ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM
CKD- Mineral Bone Disorder

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Definition of 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

Homeostasis of CKD-MBD

"Calcium" regulated by PTH and FGF23:
- PTH stimulates 1alpha hydroxylase activity, increasing 1,25(OH)₂D.
- Increased 1,25(OH)₂D increases calcium reabsorption.
- FGF23 decreases 1,25(OH)₂D, inhibiting calcium reabsorption.

Phosphorus regulation:
- Increased PTH activity increases phosphorus excretion.
- Decreased FGF23 decreases phosphorus excretion.

Increased Renal phosphorus excretion leads to:
- "Calcium" decrease
- "Calcium" increase

Diagram notes:
- Solid line = stimulates
- Dotted line = inhibits
Renal Osteodystrophy: A skeletal component of CKD-MBD that is assessed with bone biopsy/histomorphometry

<table>
<thead>
<tr>
<th>Bone Formation Rate</th>
<th>Osteoblast Bone Formation and cell number</th>
<th>Osteoclast Bone Resorption and cell number</th>
<th>Osteoid (not yet mineralized bone) as a percentage of bone surface</th>
<th>Fibrosis (cell differentiation not normal)</th>
</tr>
</thead>
<tbody>
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</table>

**Osteitis Fibrosa Cystica:** due to persistent and severe hyperparathyroidism

```
```
```
```
normal
```

**Mild Hyperparathyroid disease** - due to elevated PTH

```
```
```
```
normal
None

**Osteomalacia** - due to Hypophosphatemia, decreased vitamin D, ?’ FGF23

```
```
```
```
to normal
```
```
to normal
```
```
None

**Mixed Uremic Osteodystrophy** due to a combination of hyperparathyroidism and mineralization defect

```
```
```
```
```
None

**Adynamic bone disease** due to abnormal cell differentiation, oversuppression of PTH, older age, diabetes

```
```
```
```
```
```
No osteoid
None


Components of Bone Strength: There is increased fractures in CKD because of both abnormal quantity and quality.

**Bone Quantity**
- Mass
- Mineral Density
- Size

Assessed by DXA and qCT

**Bone Quality**
- Bone turnover
  - Resorption/Formation
- Macroarchitecture
  - Geometry
- Microarchitecture
  - Connectivity
- Material Properties
  - Mineralization
  - Collagen Cross-linking
  - Microfracture

Assessed in vitro only by microCT, SEM, biochemical analyses
Fractures are increased in CKD due to a number of factors:

- **MENOPAUSE**
  - Altered hormones and bone signaling

- **AGING**
  - Low peak bone mass

- **RENOPAUSE:**
  - Abnormal Bone turnover
  - Altered hormones and bone signaling

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Source: Sharon Moe, MD
We can measure a lot of things, but what is the big picture of the pathogenesis and consequences (morbidity and mortality) of CKD-MBD?

Abnormal levels and bioactivity of laboratory parameters in CKD:

<table>
<thead>
<tr>
<th>Laboratory Surrogate Outcomes</th>
<th>PTH</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>25(OH)D</th>
<th>1,25(OH)2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High*</td>
<td>Normal*</td>
<td>Normal*</td>
<td>Normal*</td>
<td>Normal*</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal*</td>
<td>Normal*</td>
<td>Normal*</td>
<td>Normal*</td>
<td>Normal*</td>
</tr>
<tr>
<td>Low</td>
<td>Low*</td>
<td>Low*</td>
<td>Low*</td>
<td>Low*</td>
<td>Low*</td>
</tr>
</tbody>
</table>

Bone and CVD Surrogate Outcomes:
- Bone turnover: Osteocalcin, Bone specific alkaline phosphatase, C-terminal cross links
- Bone mineralization/density: DXA, qCT, qUS
- Bone turnover, mineralization & structure: Histology

Bone disease: abnormal structure or function
- Fractures, Pain, Decreases in mobility, strength or growth
- Disability, Decreased QOL, Hospitalizations, Death

Cardiovascular Disease events
- Vessel and valve disease: abnormal structure or function
- Vessel stiffness: Pulse wave velocity, pulse pressure
- Vessel / valve calcification: X-ray, US, CT, EBCT, MSCT, IMT
- Vessel patency: Coronary angiogram, Doppler Duplex US

Clinical Outcomes

KDIGO guidelines, KI 2009
Concerns at the time: Bone Disease and pain, systemic effects of PTH, hypocalcemia was cause of PTH and so give more calcium.

Concerns evolved to studies showing increased fracture, and data linking high phosphorus to elevated PTH, mortality, and arterial calcification.
## Comparison of KDIGO vs. KDOQI clinical practice guidelines for CKD-MBD

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Approach</strong></td>
<td>Systematic review of interventions in adults or children. Used only RCTs with prior determined criteria: trial duration greater or equal to 6 months and minimum N of 50 patients, except for studies of bone histomorphometry outcomes, which required a minimum N of 20.</td>
<td>Systematic review but used all types of studies (not just RCT). Prior determined criteria were minimum N was 10 patients per arm, except for cross over studies where 5 per arm were included.</td>
</tr>
<tr>
<td><strong>Grading</strong></td>
<td>Used international GRADE classification system: Level 1 or 2 for strength of recommendation; followed by A, B, C, D for quality of evidence</td>
<td>Only opinion or evidence; based on work group assessment</td>
</tr>
</tbody>
</table>
### KDOQI (in red) and KDIGO (in blue) “Target” values

<table>
<thead>
<tr>
<th></th>
<th>CKD Stage 3</th>
<th>CKD Stage 4</th>
<th>CKD Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosph (mg/dl)</strong></td>
<td>2.7-4.6 mg/dl (Opinion) “Normal” (2C)</td>
<td>2.7-4.6 mg/dl (Opinion) “Normal” (2C)</td>
<td>2.7-5.5 mg/dl (Evidence) Towards the normal range (2C)</td>
</tr>
<tr>
<td><strong>Calcium (mg/dl)</strong></td>
<td>Normal (Opinion) “Normal” (2D)</td>
<td>Normal (Opinion) “Normal” (2D)</td>
<td>8.4-9.5; Hypercalcemia = &gt;10.2 (Evidence) “Normal” (2D)</td>
</tr>
<tr>
<td><strong>Intact PTH (pg/ml)</strong></td>
<td>35-70 pg/ml (Opinion) Ideal level unknown</td>
<td>70-110 pg/ml (Opinion) Ideal level unknown</td>
<td>150-300 pg/ml (Evidence) &gt;2 and &lt; 9 times the upper limit of normal [if TREND changing within that range, adjust RX (2C)]</td>
</tr>
</tbody>
</table>
General Approach of treatment of CKD-MBD in stages 3-5 not on dialysis

Decrease total body phosphorus burden by avoiding processed foods with phosphate additives, dietary protein restriction (or vegetarian diet) and/or phosphorus binders.

- No data supporting starting binders prior to hyperphosphatemia (Block JASN 2012)

Treat nutritional vitamin D deficiency

- KDOQI recommended using cut off of 30 ng/ml; Institute of Medicine recommended 20 ng/ml
- Ergocalciferol or cholecalciferol may lower PTH in some patients (Zisman AJN 2007, Moe CJASN 2010; Kovesdy AJKD 2012; Kandula CJASN 2012)
- There may be autocrine effects, but unproven in CKD

Normalize serum calcium

- This may help suppress PTH
- Avoid excessive calcium intake (>1000 mg/day by diet or binder); studies demonstrate positive calcium balance will result (Spiegel, KI 2012; Hill, KI 2013) although consequence unproven. If PTH is elevated, best mechanism to normalize calcium is through vitamin D.

Treat elevated PTH with calcitriol or other “less hypercalcemic” vitamin D analogues

- No comparative data between therapies to lower PTH (see next slides)
Reduction of phosphorus is best achieved by avoiding processed foods.

### Dietary Management of Phosphorus

<table>
<thead>
<tr>
<th>Source</th>
<th>Examples</th>
<th>Phos Content*</th>
<th>Phos Type</th>
<th>Phos Absorbed**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant-based foods</td>
<td>Most fruits and vegetables</td>
<td>↓</td>
<td>Organic phytate or phytic acid</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td></td>
<td>Nuts, seeds, legumes</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal-based foods</td>
<td>Meat, fish, poultry, dairy products, eggs</td>
<td>↑</td>
<td>Organic phosphate</td>
<td>40 – 60%</td>
</tr>
<tr>
<td>Processed or enhanced foods</td>
<td>Certain beverages, processed meats and cheeses, bakery mixes, frozen meals, fast foods</td>
<td>↑↑</td>
<td>Inorganic phosphate salts (PO4 additives)</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>

*Consider phosphorus to protein ratio  
**Phosphorus absorption rates may vary, e.g. higher absorption can be observed upon vitamin D administration.

Drugs that lower PTH

Vitamin D

Vitamin D and natural metabolites
- Vitamin D₃ cholecalciferol
- Vitamin D₂ ergocalciferol

Vitamin D prodrugs
- 1±(OH)D₃
- 1±(OH)D₂ doxercalciferol

“Active” Vitamin D
- 1,25(OH)₂D₃ calcitriol

Vitamin D analogues
- 19-nor-1±25(OH)₂D₂ paricalcitol, 22-oxacalcitriol

Calcimimetics
- cinacalcet
Lowering PTH in CKD stage 3-4

Percent Change in Parathyroid hormone in placebo controlled trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxercalciferol (Coburn 2004)</td>
<td>N = 55 24 weeks</td>
</tr>
<tr>
<td>Paricalcitol (Coyne 2006)</td>
<td>N = 220 24 weeks</td>
</tr>
<tr>
<td>Cinacalcet (Chonchol 2009)</td>
<td>N = 404 32 weeks</td>
</tr>
</tbody>
</table>

-46% 0% -45% 0% +13% -43%
Lowering PTH in CKD stage 3-4
Change in Calcium levels (mg/dl)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxercalciferol</td>
<td>8.6</td>
<td>8.2</td>
</tr>
<tr>
<td>(Coburn 2004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>9.2</td>
<td>9.8</td>
</tr>
<tr>
<td>(Coyne 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>9.6</td>
<td>10.0</td>
</tr>
<tr>
<td>(Chonchol 2009)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = p < 0.05 compared to pre

Doxercalciferol (Coburn 2004)
Paricalcitol (Coyne 2006)
Cinacalcet (Chonchol 2009)
Lowering PTH in CKD stage 3-4
Change in Phosphorus levels (mg/dl)

* = p < 0.05 compared to pre
What effects do these treatments have on biochemical parameters?

- **Low Phosphate diet**
  - 
  - **Phosphate binder**
  - “Phosphorus”
  - ↓PTH↓
  - FGF23, ↑1,25D (if Ca binder↑FGF23)

- **Cinacalcet**
  - “PTH”
  - “FGF23” Ca Phosph (‘ in CKD, “ in ESRD)

- **Calcitriol**
  - “PTH”
  - “PTH’ FGF23‘ Ca ‘ Phosph
  - ‘1,25D??
  - Autocrine may “PTH’ FGF23
  - Without change in Ca, Pi

- **Cholecalciferol**
  - “PTH?”
General Approach of treatment of CKD-MBD on dialysis when the kidneys no longer control homeostasis

• **Normalize serum phosphorus:** By diet, phosphorus binder therapy, and more dialysis

• **Normalize serum calcium:** Targeting the lower end of normal allows more flexibility in treatments

• **Treat elevated PTH:** With calcitriol or other “less hypercalcemic” vitamin D analogues

• **Lower FGF23:** but we don’t know how to do this yet

**Ultimately want to improve biochemical parameters in order to**

• Reduce cardiovascular calcification
• Improve LVH
• Treat renal osteodystrophy (bone abnormalities)
• Reduce fractures
Will treatments impact

LVH and Vascular Calcification

Cardiovascular Events

PTH, Ca, Pi Bone Remodeling

Fractures

Hospitalizations

Quality of Life

Mortality
CKD stage 5: Lower the phosphorus towards the normal range

- Animal and in vitro studies demonstrate that phosphorus is a direct vascular toxin, can induce LVH, and increases PTH.
- Many associative data demonstrate increased mortality when phosphorus is above a certain value; what the inflection point at which this risk increases depends in part on what the reference range was set at.
- Meta analysis of studies evaluating an association of phosphorus with adverse outcomes demonstrate a relative risk of 1.18 (1.12-1.25 95% CI) per unit increase of phosphorus for all cause mortality, and 1.10 (1.06-1.13) per unit increase for phosphorus and cardiovascular mortality. (Palmer, JAMA 2011)
- No study has been done to demonstrate that lowering phosphorus to a specific level is associated with an improved outcome; thus the ideal ‘target’ is unknown and thus “toward the normal range” was used in the KDIGO guidelines
- Must individualize treatment in each patient to optimize phosphorus lowering while minimizing side effects
Phosphorus removal with dialysis

• The majority of phosphorus is not in the extracellular space. Thus conventional hemodialysis will lower phosphorus, but with rebound after dialysis is done.

• Dialysis with maximal convection and maximal time will yield greatest removal of phosphorus (see Kuhlmann, Blood Purification 2010)
  • Standard thrice weekly HD removes ~ 2.4 g/week
  • Hemodiafiltration removes ~ 3.6 g/week
  • Short daily HD (SDHD) removes ~ 2.5 g/week
  • Nocturnal HD removes ~ 8 g/week
  • CAPD removes ~ 2.8 g/week
  • CCPD removes ~ 2.8 g/week

• In the randomized trial of thrice weekly vs. SDHD, there was a greater reduction in pre dialysis phosphorus concentration over the 12 months in frequent compared to thrice weekly dialysis (- 0.56 mg/dl (95% CI -0.91 to -0.22). (Chertow et al, NEJM 2010)

• The average person (in US) eats 1.4 g or ~ 9 to 10 g/wk! So, there is also a need for a reduction in diet and binders.
## Comparing Phosphate Binders (and all binders lower phosphorus compared to placebo or they would not be FDA approved!)

<table>
<thead>
<tr>
<th></th>
<th>Aluminum</th>
<th>Calcium carb or acetate</th>
<th>Magnesium</th>
<th>Lanthanum carbonate</th>
<th>Sevelamer HCl or carbonate</th>
<th>Sucroferric oxyhydroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacious</strong></td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td><strong>Absorbed</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Accumulates</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Contributes to Ca x P</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lipid effect</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes-Lowers LDL</td>
<td>No</td>
</tr>
<tr>
<td><strong>Improves endpoints other than Pi</strong></td>
<td>No</td>
<td>Yes-Bone Bx and VC data</td>
<td>No</td>
<td>Yes-Bone Bx</td>
<td>Yes-Bone Bx and VC data</td>
<td>No</td>
</tr>
</tbody>
</table>
Will treatments with phosphate binders impact any of these end points?

**LVH and Vascular Calcification**

**Vascular Calcification:** Studies evaluating arterial calcification in humans have compared sevelamer vs. calcium carbonate or acetate. Results are mixed and depend on study design.

**PTH, Ca, Pi Bone Remodeling**

**Bone Remodeling:** Ca binder will suppress bone remodeling more than non Ca binder.

**Hospitalizations Quality of Life Mortality**

**Ca:** Ca binder will cause hypercalcemia more than non Ca binder.

**PTH:** Ca binder will suppress PTH more than non Ca binder.
Will treatments with phosphate binders impact any of these end points?

LVH and Vascular Calcification

PTH, Ca, Pi Bone Remodeling

Fractures

Mortality: In CKD 5 on dialysis, Block (KI 2006) showed reduced mortality with sevelamer compared to calcium, but Suki study (DCOR, KI 2007) did not. Meta analysis showed benefit of non calcium vs. calcium based binder on mortality (0.87; 95% CI 0.77-0.97; Jamal Lancet 2014)

No data that any treatment improves fractures

Hospitalizations Quality of Life Mortality

(Evidence from RCTs summarized in grey boxes, see KDIGO guidelines for references)
Why measure and lower PTH?

- **Surrogate of Bone turnover**
  - Associated with fractures
    - Weak correlations and depends on study

- **Uremic toxin**
  - Elevated levels associated with mortality

- **Symptoms that improve after parathyroidectomy:**
  - Bone pain goes away
  - Muscle strength improves
  - Decrease Itching
  - Anemia improves
  - Nerve conduction studies/EEG changes improve
  - Mentation/focus and sexual function improves
  - Maybe blood pressure and cardiac output improves
Severe hyperparathyroidism leads to cortical bone erosion
Drugs that lower PTH in dialysis patients

**Vitamin D**

*Vitamin D prodrugs*
- $1\pm(OH)D_3$
- $1\pm(OH)D_2$ doxercalciferol

*“Active” Vitamin D*
- $1,25(OH)_2D_3$ calcitriol

*Vitamin D analogues*
- 19-nor-$1\pm25(OH)_2D_2$ paricalcitol, 22-oxacalcitriol

**Calcimimetics**
- cinacalcet

- All of these agents lower PTH compared to placebo in randomized controlled trials in dialysis patients
- Comparative trials show mixed results in the efficacy of lowering PTH
- Vitamin D and analogues may raise serum calcium and phosphorus compared to placebo; calcimimetics lower calcium and phosphorus compared to placebo. This should guide your choice of treatment.
Will treatments that lower PTH impact any of these endpoints?

LVH: Paricalcitol vs. placebo in CKD stage 3-4, no difference on LVH in RCT (Thadhani, JAMA 2012); shorter hospitalizations in secondary analysis.

Vascular Calcification: Cinacalcet vs. vitamin D did not reduce VC in RCT in dialysis patients, but secondary analyses using alternative method for VC scoring was significant (Raggi, NDT 2011).

Cardiovascular Events

Mortality: No RCT evaluating any vitamin D therapy. EVOLVE study evaluating cinacalcet (next slides).

Hospitalizations, Quality of Life, Mortality
EVOLVE study: Randomized trial of cinacalcet compared to placebo on background of standard of care

- Study of 3883 prevalent dialysis patients with intact PTH > 300 pg/ml followed for up to 64 months; nearly 90% on phosphate binder and 60% on vitamin D therapy.
- Primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event.
- **Intention to treat primary analysis of unadjusted results did not show difference (HR 0.93, 95% CI: 0.85-1.02, p = 0.11)**
- More adverse events in the cinacalcet arm leading to drug discontinuation (18.1 vs 13%); Study had high drug discontinuation for protocol and non protocol reasons and use of commercial cinacalcet in placebo arm.
- **Secondary analysis showed benefit of cinacalcet** in adjusted primary end point (HR 0.88; 95% CI 0.79-0.97, p = 0.008) and in lag censoring analysis (censored at 6 months post last treatment; HR 0.85; 95% CI 0.73-0.96, p = 0.009).
Summary of studies lowering PTH in CKD-5D

Calcitriol and vitamin D analogs all lower PTH
No human studies show clear differences between calcitriol and the analogs
Cinacalcet lowers PTH and lowers calcium and phosphorus.

RCTs comparing calcitriol/analogs to cinacalcet have mixed results (Fishbain CJ ASN 2008 and Ketteler NDT 2012)

EVOlVE study was a large RCT comparing cinacalcet to placebo on background of vitamin D and phosphate binders. Primary unadjusted end point (mortality and CV events) was not significant; when adjusted as planned secondary analysis cinacalcet reduced mortality (Chertow NEJM M 2012).

Parathyroidectomy remains a viable option, especially in transplant candidates
THE END