Bone Imaging and Fracture Discrimination

Sophie A Jamal, MD, PhD, FRCPC
Associate Professor of Medicine, Division of Endocrinology and Metabolism
University of Toronto
Disclosure of Interests

- Consultant: Genzyme, Novartis, Shire, Warner-Chillcott

- Speaker Bureau with: Amgen, Genzyme, Novartis, Shire, Warner-Chillcott
Objectives

- Etiology of fractures
- Epidemiology of fractures
- Bone imaging and fracture discrimination
- Potential bone quality guidelines that may need to be updated
Why Bones Break

Applied Load

\[ \frac{\text{Bone Strength}}{\text{Bone Strength}} > 1, \text{ fracture will occur} \]

Bouxsein MJ Bone Joint Surg Am. 2001
Contributors to Bone Strength

- Bone Density
- Bone Turnover
- Bone Architecture
- Bone Mineral
A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Vascular or other soft tissue calcification
- Abnormalities of calcium, phosphorus, PTH or Vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth or strength

Moe et al. KI. 2006.
"a skeletal disorder characterized by **compromised bone strength** predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of **bone density and bone quality**"
Fractures in Stage 5D

- Fracture rates /post discharge outcomes from 2000-2009 using medicare data (US Renal Data System)
- Constant rate of fracture over time; high
- Pelvis/hip: 20.6 per thousand patient years
- Higher morbidity and mortality if admitted with fracture
  - 3.8 to 5.2 more hospitalizations
  - 47% discharged to skilled nursing facility
  - Mortality 2x higher

Beaubreun A et al JASN 2013
Hip Fractures in 5D

- 2 cohorts using medicare data
  - HD cohort
  - Non ESRD (age >65, medicare)

- Hip fractures 93-2010
- Decline in fractures since 2003
  - Calcium based binders
  - Cinacalcet use
  - NKF-KDOQI guidelines 2003

Areneson TJ et al AJKD 2013
Fractures Across the Spectrum of CKD

Women

Men

Estimated Glomerular Filtration Rate (mL/min/1.73 m²)

Naylor et al. 2013 ASN Abstract
Summary

- Fractures are due to impaired bone strength
- Fracture rates are higher in CKD than non-CKD
- Noninvasive methods to assess fracture risk
3.2.2.

In patients with CKD stages 3 - 5D with evidence of CKD-MBD we suggest that BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)
KDIGO RATINGS

• Level 2B: we suggest –
  – The majority of people in your situation would want the recommended course of action, but many would not (patient perspective)
  – Different choices will be appropriate for different patients (clinicians)
  – The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined (policy makers)
  – B: Moderate evidence – the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different
Revisit the Recommendation?

- Are there important and relevant new data?
- Do the data suggest the recommendation might or should change?
A Shift in the Balance
Strengths of DXA

- Quick, noninvasive
- Measurements correlate with fracture risk
- Predictive ability similar to that of BP to predict stroke
- Better than ability of cholesterol to predict coronary artery disease
Limitations of DXA

- No threshold
- Static assessment of bone
- Areal bone mineral density
- No data on microarchitecture
- Results are meant for diagnosis
Limitations with DXA in CKD

Normal bone
- Normal Bone mass
- Normal Mineralisation
- 1.250g/cm²

Osteoporosis
- Low Bone mass
- Normal Mineralisation
- 0.625g/cm²

OM
- Normal Bone mass
- Normal Mineralisation
- 0.625g/cm²

ABD
- Low Bone mass
- Mineralisation increased
- 0.625g/cm²

II HPT
- Normal or high Bone mass
- Mineralisation decreased
- 0.625g/cm²
### Total Hip BMD by DXA

#### 1.2.1 Dialysis Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Ambrus 2011</td>
<td>0.66</td>
<td>0.18</td>
<td>21</td>
</tr>
<tr>
<td>Cejka 2011</td>
<td>0.573</td>
<td>0.048</td>
<td>24</td>
</tr>
<tr>
<td>Fontaine 1999</td>
<td>0.62</td>
<td>0.13</td>
<td>11</td>
</tr>
<tr>
<td>Limori 2012</td>
<td>0.567</td>
<td>0.133</td>
<td>46</td>
</tr>
<tr>
<td>Jamal 2002</td>
<td>1.3</td>
<td>0.23</td>
<td>54</td>
</tr>
<tr>
<td>Jamal 2006</td>
<td>0.76</td>
<td>0.17</td>
<td>27</td>
</tr>
<tr>
<td>Urena 2003</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>204</td>
<td></td>
<td>776</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $Chi^2 = 8.78$, df = 5 ($P = 0.12$); $I^2 = 43\%$

Test for overall effect: $Z = 4.81$ ($P < 0.000001$)

#### 1.2.2 Non-dialysis Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Nickolas 2010</td>
<td>0.621</td>
<td>0.0718</td>
<td>23</td>
</tr>
<tr>
<td>Nickolas 2011</td>
<td>0.677</td>
<td>0.127</td>
<td>32</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>55</td>
<td></td>
<td>118</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $Chi^2 = 1.61$, df = 1 ($P = 0.21$); $I^2 = 38\%$

Test for overall effect: $Z = 4.47$ ($P < 0.000001$)

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.67</td>
<td>0.09</td>
<td>259</td>
<td>100.0%</td>
<td>-0.08 [-0.11, -0.06]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $Chi^2 = 11.33$, df = 7 ($P = 0.12$); $I^2 = 38\%$

Test for overall effect: $Z = 6.91$ ($P < 0.000001$)

Test for subgroup differences: $Chi^2 = 1.21$, df = 1 ($P = 0.27$), $I^2 = 17.5\%$
### Lumbar Spine BMD by DXA

#### 1.3.1 Dialysis Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Ambrus 2011</td>
<td>0.92</td>
<td>0.22</td>
<td>21</td>
</tr>
<tr>
<td>Cejka 2011</td>
<td>0.81</td>
<td>0.06</td>
<td>24</td>
</tr>
<tr>
<td>Fontaine 1999</td>
<td>0.85</td>
<td>0.16</td>
<td>11</td>
</tr>
<tr>
<td>Ilimi 2012</td>
<td>0.57</td>
<td>0.16</td>
<td>46</td>
</tr>
<tr>
<td>Inaba 2005</td>
<td>0.53</td>
<td>0.085</td>
<td>21</td>
</tr>
<tr>
<td>Jamal 2002</td>
<td>0.86</td>
<td>0.17</td>
<td>54</td>
</tr>
<tr>
<td>Jamal 2006</td>
<td>1.19</td>
<td>0.24</td>
<td>27</td>
</tr>
<tr>
<td>Kaji 2002</td>
<td>0.92</td>
<td>0.048</td>
<td>14</td>
</tr>
<tr>
<td>Urena 2003</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Yamaguchi 1986</td>
<td>0.76</td>
<td>0.059</td>
<td>27</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>266</strong></td>
<td><strong>135</strong></td>
<td><strong>130</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 0.00, Chi² = 73.01, df = 8 (P < 0.000001), I² = 99%
**Test for overall effect:** Z = 2.35 (P = 0.02)

#### 1.3.2 Non-dialysis patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Jamal 2012</td>
<td>1.01</td>
<td>0.2</td>
<td>74</td>
</tr>
<tr>
<td>Nickolas 2010</td>
<td>0.83</td>
<td>0.151</td>
<td>23</td>
</tr>
<tr>
<td>Nickolas 2011</td>
<td>0.95</td>
<td>0.173</td>
<td>32</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>129</strong></td>
<td><strong>255</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 0.00, Chi² = 0.46, df = 2 (P = 0.79), I² = 0%
**Test for overall effect:** Z = 5.05 (P < 0.00001)

**Total (95% CI):**

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>395</td>
<td>1390</td>
<td>100.0%</td>
<td>-0.07 [-0.10, -0.03]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 0.00, Chi² = 74.69, df = 11 (P < 0.000001), I² = 85%
**Test for overall effect:** Z = 3.58 (P = 0.0003)
**Test for subgroup differences:** Chi² = 2.73, df = 1 (P = 0.10), I² = 63.3%
Mid 3rd Radius by DXA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>1.4.1 Dialysis Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrus 2011</td>
<td>0.77</td>
<td>0.28</td>
<td>21</td>
</tr>
<tr>
<td>Fontaine 1999</td>
<td>0.61</td>
<td>0.09</td>
<td>11</td>
</tr>
<tr>
<td>Ilmori 2012</td>
<td>0.566</td>
<td>0.148</td>
<td>46</td>
</tr>
<tr>
<td>Inaba 2005</td>
<td>0.4468</td>
<td>0.094</td>
<td>21</td>
</tr>
<tr>
<td>Kaji 2002</td>
<td>0.49</td>
<td>0.039</td>
<td>14</td>
</tr>
<tr>
<td>Yamaguchi 1996</td>
<td>0.446</td>
<td>0.0266</td>
<td>27</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>140</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau² = 0.00; Chi² = 50.87, df = 5 (P < 0.00001); I² = 90%
| Test for overall effect: Z = 4.67 (P < 0.00001)

1.4.2 Non-dialysis patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Jamal 2012</td>
<td>0.68</td>
<td>0.1</td>
<td>74</td>
</tr>
<tr>
<td>Nickolas 2010</td>
<td>0.63</td>
<td>0.122</td>
<td>23</td>
</tr>
<tr>
<td>Nickolas 2011</td>
<td>0.652</td>
<td>0.107</td>
<td>32</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>129</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 2 (P = 0.03); I² = 73%
| Test for overall effect: Z = 3.15 (P = 0.002)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fracture Group</th>
<th>Non-Fracture Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>269</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau² = 0.00; Chi² = 70.05, df = 8 (P < 0.00001); I² = 89%
| Test for overall effect: Z = 5.54 (P < 0.00001)
| Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%
BMD and Fractures in CKD

- Prospective study
- 485 patients on HD, followed for 5 years
- 46 clinical fractures and 29 prevalent spine fractures
- BMD by DXA (hip, spine, 1/3 radius) able to predict incident fractures
  - FRAX did not improve prediction

Imori S et al NDT 2012
DXA to Predict Fracture

Imori S et al NDT 2012
FRAX in CKD

Risk assessment tool developed by the World Health Organization to identify men and women at high fracture risk. Uses ten clinical risk factors, combined either with or without femoral neck BMD, to estimate the 10-year probability of fracture (hip or major osteoporotic fracture).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Fracture</td>
<td>0.71</td>
<td>0.65 to 0.77</td>
</tr>
<tr>
<td>FRAX with BMD</td>
<td>0.67</td>
<td>0.61 to 0.73</td>
</tr>
<tr>
<td>FRAX without BMD</td>
<td>0.67</td>
<td>0.61 to 0.73</td>
</tr>
<tr>
<td>FRAX without BMD and secondary OP</td>
<td>0.67</td>
<td>0.61 to 0.73</td>
</tr>
<tr>
<td>Age</td>
<td>0.64</td>
<td>0.58 to 0.7</td>
</tr>
<tr>
<td>Femoral Neck BMD</td>
<td>0.67</td>
<td>0.61 to 0.73</td>
</tr>
</tbody>
</table>

Jamal SA et al OI In Press
High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

- Voxel size of $\sim 82 \, \mu m^3$
- Volumetric Bone Mineral Density (BMD) of the distal radius and tibia
- Distinguishes cortical and trabecular bone
Healthy postmenopausal caucasian

Predialysis CKD; no fracture

Predialysis CKD with fracture

Nickolas T L et al. JASN 2010
HR pQCT Data

- Prospective data- HR pQCT and DXA
- 53 subjects
- CKD stages 2 to 5D
- Followed for mean: 1.5 yrs
- Decreases in BMD by DXA and HR PQCT
- No fracture data

Nickolas et al JBMR 2013
BMD by DXA vs. HRpQCT 3 to 5 CKD

Jamal SA et al OI 2012
In patients with CKD stages 3 - 5D with evidence of CKD-MBD we suggest that BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)
5.5. In patients with an estimated glomerular filtration rate greater than approximately 30ml/min per 1.73m², we suggest that measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D)

D – very low quality of evidence ..the estimate is very uncertain, often will be far from the truth
DXA and Fractures Post Transplant

- 238 transplant patients; 8 year follow up
- 53 fractures in 46 patients

Figure 1. Cumulative hazard plot for time to fracture after DXA, separated according to the presence of osteopenia or osteoporosis in the lumbar region. p = 0.002.

Figure 2. Cumulative hazard plot for time to fracture after DXA, separated according to the presence of osteopenia or osteoporosis in the hip region. p < 0.0001.

Akaberi S et al Am J Transplant 2008
ECSW* and BMD

- *Stop corticosteroids on the 4th post-transplant day and manage with a calcineurin inhibitor
- Observational studies minimal fracture protection with ECSW
- Abstract Nickolas et al (ASBMR 2013):
  - 47 recipients managed with ECSW
  - Followed for 12 months

Spine BMD by DXA

Hip BMD by DXA
Peripheral Skeletal Changes: Forearm

* p < 0.05 vs. Baseline
HR-pQCT of the Radius: 12 month changes after transplantation

*Cortical Density*  
*Cortical Thickness*  
*Cortical Area*  
*Trabecular Area*  
*Trabecular Density*

* p < 0.05 vs. Baseline
HR-pQCT of the Tibia: 12 month changes after transplantation

<table>
<thead>
<tr>
<th>Metric</th>
<th>Change 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical Density</td>
<td>-1.9%</td>
</tr>
<tr>
<td>Cortical Thickness</td>
<td>-1.1%</td>
</tr>
<tr>
<td>Cortical Area</td>
<td>-1.0%</td>
</tr>
<tr>
<td>Trabecular Area</td>
<td>0.03%</td>
</tr>
<tr>
<td>Trabecular Density</td>
<td>-0.7%</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Baseline
In patients with an estimated glomerular filtration rate greater than approximately 30ml/min per 1.73m², we suggest that measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D)?
Revisit Recommendations

- BMD by DXA can predict fractures in CKD and transplant
- Cross sectional data
  - Consistent across BMD sites, studies
- Some prospective data
- HRpQCT confirms presence of disturbance in bone microarchitecture
Did you know that men over 50 suffer from osteoporosis more than prostate cancer? 

got milk?