteroids → Decreased Activity → Osteoporosis
Emphysema and Bone Mineral Density Loss

<table>
<thead>
<tr>
<th></th>
<th>Chi Square</th>
<th>p value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male : Female)</td>
<td>24.297</td>
<td>0.00019</td>
<td>1.48</td>
<td>1.27 – 1.74</td>
</tr>
<tr>
<td>Race (NHW: AA)</td>
<td>10.08</td>
<td>0.001</td>
<td>1.4</td>
<td>1.14 – 1.72</td>
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<tr>
<td>Current smoking status (Current: Former)</td>
<td>5.65</td>
<td>0.02</td>
<td>1.23</td>
<td>1.03 – 1.46</td>
</tr>
<tr>
<td>BMI (Unit Odds)</td>
<td>6.59</td>
<td>0.02</td>
<td>1.02</td>
<td>1.004 – 1.03</td>
</tr>
<tr>
<td>QCT-BMD (mg/cc) (Unit odds)</td>
<td>118.67</td>
<td>&lt;0.0001</td>
<td>0.988</td>
<td>0.986 – 0.99</td>
</tr>
<tr>
<td>Emphysema (LAA% at -950 HU) (Unit odds)</td>
<td>6.727</td>
<td>0.01</td>
<td>1.01</td>
<td>1.003 – 1.02</td>
</tr>
</tbody>
</table>

Bon et al. AJRCCM 2011; 183: 885-90.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age enrollment</td>
<td>1.03 (1.02-1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.41 (1.07-1.86)</td>
<td>0.016</td>
</tr>
<tr>
<td>Reported osteoporosis</td>
<td>1.65 (1.18-2.31)</td>
<td>0.004</td>
</tr>
<tr>
<td>Reported hip fracture</td>
<td>5.87 (3.64-9.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reported rheumatoid arthritis</td>
<td>1.79 (1.24-2.59)</td>
<td>0.002</td>
</tr>
<tr>
<td>Reported diabetes</td>
<td>1.64 (1.20-2.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total exacerbations</td>
<td>1.06 (1.04-1.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*41,604 person years follow up; 215 hip fractures*

COPDGene *unpublished data*
Systemic Inflammation Linking Lung and Bone

Lung Inflammation

Systemic Inflammation CRP, IL-6, TNF-α, fibrinogen

Cardiovascular Disease

- Low BMI
- Muscle dysfunction
- Osteopenia
- Diabetes
- Anemia
- Depression
Systemic Inflammation Linking Lung and Bone

- CRP, IL-6, TNF-α
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Lung Inflammation

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Systemic Inflammation
### Systemic Inflammation Linking Lung and Bone

#### Table of Associations

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<tr>
<td>Age (years)</td>
<td>1.09</td>
<td>0.61–1.32</td>
<td>0.082</td>
</tr>
<tr>
<td>Female gender (n, %)</td>
<td>1.38</td>
<td>0.86–2.97</td>
<td>0.098</td>
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<tr>
<td>Use of ICS (n, %)</td>
<td>2.01</td>
<td>0.69–3.72</td>
<td>0.26</td>
</tr>
<tr>
<td>FEV₁%pred (%)</td>
<td>1.37</td>
<td>0.78–3.24</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Systemic inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present vs. none</td>
<td>3.10</td>
<td>1.48–5.06</td>
<td>0.014</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.55</td>
<td>0.92–3.03</td>
<td>0.062</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>3.22</td>
<td>1.48–6.77</td>
<td>0.010</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.58</td>
<td>1.32–4.56</td>
<td>0.023</td>
</tr>
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**Notes:**
- BMI: Body Mass Index
- ICS: Inhaled Corticosteroids
- COPD: Chronic Obstructive Pulmonary Disease
- BMD: Bone Mineral Density
Systemic Inflammation

CRP, IL-6, TNF-α, fibrinogen

Lung Inflammation

Cardiovascular Disease

• Low BMI
• Muscle dysfunction
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Systemic Inflammation Linking Lung and Bone


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<tr>
<th>Marker</th>
<th>CTx*</th>
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<td>IL-2</td>
<td>N.S.</td>
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<td>0.005</td>
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<td>0.01</td>
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<tr>
<td>IFN-γ</td>
<td>N.S.</td>
<td>0.30</td>
<td>0.10 (+)</td>
<td>0.02</td>
</tr>
<tr>
<td>RANTES</td>
<td>0.11 (-)</td>
<td>0.01</td>
<td>0.08 (-)</td>
<td>0.02</td>
</tr>
<tr>
<td>eotaxin</td>
<td>0.21 (-)</td>
<td>0.003</td>
<td>0.17 (-)</td>
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*Adjusted for bisphosphonate and steroid use.
*Type I collagen c-telopeptides; R² value(direction)
**Procollagen type I amino-terminal propeptide; R² value(direction)
Autoimmunity Linking Lung and Bone


Prevalence of Emphysema and Low BMD Increased with anti-GRP78 Autoantibody Positivity
Osteoporosis Screening in COPD
A 60-year old man with COPD comes into your office for a routine office visit. He is a former smoker of ½ pack per day for 30 years. He reports that his exertional tolerance is stable and that he continues to walk slower than in his friends. He rarely needs to use his albuterol inhaler and has not had any acute exacerbations over the past year. FEV1 measured at the time of his last visit six months ago was 2.2 L (66% predicted). Which of the following tests is recommended in the management of this COPD patient?

A. Spirometry
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C. Bone densitometry
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Women > 65 or < 65 if risk factors; “current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.”

“Data are insufficient in men to determine whether the presence of respiratory disease..........increase the risk for low-BMD mediated fracture.”
Osteoporosis is a major comorbidity that is often under-diagnosed and associated with poor health status and prognosis. Osteoporosis is often associated with emphysema, decreased body mass index, and low fat-free mass. Low bone mineral density and fractures are commonly in COPD patients even after adjustment for steroid use, age, pack-years of smoking, current smoking, and exacerbations. Osteoporosis should be treated according to usual guidelines.
# Prevalence of Low BMD in NHANES III

## Severity of Airflow Obstruction

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Prevalence of Low BMD by Obstruction Severity

Prevalence Low BMD UofPitt Smoking Cohort

With lung disease:
- Mean FEV1 76.7%
- ICS = 27%
- 61% females, 40% males

P(trend) = 0.002
(My) Approach to Screening

• All COPD patients > 65 years of age (men and women)
• All COPD patients with history of fracture
• COPD patients 50 - 64 years of age with any of the following:
  • Severe airflow obstruction (FEV1 < 50% predicted)
  • Chronic oral steroid use (rare)
  • Frequent acute exacerbations of COPD requiring short courses of systemic steroids
  • Significant radiographic emphysema detected on chest imaging
Treatment of COPD-Related Osteopenia and Osteoporosis
Who to treat?

- T score $\leq -2.5$ or fragility fracture
- FRAX score with 10-year probability of hip fracture or combined major osteoporotic fracture of $\geq 3$ or $\geq 20$ percent, respectively
How to Treat

• Lifestyle modifications
  • Weight-bearing exercise
  • Avoid smoking, excess alcohol intake
• Assure adequate calcium and vitamin D intake
  • Calcium 1000 – 1200 mg daily
  • Vitamin D supplementation 600 to 800 IU/day, check levels
• Treatment of secondary causes (hypogonadism in men)
• Bisphosphonate therapy (first-line)
• Denosumab
• Teriparatide (severe osteoporosis)
• SERMs (raloxifene)
Summary

• Osteoporosis is prevalent in COPD, occurs independently of traditional osteoporosis risk factors, and contributes significantly to morbidity and mortality

• Multiple mechanisms, including systemic inflammation and autoimmunity, likely contribute to bone loss in COPD

• Future research efforts should focus on delineating mechanisms of bone loss, establishing disease-specific screening guidelines, and assessing response to therapy