Pathogenesis of Metabolic Bone Disease

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• Consultant: Amgen, Fresenius, NPS Pharma, OPKO, Vifor
• Honoraria: ASN

Summary Outline

• Definitions
• KDIGO/KDOQI
• Bone Physiology
• Bone Pathophysiology
• Extra-skeletal Mineralization

Bone Disease in Kidney Failure

Decreased 1,25-vitamin D from renal failure
Amyloid
Type II osteoporosis associated with aging
Hypogonadal
Postmenopausal
Hyperparathyroidism
Metabolic acidosis
Bone Disease
Calcification of extraskeletal tissue
Vascular or other soft tissue mineralization
Aluminum-related osteomalacia
Medications

CKD-Mineral Bone Disorder (MBD)

• A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
  • Laboratory abnormalities
    – Ca, P, PTH, or vitamin D metabolism
  • Bone disease
    – Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
  • Calcification of extraskeletal tissue
    – Vascular or other soft tissue mineralization

Definition of Renal Osteodystrophy

• Alteration of bone morphology in patients with CKD.
• It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by bone histomorphometry.

**Guidelines**

<table>
<thead>
<tr>
<th>Monitoring of Ca, phos, PTH</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting at CKD stage 3. Include Alk Phos: high or low levels may predict bone turnover</td>
<td>Same, no comment on alk phos</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Goal Calcium</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range stages 3-5</td>
<td>Same, weighted to lower end nl range (8.4-9.5 mg/dl) in CKD 5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Goal Phosphorus</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range stages 3-5</td>
<td>Range 2.7-4.6 mg/dl stages 3-4, up to 5.5 mg/dl stage 5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Goal PTH</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eval pts with PTH above upper limits of nl for correctable factors: low phos/ca, low vitamin D CKD5 2-9 ULN</td>
<td>Target ranges CKD3 35-70 pg/ml CKD4 70-110 pg/ml CKD5 150-300 pg/ml</td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines**

<table>
<thead>
<tr>
<th>25 vitamin D</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure levels stage 3-5. Correct as in general population</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PTH assays</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical labs should report assay method, handling &amp; sampling sources. 2nd gen assay recommended.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMD</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not recommended routinely in CKD 3-5 if CKD-MBD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone Biopsy</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable in various settings and prior to bisphos in CKD-MBD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Histologic Classification of ROD (Classic)**

- Normal bone
- Osteomalacia
- Adynamic bone
- Mixed lesion (MUO)
- Osteitis fibrosa cystica

**Classification of ROD (KDIGO)**

- Turnover: High, Normal, Low
- Mineralization: Normal, Abnormal
- Volume: High, Normal, Low

**Prevalence of Renal Osteodystrophy**

<table>
<thead>
<tr>
<th>CKD 3-5</th>
<th>Hemodialysis</th>
<th>Peritoneal Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=711</td>
<td>n=7900</td>
<td>n=371</td>
</tr>
<tr>
<td>Osteitis Fibrosa</td>
<td>32%</td>
<td>34%</td>
</tr>
<tr>
<td>Mild OF</td>
<td>6%</td>
<td>32%</td>
</tr>
<tr>
<td>MUO</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>Normal</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Adynamic</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Sprague M. J Clin Endo Dial 2010
### TMV Distribution of Bone Lesions in CKD Stage 5

<table>
<thead>
<tr>
<th>Mineralization</th>
<th>Turnover</th>
<th>Volume</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Low</td>
<td>1: Low</td>
<td>166</td>
<td>24.95</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>55</td>
<td>11.25</td>
</tr>
<tr>
<td></td>
<td>3: High</td>
<td>46</td>
<td>6.91</td>
</tr>
<tr>
<td>2: Normal</td>
<td>1: Low</td>
<td>38</td>
<td>5.71</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>32</td>
<td>6.54</td>
</tr>
<tr>
<td></td>
<td>3: High</td>
<td>15</td>
<td>2.37</td>
</tr>
<tr>
<td>3: High</td>
<td>1: Low</td>
<td>25</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>21</td>
<td>4.29</td>
</tr>
<tr>
<td></td>
<td>3: High</td>
<td>10</td>
<td>1.57</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Low</td>
<td>1: Low</td>
<td>8</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>7</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>3: Normal</td>
<td>5</td>
<td>1.02</td>
</tr>
<tr>
<td>2: Normal</td>
<td>1: Low</td>
<td>17</td>
<td>3.48</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>18</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td>3: High</td>
<td>10</td>
<td>2.04</td>
</tr>
<tr>
<td>3: High</td>
<td>1: Low</td>
<td>4</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>2: Normal</td>
<td>10</td>
<td>2.04</td>
</tr>
<tr>
<td></td>
<td>3: High</td>
<td>74</td>
<td>13.45</td>
</tr>
</tbody>
</table>

**Sprague et al. ASN 2010**

### Distribution of bone biopsies stratified by TMV

**Lamellar Bone**

**Woven Bone**
Regulation of Osteoblastic Differentiation

- A key regulatory transcription factor in Osteoblastic differentiation:
  - Core-binding factor-a subunit 1 (Cbfa1) (RUNX2)/Osteoblast-specific factor-2 (Osf2)
- Cbfa1 (RUNX2) regulate the expression of bone matrix proteins (type I collagen, osteocalcin, osteopontin)
- Cbfa1(-/-) mouse shows a total lack of bone
- Overexpression of cbfa1 in fibroblasts cells induces expression of the osteoblastic genes
- Osteocyte Wnt/β-catenin

Mediators of Osteoblastic Bone Formation

- Osteoblast Genes
  - Type I Collagen
  - Collagenase
  - IGF-1
  - IGFBP-5
  - IGFBP-6
- Growth Factors
  - TGF-β
  - Noggin
  - BMP
  - IGF-2
  - Osteoblast Number
  - Matrix Formation

Calcification in Bone

Pinching off of cell membrane of osteoblasts into matrix vesicles which contain Ca and P
The Ca X P concentration within the vesicle rises to form hydroxyapatite
The hydroxyapatite ruptures the vesicle membrane and is released
The non-collagenous proteins are now known to “guide” and regulate the process
Receptor Activator for Nuclear Factor κB

Mechanisms of Action for OPG, RANKL, and RANK

Renal Osteodystrophy: Altered Balance of Bone Resorption and Bone Formation

**Pathogenesis of Adynamic Bone Disease**

- Better Pi Control
- Diabetes
- Age
- Uremic Toxins
- Relative Hypoparathyroidism
- Decreased BFR
- Altered Growth Factors and Cytokines
- Al + Fe
- Fe
- VDR Polymorphism
- Decreased BMP-7
- Decreased TGFB
- Decreased TGF-β3
- Decreased FGF23
- Decreased Wnt

**Prevalence of Vertebral Fractures by Tertiles of Intact PTH**

- Bone Pain
- Proximal Myopathy
- Fractures
  - Increased vertebral\(^1\)
  - No effect on hip fractures\(^2\)
- Hypercalcemia
- Extraskeletal calcifications
- Mortality
  - Inverse relationship between PTH and 1 and 5 year survival\(^3,4\)

\(^1\) Atsumi et al. AJKD 1999
\(^2\) Stehman-Breen et al. KI 2000
\(^3\) Hercz et al. JASN 1994
\(^4\) Akizawa et al. JASN 1999

**Morbidity Associated with Low Bone Turnover**

- Bone Pain
- Proximal Myopathy
- Fractures
- Hypercalcemia
- Extraskeletal calcifications
- Mortality

**Adynamic Bone Disease**

- Low turnover - Aluminum Induced Osteomalacia
Pathogenesis of High Turnover Bone Disease
Secondary Hyperparathyroidism

Bone Disease
- osteitis fibrosa
- demineralization
- fractures
- bone pain

↓ Ca++

↑ PTH

↓ 1,25 D

↑ FGF-23

↓ 25 (OH)D

Systemic Toxicity
- nervous system
- cardiac
- endocrine
- immunologic
- cutaneous

Renal Failure

Periarticular Calcification

Possible Effect of Bone Turnover on Extraskeletal Mineralization
Key Points
Board Review

- CKD-MBD
  - A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of laboratory abnormalities, bone disease, or extraskeletal calcification.
  
- Renal Osteodystrophy
  - Alteration of bone morphology in patients with CKD. It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by bone histomorphometry.
  
- Classification of Renal Osteodystrophy
  - Turnover, mineralization, volume

Key Points
Board Review

- High turnover bone disease
  - Predominantly a function of hyperparathyroidism and is characterized by increased cellular activity, increased resorption and formation, increased tetracycline uptake, presence of woven bone, marrow fibrosis, may have variable change in bone volume, and may be associated with normal or defective mineralization.

- Low turnover bone disease
  - Characterized by metabolically inactive bone and may be a function of numerous factors including relative PTH resistance, excessive VDRA and Ca administration. Characterized by decreased or absent cellular activity, lack of tetracycline uptake, may have variable change in bone volume, and may be associated with normal or defective mineralization.
Key Points Update

- Kidney – Bone – Parathyroid Axis
  - FGF23
    - Produced in bone
    - Increased by calcitriol, phosphorus and PTH
    - Promotes phosphaturia
    - Inhibits calcitriol production
    - Stimulates PTH in normal kidney function
  - PTH
    - Promotes phosphaturia
    - Stimulates bone resorption
    - Stimulates Cyp 27B1 production (Calcitriol)

Key Points Update

- Kidney – Bone – Parathyroid Axis
  - VDRA
    - Activates the VDR
    - Enhances calcium and phosphate GI absorption
    - Enhances renal calcium reabsorption
    - Promotes bone remodeling
    - Stimulates FGF23 production
    - Inhibits PTH
    - Cell growth, differentiation and survival
    - Cancer prevention
    - Immune modulation
    - Endocrine regulation
    - Cardiovascular system
    - Inflammation-fibrosis

Thank You