Osteoporosis in Patients with Impaired Renal Function: To Treat or Not to Treat?

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Objectives

- Review the epidemiology of fractures in patients with CKD – a specific focus on osteoporosis
- Review the etiology of fractures
- Review the methods to assess fracture risk
- Outline treatment options for patients with fracture and CKD
## Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular Filtration Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60 to 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30 to 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15 to 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>
Fractures in Patients with CKD

- Increased hip fracture risk with worsening renal function:
  - Data NHANES: eGFR < 60 ml/min: OR = 2.12 (1.18 to 3.8) (Nickolas TL et al J Am Soc Nephrol 2006)
  - Data from SOF: eGFR 45-59 ml/min: HR = 1.57
eGFR < 45 ml/min: HR = 2.32 (Ensrud et al Arch Int Med 2007)

- Patients with stage 5 CKD:
  - Up to 50% prevalence of fractures
  - Up to 50% excess mortality
  - Fractures occur at least 10 years earlier
The Dilemma

Q: I have a dialysis patient with a hip fracture and a T-score of -4.0. What drug should I prescribe?

A: What disease do they have?
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.
Fractures are Multifactorial

Osteoporosis

Bone Mass
Bone Strength
Material Properties
Shape and Architecture
Remodeling
Nutrition
Exercise and Lifestyle

Falls
Postural hypotension
Myopathy
Peripheral Neuropathy

Soft Tissue Padding
Postural Reflexes

FRACTURE

Nutrition
Hormones
Metabolic Bone Disease

Osteoporosis
Chronic Heparin, Steroids,
Hypogonadism, Hyperprolactinemia
Poor Nutrition, Vitamin D deficiency
Hyperparathyroidism, Metabolic acidosis, Limited physical activity

Adapted from Heaney RP, Bone. 2003;33:457-465.
Diagnosing Renal Bone Disease

- Quantitative bone histomorphometry
- Classification based on turnover and mineralization:
  - Hyperparathyroid bone disease
  - Osteomalacia
  - Adynamic bone disease
  - Mixed bone disease

NKF K/DOQI Guidelines AJKD 2002
Normal Bone Histomorphometry
Osteomalacia

Osteomalacia

Normal Bone
Osteitis Fibrosa Cystica

Normal Bone
Adynamic Bone Disease
What is Ideal Bone Turnover?

Too Little Turnover:
- Aging bone, un-repaired micro-damage, over-mineralized bone?

Too Much Turnover:
- Loss of bone mass and structure, stress risers, under-mineralized bone?
Adynamic Bone Disease

- Increasing prevalence
  - 1973: 0%
  - 1993: 49%

- Consequences of ABD
  - Hyperphosphatemia - mortality
  - Fractures ?

- Etiology
  - Vigorous suppression of PTH
  - CKD decreases anabolic activity at skeleton
    - Decreased BMP-7, Wnt
    - Decreased calcitriol
    - Increased phosphate, increased FGF23
Normal bone turnover
Limitations of Histomorphometry

- Invasive
- Specialized expertise
- Costly
- Histology may be “fluid”
Bone and Mineral Disorders in ESRD and After Transplantation

- HyperPTH
- Mineralization Defect (OM)
- Low Turnover: Adynamic
- Low Turnover: Aluminium
- Osteoporosis

Time

ESRD    Dialysis    Post-Tran    ESRD

60 ml/min
30 ml/min
10 ml/min

Elder, JBMR 02
Identifying the Type of Bone Disease is Critical

- Different bone diseases have different treatments
- BP can make adynamic bone disease worse
Exceptions to the Biopsy Rule?

- When certain there is no adynamic bone disease
  - Prevalence is felt to be low before stage 4 CKD
- If ruled out hyperparathyroidism/osteomalacia
  - 25 hydroxy vitamin D level
  - Serum PTH
- Then WHO criteria and/or the fragility fractures can be used to diagnose osteoporosis in Stages 1-3 CKD
What Do We Do in Stages 4/5 CKD?

- Markers of mineral metabolism - PTH and alkaline phosphatase
- Bone mineral density (BMD) by DXA
- Peripheral quantitative computed tomography (pQCT)
## Profiling by PTH Levels

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum intact PTH Levels (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>200-400</td>
</tr>
<tr>
<td>Moderate</td>
<td>350-800</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 700</td>
</tr>
<tr>
<td>Aluminum Bone</td>
<td>10-500 (mostly &lt; 100)</td>
</tr>
<tr>
<td>Adynamic Bone</td>
<td>&lt; 100-150</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Normal/mildly elevated</td>
</tr>
</tbody>
</table>

Miller P and Shane E 2004
## Profiling by BSAP Levels

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum intact BSAP Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Normal</td>
</tr>
<tr>
<td>Moderate</td>
<td>Normal to elevated</td>
</tr>
<tr>
<td>Severe</td>
<td>Elevated</td>
</tr>
<tr>
<td>Aluminum Bone</td>
<td>Normal</td>
</tr>
<tr>
<td>Adynamic Bone</td>
<td>Normal to low</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Mildly elevated</td>
</tr>
</tbody>
</table>

Miller P and Shane E 2004
Bone Mineral Density Testing

- BMD is strongly associated with fracture risk in postmenopausal women.
- May not be so in patients with CKD:
  - Altered microarchitecture
  - Abnormal elasticity
  - Altered rates of bone turnover
Stage 5 CKD - No Difference in BMD by Fracture

Test for trend $p > 0.05$

Jamal SA et al. AJKD 2002
Association between Forearm BMD and Fracture

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Fracture</th>
<th>No fracture</th>
<th>SMD (random) 95% CI</th>
<th>Weight %</th>
<th>SMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fontaine et al 2000</td>
<td>0.35 (0.06)</td>
<td>0.38 (0.08)</td>
<td>-0.38 [-1.02, 0.25]</td>
<td>31.78</td>
<td></td>
</tr>
<tr>
<td>Kaji et al 2003</td>
<td>0.31 (0.09)</td>
<td>0.37 (0.03)</td>
<td>-1.59 [-2.16, -1.02]</td>
<td>33.17</td>
<td></td>
</tr>
<tr>
<td>Yamaguchi et al 1996</td>
<td>0.26 (0.04)</td>
<td>0.37 (0.07)</td>
<td>-1.69 [-2.16, -1.21]</td>
<td>35.05</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.32 (0.04)</td>
<td>0.37 (0.07)</td>
<td>-1.24 [-2.01, -0.47]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 11.53, \text{df} = 2 (P = 0.003), I^2 = 82.7\% \)

Test for overall effect: \( Z = 3.14 (P = 0.002) \)

BMD lower in fracture group | BMD lower in non fracture group

Jamal SA et al. AJKD 2007
pQCT Measures and Fracture

- Trabecular density, area
- Cortical density, area and thickness
- Derive bending strength, twisting strength
Trabecular Density does NOT Identify Patients with Fractures

- p-value for difference = 0.728

Trabecular density (mg/cm^3) [0.52]
Hip BMD [0.56]

Jamal SA et al JBMR, 2006
Cortical Density Identifies Patients With Fractures

Jamal SA et al JBMR, 2006
The Relationship Between BMD (AUC 0.6), TUG (AUC 0.8) and Fracture

Jamal SA et al OI, 2006
What We Know

○ Patients with CKD have fractures
○ Cause of fractures is multifactorial
○ Stages 1 to 3 can likely use T scores, fragility fractures, PTH and vitamin D to impute cause
○ Stage 4 and 5 – consider bone biopsy
How Can We Prevent Fractures

- Control PTH
- Exercise
- Prevent fall related injuries
- Drugs??
Hip protectors-Prevent Fall Related Injuries

Kannus et al, NEJM 2000; 343:1506-13
Oral bisphosphonates are NOT recommended in patients with creatinine clearance 
< 30 mL/min (Stage 4-5 CKD)

Adapted from P.D. Miller
Mean baseline eGFR
(determined by the Cockcroft-Gault Method)

Miller PD et al. JBMR 2005
Change in Serum Creatinine Over Two Years

Renal insufficiency

Miller PD et al JBMR 2005
Vertebral Fracture Risk Reduction with Risedronate

- **Control**: 32% (14.46%) with p=0.001
- **5mg RIS**:
  - Mild: 45% (31.57%) with p<0.001
  - Moderate: 56% (11.78%) with p=0.021

**Baseline Renal Impairmenta**
- Mild: N=3000
- Moderate: N=2423
- Severe: N=232

*a Creatinine clearance estimated using the Cockcroft and Gault method [9]

N  Number of patients with evaluable paired spinal radiographs

Miller PD et al. JBMR 2005
Women with Normal Creatinine, Decreased Clearance (n = 581) Participating in FIT (n = 6458)

Jamal SA et al. JBMR 2007
# Fracture Risk with Alendronate by Creatinine Clearance

<table>
<thead>
<tr>
<th>Site</th>
<th>CrCl</th>
<th>OR (95%CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 ml/min</td>
<td>0.78</td>
<td>(0.51 to 1.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>45 ml/min or higher</td>
<td>0.81</td>
<td>(0.70 to 0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>Spine Fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 ml/min</td>
<td>0.72</td>
<td>(0.31 to 1.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>45 ml/min or higher</td>
<td>0.50</td>
<td>(0.32 to 0.76)</td>
<td></td>
</tr>
</tbody>
</table>

Jamal SA et al. JBMR 2007
Change in Femoral Neck BMD by Creatinine Clearance

Annualized % Change in BMD

- placebo
- raloxifene

Treatment Assignment
- <45
- 45 to 59
- ≥ 60

Ishani et al, JASN 2008
Change in Lumbar Spine BMD by Creatinine Clearance

Annualized % Change in BMD

p for interaction = 0.535

p < 0.001

p = 0.006

Treatment Assignment

- <45
- 45 to 59
- ≥ 60

Ishani et al, JASN 2008
Effect of Renal Function on Changes In Bone Mineral Density with Teriparatide

Lumbar Spine BMD (18 months)

Femoral Neck BMD (12 months)

Mean Percent Change in BMD ± SE

* P<0.05 from Placebo

Effect of Renal Function on Fracture Efficacy of Teriparatide

Vertebral Fracture

- Normal Renal Function (> 80 ml/min): 27/244
- Abnormal Renal Function (≤ 80 ml/min): 23/483

RR = 0.43 (0.25, 0.73)

Non-Vertebral Fracture

- Normal Renal Function (> 80 ml/min): 15/282
- Abnormal Renal Function (≤ 80 ml/min): 16/593

RR = 0.53 (0.26, 1.05)

RR = 0.37 (0.17, 0.80)

Treatment of Osteoporosis in CKD - What do the data tell us?

- **Stages 1-3 CKD**
  - Treatment not different from PMO since clinical trials randomized patients down to “GFR” of 30 ml/min

- **Stage 4 CKD**
  - Post-hoc analysis show efficacy and safety through 3 years of risedronate, alendronate and raloxifene down to GFR of 15 ml/min
Bisphosphonate Use in Stage 5 CKD Patients: Caution Still Advised

- No data on benefit or harm in patients with stage 5 chronic kidney disease (GFR <15 mL/min).
- Use only in very specific circumstances
  - Specific fragility fractures
  - Clear diagnosis.
  - ½ of registered dose for PMO /men or GIOP for no longer than 2-3 years.
- Bone retention over time with bisphosphonates in patients with low GFR unknown

Miller PD Seminars Dialysis 2007
Miller PD Seminars Nephrology 2009
Q: I have a dialysis patient with a hip fracture and a T-score of -4.0.

A: What disease do they have?
   If bone biopsy available – just do it!
   If not – first do no harm
Summary

- Fractures are common in patients with CKD
- Fractures are multifactorial
- Patients with stages 1-3 CKD and low T-scores/fragility fractures likely to have OP
- CKD stages 4,5 may require a bone biopsy especially in those that fracture and in whom bisphosphonates are being considered
- Bisphosphonates are safe and effective to treat high risk patients down to stage 4 CKD for a short time
- Teriparatide down to stage 3 CKD
Acknowledgements

- CIHR New Investigator Award
- CIHR Operating Grant
- Kidney Foundation of Canada
- Paul Miller, Charmaine Lok, Areef Ishani

Kanis 2001
Did you know that men over 50 suffer from osteoporosis more than prostate cancer? got milk?
Case Presentation
2001:
- 51 year old; 2 years postmenopausal
- Menarche: 13 years old
- ? Metatarsal fractures
- Mother with vertebral fracture, sister with wrist fracture
- BMD testing (T scores): L1-L4: -2.4; neck: -0.6 and total hip: -0.4
- Started on alendronate 10mg/day
2003:
- Sudden onset L groin pain while stepping off curb
- Treated with physiotherapy and analgesics for 2 weeks – no improvement
- X ray: fracture of L proximal femur; hip screw placed and sent to clinic
Assessments

- Several metatarsal fractures between ages 35-45 while running
- Cannot recall premature loss of deciduous teeth/childhood rickets
- Physical exam: mild scoliosis and tenderness at the mid femur in area of surgery
Laboratory Results

- Normal calcium, phosphate, magnesium, albumin, bun, creatinine
- Normal CBC, SPEP
- Normal PTH, TSH, 25 (OH)D
- Alkaline phosphatase: 35 IU/L (40 – 120 IU/L); repeated: 30 IU/L then 32 IU/L
- Negative serology for celiac disease
- BTM: normal premenopausal range
Radiologic Investigations

- Spine x-ray: No fractures
- Skeletal Survey: Normal
- Total body bone scan: Normal
- BMD testing: L1-L4: -2.5; L hip normal

- Advised to stop alendronate (end of 2003)
Further tests:

- Bone biopsy (Feb 2004):
  - Inactive bone and increased cortical porosity
  - No excess of unmineralized osteoid
  - "Low turnover bone disease"

- Urine: elevated phosphoethanolamine
  (165 micromoles/gram creatinine; N: 48 to 93)

- Serum: elevated pyridoxal 5’-phosphate
Hypophosphatasia

- Inborn error of metabolism
- Characterized by subnormal activity of the tissue nonspecific isoenzyme of alkaline phosphatase (TNSALP)
- Results in impaired skeletal mineralization
- Classified by age disease identified
  - Perinatal, infantile, childhood and adult, dental disease only
  - Wide range of severity
- Rare, 350 cases reported to date
Adult HPP - Clinical Presentation

- Presents during middle age
- Poorly healing, recurrent metatarsal stress fractures
- Discomfort in thighs or hips - due to femoral neck pseudofractures
- Childhood rickets, premature loss of deciduous teeth
- Chondrocalcinosis from CPPD deposition
- X rays: osteopenia, stress fractures, chondrocalcinosis, proximal femoral pseudofractures
Fractures in patients with HPP

Whyte MP, JCEM 2007
Cause of Hypophosphatasia

- Molecular defect in the gene encoding TNSALP
- TNSALP an ectoenzyme attached to osteoblast cell membranes
- Role is to hydrolyze:
  - Inorganic pyrophosphate
  - Pyridoxal 5’- phosphate (form of vitamin B6)
  - Phosphoethanolamine
- Elevated levels of inorganic pyrophosphate impair hydroxyapatite formation
ATP PEA PLP
NTP-PPi-ase
PPi
5'-NT
TNSALP
PL EA Pi

ATP
PEA
PLP

PPi
Pi
AMP
Adenosine
NTP-PPi-ase
5'-NT
TNSALP
PL
EA
Pi
Diagnosis

- Low alkaline phosphatase
- Increased plasma levels of pyridoxal 5’-phosphate
  - Avoid pyridoxine containing vitamins for 1 week
- Increased urinary phosphoethanolamine -
  - Varies by age, diet and diurnal variation
- Clinical severity mirrors degree of enzyme deficiency
Treatment

- Unlike traditional OM - levels of calcium and D are normal
- Expert dental care
- PTH (one case report)
Questions?