“Osteoporosis” in CKD
the dilemmas in management

Susan Ott
October 2013

“Dilemma should be reserved for reference to a predicament in which a difficult choice must be made between undesirable alternatives” (Apple dictionary)
No conflicts of interest
“Osteoporosis” is a measurement on a bone density and not a diagnosis.

Similar to anemia which is a measurement on a blood sample but not a diagnosis.
Anemia

- Iron deficiency
  - GI Blood loss
    - Surgical resection
  - Poor diet
    - Iron supplements
- Hemolytic
  - Thalassemia
    - DFO, transfusions
  - Autoimmune
    - Prednisone
- Hypoproliferative
  - Chronic disease
- Acute bleeding
  - CKD
    - Erythropoietin
  - Repair trauma
    - Transfusion
Low Bone Density

Decreased bone formation

Increased bone resorption

Increased bone resorption plus decreased formation

Aging
Diabetes
CKD

Menopause
Inflammation
Hyperparathyroid
Hyperthyroid

Liver disease
Steroids
Malnutrition

Lytic lesions

Osteomalacia

Vitamin D deficiency
Aluminum toxicity

Myeloma

Abnormal collagen

Aging

Diabetes
CKD

Menopause
Inflammation
Hyperparathyroid
Hyperthyroid

Liver disease
Steroids
Malnutrition

Lytic lesions

Osteomalacia

Vitamin D deficiency
Aluminum toxicity

Myeloma

Abnormal collagen
Low Bone Density

Bisphosphonates
Bone density in Dialysis Patients

Ott, Nephrology, 2009
Fracture Prevalence in CKD 5D
## Bone density in Dialysis Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>N</th>
<th>N Fx</th>
<th>Fracture</th>
<th>BMD: Skeletal Site</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spine</td>
<td>Hip</td>
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<tr>
<td>Yamaguchi</td>
<td>96</td>
<td>124</td>
<td>27</td>
<td>Clinical, vertebral</td>
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<tr>
<td>Atsumi</td>
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<td>39</td>
<td>Vertebral</td>
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<td>62</td>
<td>7</td>
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<tr>
<td>Fontaine</td>
<td>00</td>
<td>88</td>
<td>11</td>
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<tr>
<td>Jamal</td>
<td>02</td>
<td>104</td>
<td>54</td>
<td>Clinical, vertebral</td>
<td>NO*</td>
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<tr>
<td>Kaji</td>
<td>02</td>
<td>183</td>
<td>14</td>
<td>Hip</td>
<td>NO*</td>
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<tr>
<td>Urena</td>
<td>03</td>
<td>70</td>
<td>21</td>
<td>Clinical, vertebral</td>
<td>NO*</td>
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<tr>
<td>Negri</td>
<td>04</td>
<td>65</td>
<td>6</td>
<td>Clinical</td>
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<tr>
<td>Inaba</td>
<td>05</td>
<td>114</td>
<td>21</td>
<td>Vertebral</td>
<td>NO*</td>
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<tr>
<td>Elder</td>
<td>06</td>
<td>242</td>
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<td>Clinical, vertebral</td>
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<tr>
<td>Ersoy</td>
<td>06</td>
<td>292</td>
<td>24</td>
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<tr>
<td>Jamal</td>
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<td>52</td>
<td>27</td>
<td>Clinical, vertebral</td>
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<tr>
<td>Dolgos</td>
<td>08</td>
<td>133</td>
<td>38</td>
<td>Clinical</td>
<td>nr</td>
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<tr>
<td>Mares</td>
<td>09</td>
<td>73</td>
<td>15</td>
<td>Vertebral</td>
<td>NO*</td>
</tr>
<tr>
<td>Limori</td>
<td>12</td>
<td>485</td>
<td>46</td>
<td>Clinical</td>
<td>NO*</td>
</tr>
</tbody>
</table>
New studies with HRpQCT

• With these research tools patients with CKD have lower bone density than normal controls.
Bone density by eGFR

data from NHANES

Klawansky, Osteo Int, 2003
<table>
<thead>
<tr>
<th>CKD-MBD</th>
<th>Ordinary Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased PTH and alkaline phosphatase</td>
<td>Normal PTH and alkaline phosphatase</td>
</tr>
<tr>
<td>Bone density weakly related to fractures</td>
<td>Bone density predicts fractures</td>
</tr>
<tr>
<td>Bone loss mostly in cortical bone</td>
<td>Bone loss in trabecular and cortical bone</td>
</tr>
<tr>
<td>High prevalence of adynamic bone or very high bone formation</td>
<td>Bone formation generally normal to slightly high</td>
</tr>
<tr>
<td>Associated with vascular calcifications</td>
<td>Weakly associated with vascular calcifications</td>
</tr>
<tr>
<td>Abnormal calcium, phosphate, FGF23, BMP7, Klotho, 1,25-vitamin D, iron, bicarbonate, sclerostin, and cytokines</td>
<td>Normal or mildly abnormal</td>
</tr>
</tbody>
</table>
Progressive abnormalities in CKD
FGF23 and fractures

KDIGO

eGFR > 71

Mirza, JBMR, 2010
Treatment of Bone Disease in CKD patients
CKD stage 3

Post-hoc analysis of studies of osteoporosis medications (bisphosphonates, raloxifene, teriparatide and denosumab) that included subjects with age-related CKD stage 3 found fracture benefit, similar to patients with normal eGFR.

These studies excluded sick patients. The subjects had normal calcium, PTH, and alkaline phosphatase.
N = 6458  Age 55 to 80  with low bone density
Exclusion: creat>144\(\mu\text{mol/L}\)
Normal serum PTH, calcium, vitamin D, thyroid, alk. phos.
Patients with stage 4 CKD were excluded

Using a modified Cockcroft-Gault, 581 (9.9%) had eGFR <45
Women with eGFR <45 had greater number of fractures

With alendronate (3 to 4.5 years) vs. placebo:
Similar odds ratio for clinical fracture (0.80 with CKD vs. 0.78)
Odds ratio for Spine fracture not significantly different
(0.72 with CKD vs. 0.50)
Treatment of bone disease
Stage 4-5 CKD
Pharmacokinetics of bisphosphonates

Cleared only by kidney
Very poor oral absorption
About 50% of dose deposited in the skeleton
Deposits in calcified tissues
Remains in skeleton for longer than 10 years
Pamidronate clearance 69 ml/min
A Pervasive Myth: bone formation with bisphosphonates is normal

“Reduction of bone turnover . . . without any signs of adynamic bone” – Recker, 2007

“Most patients on bisphosphonates show reductions in remodeling to the range seen in healthy premenopausal women” – Khosla et al, 2012

“BPs decrease the rate of bone turnover into the premenopausal range” – Papapoulos 2008

“reducing bone turnover to premenopausal levels – the level of bone resorption seen in many users of bisphosphonates” – Abrahamsen, 2012

“I find the key point statement “Bisphosphonates severely reduce bone formation and cause adynamic bone disease” too strong.” – 2013 reviewer

“The statement that bisphosphonates cause adynamic bone disease is unproven” – 2013 reviewer
Mineralizing surface/bone surface, %
Alendronate vs placebo: baseline P1NP tertiles

Bauer, JBMR, 2006

Non-spine fractures

KDIGO

Bauer, JBMR, 2006
Below a 35-40% decrease in NTX there was no further decrease in vertebral fracture risk

Eastell, JBMR, 2007
Incidence of atypical femur fracture

Rate/100,000/yr

Duration bisphosphonate use, yrs

KDIGO

Dell, JBMR, 2012
Alendronate in CKD stage 3-4

- RCT of 51 patients, mean eGFR 34
- 18 months duration
- NO difference in progression of cardiovascular calcification
- Higher PTH with alendronate
Alendronate in CKD stage 3-4

- Spine increase 0.3 T-score units more with alendronate than with placebo.
- Fem neck 0.03 T-score units higher (not significant)

Toussaint, AJKD 2010
Vascular calcifications and bone turnover

Model proposed by Cannata & Hruska
Bisphosphonates and vascular calcification

• Etidronate directly inhibits mineralization

• In some animal models bisphosphonates inhibit development of vascular calcifications

• If bone resorption is high, treatment can lower calcium and phosphate by decreasing bone resorption

• However, these drugs severely decrease bone formation and this will lead to unstable serum mineral levels because bone can not buffer calcium or phosphate
Bisphosphonates and vascular calcification

- In women with osteoporosis, vascular calcifications increased after treatment with alendronate or ibandronate, but this was not different from controls.

- In the MESA study, bisphosphonate users younger than 65 yrs had higher prevalence of vascular calcifications than non-users, but those older than 65 yrs had lower prevalence than non-users. There was no reason found to explain this difference.

- Studies of cardiovascular adverse effects in bisphosphonate users are inconsistent.
## Cardiovascular events (MI) in bisphosphonate users: Mixed results

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>Population</th>
<th>N on bis</th>
<th>Design</th>
<th>Duration</th>
<th>Risk of heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris</td>
<td>2000</td>
<td>PMOP</td>
<td>1638</td>
<td>letter about RCT results</td>
<td>3 yrs</td>
<td>MI placebo 1.6% rise 1.5%</td>
</tr>
<tr>
<td>Bunch</td>
<td>2009</td>
<td>Utah health plan</td>
<td>7489</td>
<td>users vs controls (4:1)</td>
<td>~ 4 yrs</td>
<td>MI: 1% in both</td>
</tr>
<tr>
<td>Bunch</td>
<td>2009</td>
<td>Utah cath. pts</td>
<td>9623</td>
<td>retrospective database review</td>
<td>~ 4 yrs</td>
<td>MI: 8% nonusers, 10% users; HR CV mortality 1.38 (.96-1.99)</td>
</tr>
<tr>
<td>Camm</td>
<td>2010</td>
<td>PMOP</td>
<td>4916</td>
<td>post-hoc of RCT</td>
<td>3 yrs</td>
<td>No difference in MI Zol vs. placebo</td>
</tr>
<tr>
<td>Huang</td>
<td>2010</td>
<td>Taiwan</td>
<td>21,037</td>
<td>retrospective cohort</td>
<td>x 1 yr</td>
<td>RR MI 2.24 in users &gt;1 yr with hx CV disease; 1.20 in all women vs. raloxifene</td>
</tr>
<tr>
<td>Lu</td>
<td>2011</td>
<td>Taiwan OP pts</td>
<td>6949</td>
<td>retrospective cohort</td>
<td>1 yr</td>
<td>Alendronate 10mg/day worse than 70mg/day</td>
</tr>
<tr>
<td>Kang</td>
<td>2012</td>
<td>OP pts Taiwan</td>
<td>1548</td>
<td>matched cohort</td>
<td>2 yr</td>
<td>HR 0.37 vs. untreated fracture patients</td>
</tr>
<tr>
<td>Vestergaard</td>
<td>2012</td>
<td>Denmark</td>
<td>57,221</td>
<td>cohort study</td>
<td>2.8 yrs</td>
<td>RR 1.36 (1.18-1.57)</td>
</tr>
<tr>
<td>Hartle</td>
<td>2012</td>
<td>CKD stage 3-4</td>
<td>3234</td>
<td>cohort</td>
<td>x 3.9 yrs</td>
<td>overall HR mortality 0.78 (0.67-0.91) but CV mortality 1.17 (0.96-1.42)</td>
</tr>
</tbody>
</table>

**Note:**
- RR: Relative Risk
- HR: Hazard Ratio
- CV: Cardiovascular
Be cautious about bisphosphonates in patients with CKD stages 4-5

1) Inadequate studies in this population.
2) Data from patients with early stages of CKD may not reliably be extrapolated to later stages because many features of bone disease appear in stages 4-5.
3) Bisphosphonates can increase PTH.
4) Bisphosphonates markedly reduce the bone formation rates.
5) Some rare but serious side effects have been reported with prolonged use.
Denosumab in CKD

Jamal, JBMR, 2011
### Denosumab lowers serum calcium in CKD

#### Number with calcium <7.5

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td><strong># with low Ca</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Raloxifene in women on dialysis

| One year BMD results | Placebo  
N = 25 | Raloxifene  
N = 25 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>.952 - .949</td>
<td>.942 - .973*</td>
</tr>
<tr>
<td></td>
<td>.745 - .753</td>
<td>.722 - .727</td>
</tr>
</tbody>
</table>

Hernandez, 2003, Kidney Int
Fig. 1. Mean (SD) percentage changes from baseline in serum pyridinoline crosslinks levels in postmenopausal hemodialyzed women given raloxifene (60 mg/day) (●) or placebo (■) for 1 year. *P < 0.01 vs. placebo.
Osteoporosis medicines in CKD-MBD

- 102 with 2 DXA’s
  - 66 T-score ≤ -2.5
  - 36 T-score ≥ -2.5
    - 38 bone biopsy
    - 28 refused
      - 22 Osteitis fibrosa
        - lower PTH: 11 ibandronate
        - higher PTH: 11 cinacalcet
      - 9 adynamic
      - 7 mild
        - 9 teriparatide
        - no treatment

Mitsopoulos AJN 2012
Osteoporosis medicines in CKD-MBD

N = 5; PTH = 267

Mitsopoulos AJN 2012
Osteoporosis medicines in CKD-MBD

N = 8; PTH = 487

Mitsopoulos AJN 2012

KDIGO
Osteoporosis medicines in CKD-MBD

\[ N = 7; \text{PTH} = 250 \text{ pg/ml} \]

Mitsopoulos AJN 2012
Osteoporosis medicines in CKD-MBD

N = 8; mean PTH = 150 pg/ml

Mitsopoulos AJN 2012
Teriparatide in CKD-MBD

N = 7; hx PTX in 6

Cejka, Kidney BP Res 2010
Wnt signalling pathway

Wnt-signalling pathway is necessary for osteoblastic cell differentiation.

Inhibitors of this pathway include sclerostin, dickkopf, wnt-inhibitory factor and secreted frizzled related protein.
Sclerostin antibodies increase formation of normal bone
SOST inhibits prostate cancer invasion

Bryan Hudson, Gabriela Loots, Nick Hum, Cindy Thomas. Lawrence Livermore National Laboratory: ASBMR 2012

SOST did not change the proliferation of prostate cells in culture.

In a double-chamber system, adding SOST decreased the invasiveness of the prostate cancer cells.

Bone from Sost k/o mice had increased invasion of prostate cancer cells.

Sost k/o mice had more tumor formation when injected with prostate cancer cells; Lrp5 k/o mice had decreased tumor formation.
Wnt signalling: potential concerns

- Sclerostin involved in FGF23 secretion
- Wnt signalling increases conversion of vascular smooth muscle cells into osteoblasts
- Some β-catenin activated mice get AML
- Wnt signalling may worsen renal disease and cause podocyte dysfunction, proteinuria and epithelial damage.
Neuromuscular function and fracture in CKD

**Fig. 1.** Relationship between sensitivity and specificity of the 6MW and the TUG and the ability to identify patients with fracture (Fracture defined as self-reported low-trauma fracture since age 40 and/or prevalent vertebral fracture by morphometry at study entry). The area under the receiver operating characteristic curve for the 6MW was 0.87 and for TUG was 0.90 (P > 0.05).
Don’t forget about falls!