Assessment of Low BMD or Fractures in Chronic Kidney Disease

Is it CKD-MBD or Osteoporosis?

Paul D. Miller, M.D.

HOW IS OSTEOPOROSIS DIAGNOSED IN STAGE 4-5 CKD?

• By exclusion of other causes of bone disease
  – Double-tetracycline labeled iliac crest bone biopsy is required (reduced trabecular bone volume)

Miller PD J Amer Soc Nephrol 2008

www.ucosteoporosis.com
BISPHOSPHONATES IN PATIENTS WITH STAGE 5 CKD: 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
  – Fragility fractures and clear-cut diagnosis
  – Suggest half of standard dose for PMO, for no longer than 2-3 years
• Bone retention over time with bisphosphonates in patients with low GFR unknown

Miller PD Semin Dial 2007

Disclosures

• 1. Research Grants: Amgen, Merck, Lilly, Novartis, Radius Research, Agnos, Boehringer-Manheim, Takeda.
• 2. Scientific boards: Amgen, Lilly, Merck, Radius
• 3. Speakers bureaus: Alexion

• Equity: none
NKF-Stages of Chronic Kidney Disease

• Stage 1 CKD: GFR < 110 ml/min with evidence of intrinsic renal damage (proteinuria, etc)
• Stage 2 CKD: GFR < 90-60 ml/min (with evidence of intrinsic renal damage)
• Stage 3 CKD: GFR 60-30 ml/min (no need for evidence of intrinsic renal damage)
• Stage 4 CKD: GFR 30-15 ml/min
• Stage 5 CKD < 15 ml/min or ESRD

KDOQI Guidelines Am J Kid Dis 2002

Aging is Associated with both Reductions in GFR and Increased Prevalence of Osteoporosis

Increase population screening by BMD testing and automatic reporting of eGFR will bring these two situations more to the forefront
Average Estimated GFR by Age

NHANES III (1999-2004)
Prevalence of CKD in USA Population

- 1. In persons 60+ years of age and older: 39%
- 2. Stage 3 CKD (GFR 60-30 ml/min) represented the greatest proportion: 20%
- 4. More common in diabetics and persons with hypertension

Coresh J et al Am J Kid Dis 2003
Fracture Risk is Very High In Stage 5 KD

- ~ 50% prevalence of fractures
- ~ 50% excess mortality as compared to age-matched controls without stage 5 CKD
- Fractures occur ~ 10 years earlier than age-matched, BMD matched patients without CKD
- Hip fractures risk 17X higher than age-matched patients without stage 5 CKD
Mortality is Much Higher Following Hip Fracture in ESRD Patients than Age-Matched Controls

1 year mortality after hip fracture in stage 5D CKD:  60%

1 year mortality after hip fracture in age-matched controls:  15% female 30% male


It’s Just Not ESRD

All stages of CKD have higher fracture risk than aged-matched persons without CKD
# Studies of Fracture Risk Associated with Age-Related Reductions in GFR

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Kidney Function</th>
<th>OR for Fracture (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukas¹</td>
<td>5,481</td>
<td>GFR: &lt;65 mL/min</td>
<td>Hip 1.57* (1.18–2.09) Vertebral 1.31* (1.19–1.55) Radial 1.79* (1.39–2.31)</td>
</tr>
<tr>
<td>Ensrud²</td>
<td>9,704</td>
<td>Tiered GFR</td>
<td>Hip† 1.0 (0.89–2.76)</td>
</tr>
<tr>
<td>Fried³</td>
<td>4,699</td>
<td>Tiered Cystatin-C</td>
<td>Men at Hip 1.0 Women at Hip† &lt;0.92 mg/L 0.91 (0.41–2.11) 0.80 (0.35–1.83) 1.25 (0.57–2.73)</td>
</tr>
<tr>
<td>Nickolas⁴</td>
<td>6,270</td>
<td>GFR: &lt;60 mL/min</td>
<td>Hip 2.12 (1.18–3.80)</td>
</tr>
</tbody>
</table>

*P<0.01; †P for trend <0.05

- Mild to moderate kidney impairment is associated with an approximate doubling in OR of all fractures as compared to age-matched people with normal kidney function.


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### Can we FRAX® it?

**Yes We Can!**
FRAX Adjustments

• 1. Fracture risk appears to be 2X greater by stage 3 CKD
• 2. FRAX did not validate GFR
• 3. Primary care and specialists see a great deal of stage 3 CKD (eGFR 60-30 ml/min)
• 4. Stage 3 CKD was present in a large proportion of all registration clinical trials for osteoporosis therapies.

Miller PD Clev Clin Med J 2009

Why is Bone Strength Impaired in CKD? theories beyond BMD/Age/Prior fracture

• 1. Elevated PTH
• 2. Phosphorus and pyrophosphate retention
• 3. Elevated FGF 23
• 4. Elevated sclerostin
• 5. Chronic metabolic acidosis
• 6. Sarcopenia and poor muscle function
The Interactions Between the Parathyroid Glands, Kidneys, Bone and Systemic Vasculature: The Bond Between Bone and Body

The Osteocyte: “The Boss”

Mechanostat
FGF-23
Sclerostin
PGE, NO, Rank-Ligand

Bonenwald L-personal communication
Sclerostin

- Serum levels go higher at each stage of chronic kidney disease (CKD)-could explain the adynamic bone disease in CKD.
- Serum levels are higher in diabetics-could explain the low bone formation seen in diabetics.
- Serum levels higher in younger patients with fragility fractures (pre-menopausal).
- GLP 1 agonists reduce serum sclerostin levels- might explain a bone potential anabolic effect of GLP 1 agonists on bone.
- Mono-clonal antibody to sclerostin may offer a novel anabolic therapy for osteoporosis (and other bone diseases associated with low bone formation).
Serum sclerostin as a function of CKD stage based on GFR measured by inulin clearance

FGF 23

Broad Clinical Implications
Perspective

FGF23
more than a regulator of renal phosphate handling?

Harald Jüppner, Myles Wolf, and Isidro B. Salusky JBMR 2010

FGF-23

- Increases renal excretion of phosphorus
- Decreases renal production of 1,25 dihydroxyvitamin D
- Increases PTH production
- Promotes vascular calcification
- Inhibits bone mineralization
Regulators of FGF-23

- 1. Serum phosphorus
- 2. Vitamin D analogues
- 3. 

Should Clinician’s be Ordering FGF-23?

- 1. In CKD?
- 2. In persistent hypophosphatemia?
- 3. In unexplained osteomalacia?
- 4. In patients with normal 25 (OH) D but low 1,25 OH D and normal GFR?
- 5. In unexplained elevated BSAP?
- 6. In RTA?

Miler PD JCD 2012
The Fracture

Is it “Osteoporosis” or is it Fracture related to decreased GFR per se?
What is Osteoporosis?

“A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.” “Bone strength is a composite of bone density and bone quality”

Clinical Risk Factors for Osteoporosis in CKD

- Chronic Heparin
- Steroids
- Hypogonadism
- Hyperprolactinemia
- Poor Nutrition
- Vitamin D deficiency
- Hyperparathyroidism
- Metabolic acidosis

Lindberg JS, and Moe SM Semin Nephrol 19: 115-122
Miller PD Current Osteoporosis Reports 2005; 3(1): 5-12

Fractures In Chronic Kidney Disease

- 1. Hyperparathyroidism
- 2. Adynamic bone disease
- 3. Osteomalacia
- 4. Post-transplantation
- 5. Osteoporosis

The Clinical Diagnosis of Osteoporosis in Specific Populations (PMO, elderly men, etc) can be made by:

• 1. Low trauma fractures (once other causes of fragility fractures are excluded, e.g. osteogenesis imperfecta, osteomalacia, etc)
• 2. World Health Organization (WHO) bone mineral density criteria using central dual energy x-ray absorptiometry (DXA): T-score - 2.5 or lower


Diagnosis of Osteoporosis in Populations with Known Reduced GFR

• 1. Stage 1-3 CKD (GFR <90 -30 ml/min): same as patients without NKF defined CKD as long as there are no other biochemical abnormalities suggesting CKD-MBD.
• 2. Stage 4-5 CKD (GFR < 30 ml/min): Cannot use WHO criteria and/or fragility fractures since all forms of severe renal osteodystrophy (histomorphometry defined) may have low T-scores or low trauma fractures

Moe S et al KI 2009
Miller PD Sem Dialysis 2008
**KDIGO:**
Kidney Disease Improving Global Outcome
(beyond just “renal osteodystrophy”)

Linking the metabolic bone abnormalities to the systemic vascular disease process:

**Chronic Kidney Disease-Bone and Mineral Disorder:**

CKD-MBD

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**Definition of Chronic Kidney Disease-Mineral and Bone Disorder CKD-MBD**

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

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

- Moe S et al  KI 2008
Clues that CKD-MBD is Present

- Persistent hyperphosphatemia
- Elevated FGF-23
- Elevated PTH

CKD-MBD

Has no ICD-9 Code
It may have an ICD-10 Code
Stage 4-5 CKD

May have CKD-MBD which is clinically suspected if patients have hyperphosphatemia or elevated PTH

Moe S et al Kid Internat 2008

Prevalence of Elevated iPTH by eGFR Intervals

Levin A et al. et al KI 2007
Secondary Hyperparathyroidism

• 1. Low 25 OH D/hypocalcemia
• 2. Calcium malabsorption or intake
• 3. Hypercalciuria
• 4. Chronic kidney disease (and acute renal failure)
• 5. Low 1,25 D despite normal 25 OH D
• 6. Lithium use
• 7. Calcyolytic agents

Miller PD JCD 2011

Diagnosis of “Osteoporosis” in Stage 4-5 CKD

Is a diagnosis of exclusion
Biochemical and Histomorphometry
Different Stages of CKD and Bone Turnover

• Stage 1-3 have rarely been associated with adynamic bone disease or osteomalacia unless there is an underlying associated condition (diabetes, aluminum accumulation, reasons for osteomalacia).
• Stage 4-5 are clearly associated with severe bone turnover abnormalities.

Diagnosis of “Osteoporosis” in Stage 4-5 CKD

Is a diagnosis of exclusion
Biochemical and Histomorphometry
Can
CKD-MBD and Osteoporosis
Co-Exist?

Biochemical Markers of Bone
Turnover
What is Turnover?
The Lifecycle of Bone

Adapted from: Baron R. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 5th ed. 2003:1-8; Bringhurst FR, et al.
Bone Turnover Markers

- Resorption Markers
  - Type I Collagen Degradation products
    - Pyridinium Crosslinks (PYD and DPD)
    - C-and N-telopeptides (CTX, ICTP, NTX)
  - Enzymes
    - Tartrate Resistant Acid Phosphatase (TRACP) 5b
    - Cathepsin K
    - MMPs

- Formation Markers
  - Matrix proteins
    - Procollagen type I propeptides
      - C-terminal (PICP)
      - N-terminal (PINP)
    - Osteocalcin (OC)
  - Enzyme
    - bone isoform of alkaline phosphatase (bone ALP)


3 BTM Markers Unaffected by GFR

- 1. BSAP
- 2. The PINP trimer (Orion radioimmunoassay: FDA approved {IDS}) and IDS trimer immunoassay (not FDA approved)
- 3. TRAP5b (unavailable commercially)
ProCollagen: Marker of Bone Formation

......synthesized by and within the osteoblast and secreted intact onto the bone matrix

ProCollagen

Procollagen Peptidase Cleaves ProCollagen into PINP outside the OB
Assays for PINP

• FDA approved: Radioimmunoassay (Orion-licensed by Immunodiagnostics (IDS). measures only the PINP trimer.
• FDA pending immunoassay (IDS): measures the PINP trimer.
• FDA not approved (science being improved): PINP intact (monomers and trimers)(Roche Diagnostics)

High Correlation Between PINP by Immunoassay vs Radioimmunoassay

Ingsonia C, et al JBMR
The Caveats of PINP and The Kidney

1. The Roche PINP immunoassay (Denmark) measures both the PINP monomers (accumulate as GFR declines) and PINP trimers.

2. IDS radioimmunoassay (Orion kit) and IDS immunoassay measures only the PINP trimer which does not accumulate as GFR declines.

3. Where is the data re PINP reference data or as a marker of anabolic response using both assays or across stages of CKD?

2 Bone Diseases to Avoid
“turning bone turnover down”

- Osteomalacia

- Adynamic bone disease
Osteomalacia: always has a cause

- Severe 25 OHD deficiency (< 8 ng/ml).
- Chronic hypophosphatemia
- Vitamin D resistant rickets
- Renal tubular acidosis
- Oncogenic osteomalacia (low serum PO⁴, elevated FGF 23, low, 1, 25 D, phosphaturia)
Biochemical Tests to Screen for Etiologies of Osteomalacia

- 25D
- 1,25D
- Serum and urine phosphorus
- Electrolytes, arterial blood gases, urine pH
- FGF 23
- Elevated BSAP

Elevated BSAP

Excludes adynamic bone disease
(unless there has been a recent fracture)
Elevated BSAP (DDX)

- 1. Severe primary hyperparathyroidism
- 2. Hyperthyroidism
- 3. Metastatic cancer in bone
- 4. Paget’s disease of bone
- 5. Recent large bone fracture
- 6. Osteomalacia
- 7. Severe (< 8-10 ng/ml) vitamin D deficiency
- 8. Space travel
- 9. Immobilization
- 10. Treatment with anabolics (teriparatide)
- 11. Treatment with strontium ranelate™ (Europe)
- 12. Future: treatment with PTHrp analogues, anti-sclerostin
- 13. High bone turnover osteoporosis

Adynamic Bone Disease

Absence of single tetracycline labels
Renal Adynamic Bone Disease

Miller PD CJASN 2007
Summary of 18 Studies Correlating PTH/BSAP with Bone Histomorphometry

- 1,211 trans iliac quantitative bone histomorphometry (1996-2010).
- Increase in prevalence of adynamic bone disease attributed to increase prevalence of diabetes, use of PTH inhibiting substances (zemplar, cinacalcet, higher Ca dialysis baths, calcium-phosphate binders), aging, obesity.

Garrett G et al CIASN 2013
Frazao JM et al Curr Opinion Nephrol Hyperten 2009

PTH and BSAP combining the best of both worlds

- 1. PTH “extremes” (< 100 pg/ml) or (> 600pg/ml) high specificity for adynamic/OFC.
- 2. Bone specific alkaline phosphatase (< 20 IU/L) has a high PPV (80%) for low bone turnover.
- 3. BSAP correlate with PTH values in stage 5D CKD: both are increased on bone biopsy in established high bone turnover.
- 4. Combining the lower quartile BSAP and PTH < 100-150 have a high PPV (90%) for adynamic bone disease.

Garrett G et al CIASN 2013
Couttenye C et al Nephrol Dialysis Transpl 2009
Remember:

Lower PTH PPV seen only in those not on PTH inhibitors

Biomarkers in Stage 4-5 CKD

1. An elevated BSAP excludes adynamic bone disease and is not seen in osteoporosis (osteomalacia, severe hyperparathyroidism), if other causes of elevated BSAP are excluded (Paget’s, metastatic Ca, etc).

2. An elevated (6X the upper limit of the normal range) intact PTH (old Nichols assay) most likely excludes adynamic bone disease; far more likely to be OFC.

3. A normal BSAP or a normal or mild elevation of PTH does not exclude adynamic bone disease.

4. A intact (1-84) PTH < 150 pg/ml and a lower quartile BSAP: high PPV for adynamic bone disease.

Miller PD. Up-to-Date 2012
Bone Biopsy in CKD

• 1. Is the “gold standard” for diagnosis of renal bone disease and for defining the bone turnover activity.
• 2. Require double tetracycline labeling for quantitative bone histomorphometry
• 3. Is safe and has very low morbidity (including post-op pain) in experienced operators
• 4. Is especially important before bone turnover is “turned down”
Renal Adynamic Bone Disease

When/Where a Bone Biopsy is Unobtainable

- Cues for adynamic bone disease:
- PTH < 150pg/ml
- TNSAP in lower quartile of premenopausal range
- Hypercalcemia with suppressed PTH
- Lower BSAP
- Elevated 1-84/7-84 PTH ratio
Why

Is excluding low bone turnover an evolving important issue in systemic biology?

Preliminary Data Exists

That even in mild (stage 3) CKD (GFR: 60-30 ml/min) bone turnover may be reduced, fracture risk increased, And ........

Reduced bone turnover may be linked to the greater risk for systemic vascular disease so prevalent in CKD

Hruska K et al Seminars Dialysis 2007
Cohen G J Nephrol 2005
Dukas LC et al OI 2005
Total Alkaline Phosphatase vs BSAP

- Low BSAP is the test for possible adynamic bone disease
- Low total alkaline phosphatase is the test for possible hypophosphatasia (HPP)

Low BSAP

- HPP
- Renal adynamic bone disease
- Treatment with anti-resorptive agents
- Hypoparathyroidism
- Vitamin D intoxication (perhaps via hypercalcemia and PTH suppression)
- Celiac disease
- Cardiac bypass
- Clofibrate
- Cushing’s Disease
- Massive transfusions
- Milk alkali syndrome
- Vitamin C deficiency
- Wilson’s disease
Fracture Prediction

• 1. BMD by DXA can be used to predict fracture risk in stage 1-3 CKD- (PMO studies) though risk may be higher in patients with intrinsic renal disease than age-related reductions in GFR.

• 2. DXA is poor predictor to discriminate between fractured and non-fractured patients with stage 4-5 CKD.

Miller PD et al Clin Rev in Bone and Min Metab 2012

Trabecular density/DXA fail to discriminate fracture status in dialysis patients

Jamal SA et al., 2006.
Cortical density discriminates fracture status in dialysis patients

Jamal SA et al., 2006.

Extreme CT

Serge (Cremers) L arm!

High Resolution Peripheral QCT: Scanco Xtreme CT
Tibia for 2 Age-, and FN T-Score Matched PMO Women

Control 64 yo Female T-Score -2.7: Tibia
PMO 62 yo CKD Pt T-Score -2.5

Thicker Ct vs CKD pt
Increased Tb Separation vs CKD pt

Nickolas T et al CJASN 2010

Therapies for osteoporosis: USA

- Hormone therapy
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- Teriparatide
- Denosumab (anti-rank ligand antibody)
Treatment of Osteoporosis in CKD

• 1. Stage 1-3 CKD: Treatment does not differ as in patients with PMO since clinical trials randomized patients down to “GFR” of 30 ml/min
• 2. Stage 4 CKD: Management dependent on considerations for “off-label” use:
  • Post-hoc analysis show efficacy and safety through 3 years of risedronate, alendronate and raloxifene and denosumab down to eGFR of 15 ml/min for 2-3 years. Teriparatide to eGFR of 30.
• 3. Stage 5/5D CKD: No data- off-label consideration for fracturing patients, e.g. very high risk with established osteoporosis.

Bisphosphonates in CKD
US/European Labeling States:

Oral bisphosphonates are not recommended in patients with creatinine clearance < 30 (35) mL/min: (Stage 4-5 CKD)
Zoledronic acid contraindicated at GFR < 35 ml/min

FDA Label

• 1. Randomization excluded patients with elevated baseline serum creatinine (< 1.5/<2.4).
• 2. eGFR exclusion criteria added by HORIZON and FREEDOM.
• 2. Renal (glomerulosclerosis or ATN) seen in case reports with IV bisphosphonates.
• 3. Bone retention probably greater with reduced GFR since bisphosphonates are cleared by the kidney (both filtration and tubular secretion)
Measurements of GFR

Which method(s) would you use to screen for CKD?

A. Serum creatinine concentration
B. Estimated GFR by Cockcroft-Gault equation
C. Estimated GFR by modification of diet in renal disease (MDRD) equation (or MDRD_epi)
D. Serum cystatin C or eGFR by cystatin C
E. 24-hour urine for creatinine clearance

Levy et al
Stevens et al
Ensrud K et al CJASN 2013

Relation of Estimated GFR to Measured GFR in the Participants in the Modification of Diet in Renal Disease Study

Mean Changes in Calculated Creatinine Clearance From Baseline Over Time
Horizon: Zolendronate 5mg/yr vs Placebo

Mean (±SE) Change From Baseline in Calculated Creatinine Clearance (mL/min)

<table>
<thead>
<tr>
<th>Times</th>
<th>Placebo</th>
<th>ZOL 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3862</td>
<td>3852</td>
</tr>
<tr>
<td>12</td>
<td>3573</td>
<td>3615</td>
</tr>
<tr>
<td>24</td>
<td>3284</td>
<td>3337</td>
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<tr>
<td>36</td>
<td>2350</td>
<td>2419</td>
</tr>
<tr>
<td>Last Visit</td>
<td>3620</td>
<td>3657</td>
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</table>

ZOL n = 3608, PBO n = 3608

Black D et al NEJM 2007

HORIZON-PFT: Mean Serum Creatinine Levels From Baseline in Patients with Pre- to Post-infusion Change of >0.5 mg/100 dL (Overall Safety Population): 7,714

Mean Serum Creatinine (mg/dL)

<table>
<thead>
<tr>
<th>Times</th>
<th>Placebo</th>
<th>ZOL 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>9-11 days</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>2nd infusion</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>3rd infusion</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>1st infusion</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>2nd infusion</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>3rd infusion</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Month 36</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

ZOL n = 3608, PBO n = 3608

n, number of patients affected from the overall safety population (N = 7,714)
HORIZON-PFT Extension Study: Mean Changes in Calculated Creatinine Clearance From Baseline Comparable for ZOL vs Placebo (Safety Population)

Perform a creatinine clearance (will accept eGFR by CG) before each dosing
Managing Renal Risk with ZOL

• 1. Faster infusion time and greater risk of ARF suggests renal damage might be due to the Cmax rather than the AUC.

• 2. Slower infusion rate (30 minutes) suggested (opinion) in Stage 3 CKD (eGFR 59-30 ml/min).

• 3. Patients should be well hydrated, off diuretics for several days, and avoid NSAIDs for several days before infusion.

• 4. Off-label use in stage 4-5 CKD in established osteoporosis - suggest even slower infusion rate (60 minutes).


Vertebral Fracture Risk Reduction With Risedronate

Control 5mg RIS

<table>
<thead>
<tr>
<th>Baseline Renal Impairment</th>
<th>Percent (%) of Patients</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>32% (24.46%) P=0.001</td>
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<tr>
<td>Moderate</td>
<td>45% (31.57%) P=0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>56% (11.78%) P=0.021</td>
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</tbody>
</table>

Miller PD et al JBMR 2005
Fracture Risk with Alendronate by Estimated GFR (eGFR)

<table>
<thead>
<tr>
<th>Site</th>
<th>eGFR</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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<tbody>
<tr>
<td>All Women (n=6459)</td>
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</tr>
<tr>
<td>Clinical Fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely reduced</td>
<td>0.78 (0.51 to 1.2)</td>
<td></td>
<td>0.90</td>
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<td>Moderately reduced or normal</td>
<td>0.81 (0.70 to 0.94)</td>
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<tr>
<td>Spine Fractures</td>
<td></td>
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<tr>
<td>Severely Reduced</td>
<td>0.72 (0.31 to 1.7)</td>
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<td>0.44</td>
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<tr>
<td>Moderately reduced or normal</td>
<td>0.50 (0.32 to 0.76)</td>
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</table>

Jamal S et al JBMR 2007

Incidence of New Vertebral Fracture Through Month 36 by Baseline CrCl

- Placebo (N=3906)
- DMAb (N=3902)

<table>
<thead>
<tr>
<th>N1</th>
<th>3691</th>
<th>3702</th>
<th>33</th>
<th>31</th>
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<td>8.1</td>
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<td>*</td>
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<tr>
<td>N</td>
<td>Placebo (N=3906)</td>
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</tr>
</tbody>
</table>

N = number of randomized subjects. N1 = number of randomized subjects with an evaluation during the time period of interest. There were no subjects with a CrCl < 15 mL/min. *P < 0.05

Jamal S et JBMR 2012
Denosumab 60 mg SQ Q6Mos in PMO

- 1. Did not alter serum creatinine concentration from baseline over 3 years
- 2. Was not associated with any increase in vascular calcification as assessed by AP and lateral x-ray over 3 years within groups or between treated and placebo.

Egbuna O et al ASN 2010 (abstract)

**Effect of Renal Function on Changes in PINP Concentrations with Teriparatide**

![Graph showing the effect of renal function on changes in PINP concentrations with teriparatide.](image)

* * P<0.05 from Placebo

Effect of Renal Function on Changes In Bone Mineral Density with Teriparatide

Lumbar Spine BMD (18 months)

Mean Percent Change in BMD + SE

-5 0 5 10 15 20

Normal (≥ 80 ml/min)  Mild Impairment (50-79 ml/min)  Moderate Impairment (30-49 ml/min)

Femoral Neck BMD (12 months)

Mean Percent Change in BMD + SE

-3 -2 -1 0 1 2 3 4

Normal (≥ 80 ml/min)  Mild Impairment (50-79 ml/min)  Moderate Impairment (30-49 ml/min)

* P<0.05 from Placebo


In None of the PMO Clinical Trials

Did any patients in whom baseline PTH was measured have an elevated PTH:
Other Anabolic Agents
(BMP 7, abaloparatide, monoclonal antibody for sclerostin, PTHrpanalogue; or Odanacatib (a preserver of osteoblast function)

May offer more targeted therapy and robust data for patients with CKD and low bone turnover

Off Label Use of Anti-Resorptive/Anabolic Agents is Considered in Stage 4 CKD

• 1. In very high risk patients who have osteoporotic fractures.
• 2. Whose mortality is high because of these fractures
• 3. And where in post-hoc analysis bisphosphonates, raloxifene, HT, denosumab, and teriparatide have been shown to reduce fracture risk as compared to placebo in patients with eGFR down to 15 ml/min (30ml/min for teriparatide)

Delmas PD et al OI 2009  Miller PD  Seminars Nephrology 2009
Management Decisions in Stage 5 CKD in Fracturing Patients

No Data
Only Opinion

Bisphosphonate Use in Stage 5/5D 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 and clear-cut diagnosis.

• Bone retention over time with bisphosphonates in patients with low GFR unknown

• Effect of reducing bone turnover by any agent that reduces turnover on cardiovascular disease unknown

• In PMO observational trials, BP reduce all-cause mortality

Miller PD Seminars Dialysis 2007
Miller PD Seminars Nephrology 2009
Sambrook P et al Ost Int 2009
Conclusions

• Stage 1-3 CKD: manage as you would for PMO or idiopathic male osteoporosis.
• Stage 4-5 CKD: screen DDX with BTM-especially PTH and BSAP and serum phosphorus.
• Fractured 4-5 CKD without biochemical evidence suggesting OM or adynamic bone disease: treat on label with denosumab or off-label with bisphosphonates, or teriparatide, if not OFC.
• Fractured 4-5 CKD that you don’t know the turnover, or with a lower PTH/BSAP- treat with teriparatide first.

Thank You
Elliott
For the kind invitation

Paul D. Miller, M.D.