Renal Osteodystrophy

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Introduction

- **chronic kidney disease-mineral and bone disorders (CKD-MBD):**
  A broad syndrome in patients with CKD, in which abnormalities in bone and mineral metabolism and/or extra-skeletal calcification are observed.

- **Renal osteodystrophy:**
  An alteration of bone morphology in patients with CKD.
## Classification of Renal Osteodystrophy

<table>
<thead>
<tr>
<th>Turnover</th>
<th>Mineralization</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Low</td>
<td>Abnormal</td>
<td>Low</td>
</tr>
</tbody>
</table>
ROD is classified according to the state of bone turnover:

- High turnover bone disease
  - Osteitis fibrosa cystica

- Low turnover bone disease
  - Adynamic bone disease
  - Osteomalacia

- Combinations of these abnormalities are called mixed ROD
Osteitis fibrosa cystica

- Bone turnover is increased due to secondary hyperparathyroidism.
- Secondary hyperparathyroidism begins quite early in the course of CKD, frequently when kidney function declines to less than 60 mL/minute/1.73 m².
The main abnormalities that contribute to the pathogenesis of secondary hyperparathyroidism are:

- Phosphate retention
- Decreased free calcium level
- Decreased 1,25-dihydroxyvitamin D (Calcitriol) level
- The reduced expression of vitamin D receptors, calcium-sensing receptors, and other receptors in the parathyroid glands
Adynamic Bone Disease

- bone turnover is markedly reduced
- lack of bone cell activity (both osteoblasts and osteoclasts).
- In adynamic bone disease there is no increase in osteoid formation as seen in osteomalacia.
PATHOPHYSIOLOGY OF CKD-MBD

HIGH TURNOVER STATES

↓ GFR, ↓ Renal Mass

↓ free calcium

↓ Negative feedback on calcium sensing receptor

↓ calcitriol

Tertiary hyperparathyroidism

↑ PTH

↑ Bone turnover
↑ Bone resorption

Osteitis Fibrosa Cystica

Vascular Calcification

Adynamic Bone Disease

Bone pain, fractures, increased cardiovascular mortality

LOW TURNOVER STATES

PTH oversuppression (due to Ca-based phosphate binders/Vit D) in CKD

- Aluminum deposition in bone
- Vitamin D deficiency

↓ Bone turnover
↑ Mineralization lag-time

Osteomalacia

Source: South Med J © 2012 Lippincott Williams & Wilkins
Epidemiology

• the prevalence of osteitis fibrosa among CKD patients either on dialysis or not has markedly decreased, while non-aluminum-induced adynamic bone disease has significantly increased with variations based in part upon geographic region evaluated.
Diagnosis

• Bone biopsy remains the gold standard for the definitive diagnosis of ROD but bio-chemical parameters may be helpful in establishing the diagnosis.

• The K/DOQI guidelines recommend to measure serum calcium, phosphorus and PTH levels when GFR is $< 60 \text{ml/min/1.73m}^2$ (CKD stage 3 and above).
• PTH levels greater than 500 pg/ml are highly indicative of osteitis fibrosa,

• whereas adynamic lesion is suspected when the levels are below 100 pg/ml.

• The serum alkaline phosphatase level may be elevated in hyperparathyroidism indicating increased osteoblastic activity.
The K/DOQI guidelines provide desired ranges of calcium, phosphorus, calcium–phosphorus product, and intact PTH based on the stage of CKD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 3</td>
</tr>
<tr>
<td>Corrected calcium (mg/dL)</td>
<td>“Normal”</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>2.7–4.6</td>
</tr>
<tr>
<td>Ca × P (mg²/dL²)</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Intact parathyroid hormone (pg/mL)</td>
<td>35–70</td>
</tr>
</tbody>
</table>
Frequency of measurement of serum calcium, phosphorus, and PTH by stage of CKD, per the 2009 KDIGO guidelines

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>GFR range (mL · min⁻¹ · 1.73 m²)</th>
<th>Measurement of calcium/phosphorus</th>
<th>Measurement of PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>30–59</td>
<td>Every 6–12 mo</td>
<td>Based on baseline level</td>
</tr>
<tr>
<td>IV</td>
<td>15–29</td>
<td>Every 3–6mo</td>
<td>Every 6–12 mo</td>
</tr>
<tr>
<td>V</td>
<td>&lt;15 or dialysis</td>
<td>Every 1–3mo</td>
<td>Every 3–6mo</td>
</tr>
</tbody>
</table>
Treatment

- The aim of treatment is to reduce the occurrence and/or severity of uremic bone disease cardiovascular morbidity and mortality caused by elevated serum levels of PTH and calcium X phosphorus product.
Dietary phosphorus restriction

Calcimimetics

Phosphate binders

Vitamin D
1-Dietary phosphorus restriction

- Lowering phosphate is done initially by dietary restriction of phosphate intake to 800 to 1000 mg/day.

- Protein sources with the least amount of phosphate, such as meats and eggs, should be prescribed.
2-Phosphate binders

1. Aluminum-containing phosphate binders
2. Calcium-containing phosphate binders
3. Non-calcium, Non Aluminum phosphate binders

• Both calcium-based phosphate binders and other non-calcium, non-aluminum-containing phosphate-binding agents are effective in lowering serum phosphorus levels and may be used as the primary therapy
Phosphate binding agents in routine clinical practice

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/day</th>
<th>Clinical experience and evidence base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium hydroxide</td>
<td>1.425-2.85 g</td>
<td>Extensive clinical experience in CKD and ESRD, no RCT comparison versus placebo. Aluminium accumulates in bone and neural tissue with long-term use, avoids calcium</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>1.5-3 g</td>
<td>Limited trial evidence in ESRD. Reduction in phosphate and elevation in calcium dose-dependent</td>
</tr>
<tr>
<td>Magnesium carbonate</td>
<td>0.7-1.4 g (plus calcium carbonate 0.33-0.66 g)</td>
<td>Short-term RCT evidence in ESRD, less hypercalcemia</td>
</tr>
<tr>
<td>Calcium acetate and Magnesium carbonate combination</td>
<td>Calcium acetate 435 mg plus Magnesium carbonate 235 mg, 3-10 tablets daily</td>
<td>Short-term RCT evidence in ESRD, less hypercalcemia</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>3-6 g</td>
<td>Extensive clinical experience in CKD and ESRD, limited RCT evidence versus placebo. Reduction in phosphate and elevation in calcium both dose-dependent</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>3-6 g</td>
<td>Extensive clinical experience in ESRD; RCT evidence comparing to other binders. Reduction in phosphate and elevation in calcium dose-dependent but less than with calcium carbonate</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>3 g</td>
<td>Extensive prospective cohort evidence, RCT evidence compared to other phosphate binders. Potential for accumulation in bone and other tissues, avoids calcium</td>
</tr>
<tr>
<td>Sevelamer-HCl</td>
<td>4.8-9.6 g</td>
<td>Extensive prospective cohort evidence in ESRD; RCT evidence compared to other phosphate binders; surrogate and patient-centered outcomes, avoids calcium</td>
</tr>
<tr>
<td>Sevelamer carbonate</td>
<td>4.8-9.6 g</td>
<td>RCT evidence compared to other phosphate binders; equivalency studies compared to sevelamer-HCl, avoids calcium</td>
</tr>
</tbody>
</table>
3-Vitamin D

• Treatment with a vitamin D analog should not be given to patients with stage 3 to 5 CKD unless the serum phosphate is in the normal range and the corrected serum total calcium concentration is less than 9.5 mg/dL (<2.37 mmol/L).
• If the serum level of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), ergocalciferol therapy and all forms of vitamin D therapy should be discontinued. Vitamin D therapy should also be discontinued if intact PTH levels become persistently low.
The comparative effects of the different active oral vitamin D analogs in predialysis patients with CKD have not been established. As a result, any one of the available active oral agents (calcitriol, alfacalcidol, doxercalciferol, or paricalcitol) may be administered.

The American Food and Drug Administration (FDA) indicated that there is no difference in the ability of intravenous paricalcitol and calcitriol to suppress PTH, calcium and phosphorus levels in hemodialysis patients.
According to K/DOQI guidelines, patients with CKD who are treated with hemodialysis or peritoneal dialysis with serum PTH levels > 300 pg/ml should receive an active vitamin D sterol to reduce the serum levels of PTH to a target range of 150 to 300 pg/ml.
Recommended initial doses of vitamin D sterols based on the serum levels of intact parathormone, calcium, phosphorus, and calcium X phosphorus product

<table>
<thead>
<tr>
<th>Plasma PTH pg/ml (pmol/L)</th>
<th>Serum calcium mg/dl (mmol/L)</th>
<th>Serum phosphate mg/dl (mmol/L)</th>
<th>Ca x P product mg²/dl² (mmol²/L²)</th>
<th>Dose per HD session Caciletriol</th>
<th>Dose per HD session Paricalcitol</th>
<th>Dose per HD session Doxercalciferol</th>
</tr>
</thead>
<tbody>
<tr>
<td>300-600 (33-66)</td>
<td>&lt;9.5 (2.37)</td>
<td>&lt;5.5 (1.78)</td>
<td>&lt;55 (4.4)</td>
<td>Oral: 0.5-1.5 μg</td>
<td>2.5-5.0 μg</td>
<td>Oral: 5 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV: 0.5-1.5 μg</td>
<td></td>
<td>IV: 2 μg</td>
</tr>
<tr>
<td>600-1000 (66-110)</td>
<td>&lt;9.5 (2.37)</td>
<td>&lt;5.5 (1.78)</td>
<td>&lt;55 (4.4)</td>
<td>Oral: 1.0-4.0 μg</td>
<td>6.0-10.0 μg</td>
<td>Oral: 5-10 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV: 1.0-3.0 μg</td>
<td></td>
<td>IV: 2-4 μg</td>
</tr>
<tr>
<td>&gt;1000 (110)</td>
<td>&lt;10 (2.5)</td>
<td>&lt;5.5 (1.78)</td>
<td>&lt;55 (4.4)</td>
<td>Oral: 3.0-7.0 μg</td>
<td>10-15 μg</td>
<td>Oral: 10-20 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV: 3.0-5.0 μg</td>
<td></td>
<td>IV: 4-8 μg</td>
</tr>
</tbody>
</table>

PTH = parathormone, Ca = Calcium, P = Phosphorus, HD = Hemodialysis, IV = Intravenous.
4-Calcimimetics

- Cinacalcit could be useful in patients with secondary hyperparathyroidism that is refractory to therapy with vitamin D analogues, calcium supplements, and phosphate binders.

- should be started with the lowest dose, which is then increased progressively every two weeks until PTH levels between 150-300 pg/ml are achieved.
High-Turnover Osteodystrophy

Initially
- dietary restriction of phosphate intake

↑ P
- calcium-based (when initial serum calcium level is <9.5 mg/dL) or noncalcium-based (when initial serum calcium is >9.5 mg/dL) phosphate binders can be administered.

Vit.D <30 ng/ml
- treatment with ergocalciferol can be added as long as serum calcium does not exceed 10.2 mg/dL

PTH
- orally active vitamin D analog can be added to the regimen. These should not be given if the serum calcium is >9.5 mg/dl or when the serum phosphate levels are elevated.

Finally
- calcimimetic-like cinacalcet may be considered.
- severe hyperparathyroidism that fails to respond to medical therapy may require parathyroidectomy.
Adynamic Bone Disease

- usually treated empirically by letting the PTH levels increase, which allows for an increase in bone turnover. This can be accomplished by either decreasing the dose or eliminating agents that suppress PTH secretion, such as calcium-based phosphate binders or vitamin D.
References

• KDIGO clinical practice guidelines for the evaluation and management of chronic kidney disease 2012.


THANK YOU