Merging the definitions of osteoporosis into the framework of CKD-MBD

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DISCLOSURES

NONE
Chronic Kidney Disease (CKD) - Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR* categories: KDIGO 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or High</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly Decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to Moderately Decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to Severely Decreased</td>
</tr>
<tr>
<td>G4</td>
<td>Severely Decreased</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney Failure</td>
</tr>
</tbody>
</table>

Dialysis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Dialysis</th>
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</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
</tr>
<tr>
<td>G5</td>
<td></td>
</tr>
</tbody>
</table>

*Glomerular filtration rate (GFR) estimates how much blood passes through the glomeruli each minute.*
Merging Osteoporosis and CKD-MBD

Back to Basics

**kidney-associated bone disease** could be a more appropriate term because it emphasizes the renal osteodystrophy component and includes, in the broad term, osteoporosis as well.

Pazianis M and Miller PD Am J Kid Dis 2021
Osteoporosis: Identifying the Problem

“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”

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
Renal Osteodystrophy or Kidney Induced Osteoporosis

Can Coexists?

Moe S Curr Osteoporosis Reports 2017
Miller PD Am J Kid Dis 2017
Pathophysiology of Osteoporosis
Bone resorption exceeds bone formation
Negative Calcium Balance

Armas LAG and Recker RR: Endo Clinic North Amer 2012
Diagnosis of Osteoporosis

• By Central DXA of spine, hip, or wrist (T-score of -2.5 or lower)

• By Fragility fracture after the age of 50 years fractures of vertebrae, hip, wrist, pelvis, humerus, or tibia) once other causes of fragility fractures are excluded (osteomalacia, primary hyperparathyroidism, renal bone disease, OI, HYPP).— independent of the “T-score.”

Pathophysiology of CKD-MBD

starts with Phosphate Retention

Trade off Hypothesis

Secondary Hyperparathyroidism Occurs in Major Degree as a “Trade Off” for the Adaptation in Phosphorus Excretion Required to Maintain External Phosphorus Balance in Advancing Renal Disease

Bricker NS, Slatopolsky E, Reiss E, Avioli LV. Arch Intern Med 1969;123:543-553

1925 Biologically active Parathyroid extract
1969 Trade off Hypothesis
1972 1,25\((OH)_2\)D
1996 Pi action on Parathyroids
2000 FGF-23

Nephron
Diagnosis of CKD-MBD

• Elevated serum FGF 23 plus...
• Elevated PTH
• Elevated (at times) serum phosphorus
• Exclude other forms of renal bone disease (adynamic, osteomalacia, hyperparathyroid bone disease)

Pazianas M and Miller PD. JBMR Dec 2020
Elevated Serum Phosphorus
Is the stimulus for the early increase in FGF 23 and, later, PTH
Perspective

FGF23

more than a regulator of renal phosphate handling?

Harald Jüppner, Myles Wolf, and Isidro B. Salusky JBMR 2010
What does FGF-23 do?

• Phosphaturic
• Inhibits the kidney production of 1,25 dihydroxy vitamin D
• Inhibits PTH production and secretion
• Effect on bone microenviroment
• Effect on cardiac muscle
• The FGF23 level in patients with CKD can even indicate their life expectancy.

Juppner H. Kid Internat 2011.
Li X. Front Med 2019
Changes in the serum levels of FGF-23, 1,25 vit D, PTH and Phosphate during progression of Chronic Kidney Disease

Nature Reviews | Nephrology

Pazianas M and Miller PD
JBMR 2020
Regulation of FGF 23 Production

• Phosphorus stimulates

• PTH stimulates > Partners to collectively to decrease serum phosphorus

• 1,25 D stimulates

• FGF 23 effect on bone: disturbs osteoblast function and matrix mineralization

Goltzman D et al. Front Hormonal Res 2018
Zhang DD et al. Exp Molecular Med 2019
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?
How can we prevent hyperphosphatemia?

• Diet? Ubiquitous in all food chains.

• GI Phosphate binders?

• **GOOD LUCK**

• All poorly effective-why?
Intermittent PTH Administration in Stage 2 CKD may:

1. Hand the Control of Phosphate levels back to PTH
2. Control FGF-23 levels and Eliminate or Reduce significantly the risks associated with increased circulating FGF-23
3. Achieve a better control of \( 1,25(\text{OH})_2\text{D} \) levels
4. Reduce the risk of Atherosclerosis and Cardiovascular Disease
5. Prevent the elevation of PTH
6. Protect the Parathyroid Glands from Hyperfunction and Prevent Hyperplasia
7. Protect the Skeleton from the Catabolic Effects caused by the Continuously Elevated circulating PTH
Fractures In Chronic Kidney Disease

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

Nickolas TL et al. Kid Internat 2008; 74(6): 721-731
Diagnosis of Osteoporosis in Stage 1-3A CKD

• Use the same criteria as is used in folks without CKD
Diagnosis of “Osteoporosis” in Stage 3B-5 CKD

Is a diagnosis of exclusion

Biochemical and Histomorphometry
Biochemical Markers of Bone Turnover
PTH and BSAP
combining the best of both worlds

• 1. PTH “extremes” ( < 100 pg/ml) or ( > 600pg/ml) high specificity for adynamic and 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 CJASN 2013
Couttenye C et al Nephrol Dialysis Transpl 2009
Eastell R and Sprague S
2 Bone Diseases to avoid “turning bone turnover down”

- Osteomalacia

- Adynamic bone disease (idiopathic)

May not want to use anti-resorptive in these 2 conditions that already have a low bone turnover to start
Von Kossa, H&E Stain for Calcium and Osteoid: Osteomalacia

Unstained, Fluorescent for Tetracycline

Von Kossa, H&E Stain, Fluorescent for Osteoid

- Thick Trabeculae
- Increased Osteoid
- No label
- Diffuse label
- Single label
- Peri-osteocytic Osteoid
- Osteoid
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)
Adynamic Bone Disease
Absence of single tetracycline labels
BONE BIOPSY
Renal Adynamic Bone Disease

Von Kossa 40X
Osteopenia

Von Kossa 40X Fluorescence
Osteoid Yellow

TRAP-Azure 100X
No Osteoclasts

Unstained Fluorescence 100X
No Tetracycline Label

Miller PD CJASN 2007
Treatment of Osteoporosis

Antiresorptive agents

Anabolic agents

Treat the same at GFR’s of 90-45 ml/min (stage 1-3A CKD)
Therapies for osteoporosis: USA

- Hormone therapy
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- Teriparatide
- Denosumab (anti-rank ligand antibody)
- Abaloparatide
- Monoclonal antibody to Rank-L
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 down to eGFR of 30ml/min; and denosumab down to eGFR of 15 ml/min for 2-3 years. Teriparatide and Abaloparatide to an eGFR of 30 ml/min.

3. Stage 5/5D CKD: No data- off-label consideration for fracturing patients, e.g. very high risk with established osteoporosis.
Treatment of Osteoporosis in Stage 3B-5CKD

• Know what bone disease you are treating: adynamic, hyperparathyroidism, osteomalacia that may also be associated with osteoporosis.
• Most approved therapies for PMO have a FDA registration “warning” label to avoid use in patients with an eGFR of < 30 ml/min.
• No limitation for denosumab which can be used at eGFR <15 ml/min.
• Teriparatide and abaloparatide “warning” is < 30 ml/min.
• Both teriparatide and abaloparatide can reverse “idiopathic” renal bone disease.
• In the future, romosozumab which inhibits sclerostin binding to osteoblasts may be the targeted therapy to renal “low bone turnover” disease, since serum sclerostin levels increase as eGFR decreases.
Stage 3B -5CKD ???

• Denosumab (Prolia™). Approved REGARDLESS of GFR since it is not cleared by the kidney; has no negative effect on renal function.

• Bisphosphonates have a FDA label in their “warning section” not to use them with GFR < 35-30 ml/min-why???: bisphosphonates are cleared by the kidney and old data using IV Pamidronate had few patients had developed ATN. All recovered.

• In the IV ibandronate trials (3mg IV push Q 3 months), had no effect on renal function; and, IV zoledronic acid (Reclast™) had a transient but recoverable increase in serum creatinine, but not at an infusion rate of 30 ml/min.

• Teriparatide and abaloparatide increase renal blood flow and FDA label suggesting (“warning”) not to use them at GFR < 30ml/min is based on no studies (prospective) of effectiveness at these lower levels of GFR.

• Recent data (post-hoc) does suggest effectiveness for patients with idiopathic renal adynamic bone disease and “osteoporosis” at levels< GFR of 30ml/min.(Palcu P et al: Am J Kid Dis 2015)
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 have been shown to reduce fracture risk as compared to placebo in patients with eGFR down to 15 ml/min.

Teriparatide and Abaloparatide also down to 30ml/min.

May be useful for idiopathic renal adymanic bone disease.

Delmas PD et al OI 2009  Miller PD Seminars Nephrology 2009
Thank You ISO 2021

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