Actual Problems in Chronic Kidney Disease - Mineral and Bone Disorder (CKD – MBD)

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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

Moe et al, KI 2006, 69, 1945-53
Outline

- Regulation of bone modelling
- Vascular calcification and mortality
- Vitamin D deficiency
- Prevention and treatment
GFR and Plasma 1,25-Vitamin D3

Reichel et al. NDT 1991; 6:162
Spectrum of Renal Bone Disease

Calcium, Vitamin D

Low turnover
- Adynamic
- Osteomalacia

Normal bone formation

PTH

Mild
- Osteitis fibrosa

Mixed lesion

High turnover
Physiological Doses of PTH and 1.25(OH)$_2$D Do Not Normalize Bone Cells in Uremic Rats

<table>
<thead>
<tr>
<th></th>
<th>Sham op (solvent)</th>
<th>NX-PTX (solvent)</th>
<th>NX-PTX (PTH+1.25D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25(OH)$_2$D (pg/ml)</td>
<td>82</td>
<td>56*</td>
<td>77</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>24</td>
<td>5*</td>
<td>23</td>
</tr>
<tr>
<td>OcS / BS (%)</td>
<td>6.3</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>ObS / BS (%)</td>
<td>0.8</td>
<td>0.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Szabo et al, Eur J Clin Invest 29, 529, 1999
Bone Remodelling
New Concept: Parallel Model

Bone Marrow

Monocyte/Macrophage

Osteoclast

Microenvironment
Bone-associated proteins (like Osteoprotegerin)
Bone-morphogenetic proteins (like BMP-7)
Cytokines and growth factors

Circulating factors
Hormones
Other factors

Stem cell

Osteoblast
Lining cells
Osteocytts (entombed)
Osteoprotegerin (OPG) System for Osteoclast Differentiation

OPG-ligand = Rank-ligand

ODAR = Rank (receptor activator of NF-κB)

Committed preosteoblast

Osteoclast progenitor

Secreted OPG = osteoclastogenesis inhibitory factor (bone lineage cells, kidney, other organs)
Circulating Osteoprotegerin May Modulate Osteoclastogenesis

1. OPG attenuates the PTH induced rise of serum Ca^{++} in vivo (rats)
   OPG decreased serum Ca^{++} rapidly in established hypercalcemia
   Yamamoto et al, Endocrinology 139, 4012, 1998

2. OPG serum levels increased in uremia
   Fukagawa et al, Rinsho Byori 49, 236, 2001

3. OPG serum levels decreased by glucocorticoids
   Sasaki et al, NDT 16, 479, 2001
Regulation of Osteoclastogenesis
Convergence Hypothesis
Hofbauer et al, J Bone Miner Res 15,2,2000

**OPG-L**

- PTH, PTHrP
- 1,25 D
- Glucocorticoids
- others

**OPG**

- 1,25 D
- TGF-β
- others

Pool size of active osteoclasts

- TGF-β
- Glucocorticoids
- PGE₂
Osteoblast Differentiation Programme

BMP-7

Hruska, Pediatr Nephrol 2000
BMP-7 (Differentiation Factor)
Rh BMP -7 is available

Decreases glomerular area, glomerulosclerosis and interstitial nephritis

Inhibits monocyte chemoattractant protein-1 (mesangial cells) and renal injury
Yong-Soo Kim, J Am Soc Nephrol 13, 353A, 2002

Reverses adynamic bone disease and lowers serum PO₄
Vascular Calcification
Three-Vessel Coronary Artery Disease and Aorta Calcification in a 28-year-old Hemodialysis Patient with Childhood-Onset CRF

Oh et al. Circulation 2002;106:100-5
Coronary Artery Calcifications in Young Adults with Childhood-Onset ESRD

Oh et al. Circulation 2002;106:100-5
EBCT Calcium Score and Angiographic CAD Severity

Courtesy of John Rumberger, MD, Mayo Clinic
Long-Term Survival of Childhood-Onset ESRD Patients

Oh et al. Circulation 2002;106:100-5
Excessive Mortality in Young Adults with ESRD

Block et al. AJKD 2000
ESRD-Associated Arteriopathy:

Accelerated Atherosclerosis or Disease-Specific Pathology?
Arteriopathy in Adults with ESRD

Schwarz et al. NDT 2001

• Mönckeberg-Type Media Degeneration
• Minor Intimal Hyperplasia
• Increased Calcification of Atherosclerotic Plaques
• Diffuse Calcinosis of Tunica Media
Vitamin D

Does it contribute to vascular calcification?
Smooth Muscle Cells Produce Calcitriol

Dengler et al (unpublished)
Somjen et al. Circulation 2005
Expression of $1\alpha$-Hydroxylase and Osteopontin in Smooth Muscle Cells

% normalized RNA

1,25(OH)D3 (log M)

- Control
-10
-9
-8

1-alpha Hydroxylase
Osteopontin
Effect of Calcitriol on Vascular Calcification

- Vit.D intoxication leads to media calcification
- Vascular smooth muscle cells express Vit.D-R
- Vit.D may initiate mineralization in an osteoblast-like phenotype cell
- But, ......
Effect of Calcitriol against Vascular Calcification

- Calcitriol levels are inversely correlated with coronary calcification
  Watson et al, Circulation 96, 1755, 1997

- Vit.D upregulates matrix GLA protein in osteoblasts and smooth muscle cells
  Frazer & Price, Calcif Tissue 46, 270, 1990
Atherosclerosis in Adolescents with ESRD

Iliac artery specimens obtained at TX
Age: 12-17 yrs
Mean duration of hemodialysis: 2.3 yrs

Atherosclerotic lesions in 7/12 pts
Hypoplastic/reflux nephropathy in 6/7

Predictors of arterial lesions:
Disease Duration
Serum phosphorus
Ca x P product

Not predictive:
Blood pressure
Fasting glucose
Triglycerides, cholesterol

Nayir et al. NDT 2001; 16: 2041
### Predictors of Coronary Artery Calcification

**Stepwise Linear Regression Analysis**

<table>
<thead>
<tr>
<th>Variables offered to model:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current</strong> age, sex, BMI, current treatment modality, CRP, Hba1c, C peptide, homocysteine, CRP, C. pneumoniae IgG; total, LDL-, HDL-cholesterol</td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative</strong> duration of CRI, dialysis, transplant; Ca*Ph, PTH, blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

#### Variables selected:

<table>
<thead>
<tr>
<th>Variables selected:</th>
<th>Effect</th>
<th>Partial R²</th>
<th>Total R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Positive</td>
<td>0.5</td>
<td>0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean PTH</td>
<td>Positive</td>
<td>0.15</td>
<td>0.65</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean (Ca*P)*ESRD</td>
<td>Positive</td>
<td>0.07</td>
<td>0.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Positive</td>
<td>0.03</td>
<td>0.75</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Inflammation and Coronary Calcification in Childhood-Onset ESRD

\[ y = 55.4 \times e^{0.08x} \]

\[ r = 0.70, \ p < 0.0001 \]

Oh et al. Circulation 2002;106:100-5
Coronary Calcifications and Cumulative PTH

R = 0.931
p = 0.000
Coronary Artery Calcifications and Cumulative Ca*P Load

\[ R = 0.58; \ p < 0.0005 \]
# Potential Risk Factors for Coronary Calcifications

## Univariate Regression Analysis

**Heidelberg study**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.62</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean PTH (µmol/L)</td>
<td>0.62</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ESRD (years)</td>
<td>0.59</td>
<td>0.0007</td>
</tr>
<tr>
<td>Cumulative time on dialysis</td>
<td>0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Cumulative Ca*P (mg/dl)</td>
<td>0.58</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cumulative P (mg/dl)</td>
<td>0.30</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum homocysteine (µmol/L)</td>
<td>0.35</td>
<td>0.03</td>
</tr>
<tr>
<td>Cumulative Ca (mg/dl)</td>
<td>0.38</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Elevated Ca\(\times\)P Product Increases Mortality Risk

Block et al. AJKD 1998; 31:607-17
Relative Risk of Mortality by Serum Calcium

Calcification of Rat Aorta at a Constant Ca x P Product

Lomashvili et al, Kidney Int 2006, 69, 1464-70
Survival as a Function of Ca, P, PTH

Log-Rank Test: p = 0.176

Effects of Hyperphosphatemia

- Induction of hyperparathyroidism
  - directly (parathyroid gland)
  - indirectly

- Reduces circulating 1,25(OH)D
  - directly (renal 1α-hydroxylase)
  - indirectly (stimulates FGF-23 which down-regulates 1α-hydroxylase)

- Contributes to vascular calcification

  Mechanism?

- Non liner correlation with morbidity
Phosphate Homeostasis Regulated by FGF23

Takeda et al, J Cell Mol Med 8, 191-200, 2004
Effects of Hypercalcemia

- Decreases PTH secretion
- Decreases 1α-hydroxylase
- Contributes to vascular calcification mechanism?
- Induces low bone turnover
- Linear correlation with morbidity
Mechanisms for Vascular and Cardiac Calcification

- Adynamic bone → decreased bone buffer for Ca and P → precipitation?
  Kurz et al, Kidney Int 46, 855, 1994

- Passive process in need of inhibitors
  Schinke & Karsenty, NDT 15, 1272, 2000

- Active processes rather than precipitation
  David & Hruska, Kidney Int 60, 472, 2001
Promoters and Inhibitors of Vascular Calcification in the Microenvironment of vessel wall

Promoters:
- BMP-2
- Cbfa-1 (acting on osteocalcin)

Inhibitors:
- circulating:
  - BMP-7
  - Fetuin-A
  - Pyrophosphate
- locally acting:
  - Matrix Gla protein
  - Osteocalcin
  - Osteopontin
  - Osteoprotegerin
  - PTHrP
  - Pyrophosphate
Pathogenesis of Vascular Calcification
A Central Role for an Osteoblast-Like Cell

Pericytes and smooth muscle cells

- are derived from common marrow mesenchymal stem cells like osteoblasts
- retain their pluripotentiality and have the capability to become osteoblasts

Campbell & Campbell, Z Cardiol 89 (SII), 54, 2000
Age-Dependent Carotid Intima Media Thickness in Young Adults with Childhood-Onset ESRD

Oh et al. Circulation 2002;106:100-5
Predictors of Carotid Intima Media Thickness
Stepwise Linear Regression Analysis

Variables offered to model:
Age, sex, BMI, disease status, smoking habits, CRP, total, LDL, HDL cholesterol, HbA1c, C peptide, Chlamydia IgG, homocysteine

Variables selected:

<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
<th>Partial R²</th>
<th>Total R²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>positive</td>
<td>0.13</td>
<td>0.13</td>
<td>0.002</td>
</tr>
<tr>
<td>Chlamydia IgG</td>
<td>positive</td>
<td>0.05</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>positive</td>
<td>0.07</td>
<td>0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>C-Peptide</td>
<td>positive</td>
<td>0.05</td>
<td>0.30</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Cardiovascular Risk Factors in ESRD

**Conventional**
- Hypertension
- Hyperlipidemia
- Obesity
- Insulin Resistance

**Uremia-Related**
- Hyperhomocysteinemia
- Increased LDL oxidation
- IV iron induced AOPP
- Hypo/Hyperparathyroidism
- Ca and Ph ↑

**Dialysis-Related**
- Fluid Overload
- Infections
- Bioincompatibility
- AGE

**Endothelial Dysfunction**

**Proinflammatory Cytokine Release**

**Systemic Inflammation**

**Acute Phase Response**

**Atherosclerosis / Calcifying Vasculopathy**

**Increased Cardiovascular Mortality**
Vitamin D Deficiency in CKD

Does it matter?
Vitamin D Deficiency

Definition

Vitamin D insufficiency: Plasma 25(OH)D 10-30 ng/ml
Vitamin D deficiency: Plasma 25(OH)D < 10 ng/ml

LaClair et al, Am J Kidney Dis 2005, 45, 1026-33

Vitamin D insufficiency: Plasma 25(OH)D 16-30 ng/ml
Vitamin D deficiency: Plasma 25(OH)D < 16 ng/ml

Drueke et al (KDIGO 2006), KI 2006
Renal $1.25(\text{OH})_2\text{D}$ Production Is Tightly Regulated, but Can Become Substrate Dependent:

- Hypoparathyroidism
- Hyperparathyroidism
- Vitamin D deficiency
- Chronic renal failure
- Sarcoidosis
## Tissue Specific Micro-Endocrine Systems for Vitamin D (Extrarenal Production of Calcitriol)

<table>
<thead>
<tr>
<th>Organs</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immune Cells</td>
<td>Immune Diseases</td>
</tr>
<tr>
<td>• Muscles</td>
<td>Weakness</td>
</tr>
<tr>
<td>• Bone cells</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>• Vascular myocytes</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>• Parathyroid gland</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>• Prostate</td>
<td>Cancer</td>
</tr>
<tr>
<td>• Colon</td>
<td>Cancer</td>
</tr>
<tr>
<td>• Breast</td>
<td>Cancer</td>
</tr>
<tr>
<td>• Others</td>
<td></td>
</tr>
</tbody>
</table>
PTH levels are inversely correlated with 25(OH)D levels

- Primary hyperparathyroidism
  Rao et al, J Clin Endocrinol Metab 2000, 85, 1054,

- Secondary hyperparathyroidism
  Lemonte et al, J Nephrol 2005, 8, 96
  Holick AJKD, 2005, 6, 1119
Effect of 25(OH)-D on Primary Hyperparathyroidism

Rao DS et al., J Clin Endocrinol Metab 2000 Mar;85(3):1054-8
# Vit. D Status and PTH in Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th></th>
<th>25(OH)D (ng/ml)</th>
<th>1.25(OH)₂D (pg/ml)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;15</td>
<td>&gt;15</td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>9.3 ± 4</td>
<td>24 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.25(OH)₂D (pg/ml)</td>
<td>63 ± 22</td>
<td>61 ± 16</td>
<td>n.s.</td>
</tr>
<tr>
<td>p-gland weight (g)</td>
<td>1.1 ± 2.7</td>
<td>0.6 ± 2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>172 ± 192</td>
<td>104 ± 71</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Rao et al, J Clin Endocrinol Metab 85, 1054, 2000
Vitamin D levels in Incident Hemodialysis Patients

Wolf et al, Kidney Int 2007
Prevalence of Vitamin D Insufficiency in Dialysis Patients

Number of patients: 119
Age (years) 64 ±14
25(OH)D (ng/ml) 17 ± 7
Sufficient 25(OH)D levels (%) 9
25(OH)D after 50,000 IU D2/month 54 ±16

Saab et al, Nephron Clin Pract 2007, 105, c132-8
## Prevalence of Vitamin D Deficiency in CKD

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>201</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ±13</td>
</tr>
<tr>
<td>GFR (ml/min x1.73 m²)</td>
<td>27 ±11</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>19 ±14</td>
</tr>
<tr>
<td>Sufficient 25(OH)D levels (%)</td>
<td>29</td>
</tr>
</tbody>
</table>

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Independent correlations (multivariate analysis)
1. Positive with serum Ca++
2. Negative with serum PTH
3. No correlation with GFR

LaClair et al, Am J Kidney Dis 2005, 45, 1026-33
25(OH)D Level versus GFR

LaClair et al, Am J Kidney Dis 2005, 45, 1026-33
<table>
<thead>
<tr>
<th>Plasma 25(OH)D</th>
<th>&lt;10 ng/ml</th>
<th>10-30 ng/ml</th>
<th>&gt;30 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.6</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.6</td>
<td>1.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Wolf et al, Kidney Int, August 2007
Prevention and Therapy
## Vitamin D₃ Prophylaxis and Treatment for Vitamin D Insufficiency/Deficiency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance prevention</td>
<td>400-1,000 IU/day</td>
<td>800-1,000 IU/day</td>
</tr>
<tr>
<td>Treatment</td>
<td>5,000 IU/day</td>
<td>15,000 IU/week for 8 weeks</td>
</tr>
<tr>
<td></td>
<td>200,000 IU/3 months</td>
<td></td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance prevention</td>
<td>1,000 IU/day</td>
<td>15,000 IU bolus every 3 months</td>
</tr>
<tr>
<td>Treatment</td>
<td>15,000 IU every 2 weeks</td>
<td>15,000 IU every 2 weeks</td>
</tr>
</tbody>
</table>

Vitamin D₃ 3 times more efficient than vitamin D₂

Holick NEJM 2007
Calcitriol Treatment Recommendations

- Start low-dose daily calcitriol early in CRF (prophylaxis of parathyroid hyperplasia)

- Oral daily calcitriol as effective as and probably safer than intermittent (iv or ororal) pulse therapy

- Target PTH: according to renal function, 2-times normal in CKD V

- Monitoring policy: Check PTH and Ca^{2+} frequently, but avoid frequent dose changes (parathyroid rebound activation)!
  Check compliance!
Prevention of HPT by Calcitriol

(a) Scr < 3 mg/dL

(b) Scr > 3 mg/dL

Ritz et al. NDT 1995, 10:2228
Strategies to Control Serum Calcium and Phosphate

a. Diet: Low phosphate intake

b. Dialysis: Longer duration for hyperphosphatemia
   Lower [Ca++] dialysate for hypercalcemia

c. Vitamin D: Reduce intake if hypercalcemia and/or hyperphosphatemia

d. Phosphate binder: Ca-free binder for hypercalcemia
Control of HPT by Low-Phosphorus Diet

Combe et al. Nephron 1995, 70:287
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosphate intake</strong></td>
<td>1,000 mg/day</td>
</tr>
<tr>
<td><strong>Phosphate intestinal absorption</strong></td>
<td>600 mg/day</td>
</tr>
<tr>
<td><strong>Phosphate removal by dialysis</strong></td>
<td>2,400 mg/week</td>
</tr>
<tr>
<td><strong>Balance</strong></td>
<td>+1,800 mg/week</td>
</tr>
</tbody>
</table>
Improvement of response to GH following daily dialysis

Fischbach et al, Ped Neph 2006
Phosphorus Intake and Calcium Carbonate Requirements

Slatopolsky et al. KI 1989;36:897-903
Sources of Calcium Load in Dialysis Patients

- Dietary calcium
- Dialysate
- Calcium-containing phosphate binders
- Vitamin D therapy (increases Ca absorption)

ESRD Patients on Calcium Binders:
Where Does Excess Calcium Go?

Weekly Intake
13.7 g

Absorbed Calcium
>2.6 g

Tissue

Regulated load capacity

Plasma

Bone

Excretion
1 g

Limited routes

Total body calcium reservoir
1000 g (normal)

Low-turnover bone disease

RATE LIMITED

0.25 g (0.025%)

990 g (99%)

9.75 g (0.975%)

Limited routes

RATE LIMITED
Alternative: Non-Ca Containing Phosphate Binders

1. Sevelamer
   - Adverse event: Gastrointestinal discomfort
   - Pleiotropic effects: Correction of lipid abnormalities

2. Lantanum carbonate:
   - Adverse event: Tissue accumulation of Lantanum
Calcimimetics

- Act as allosteric modulators of the calcium-sensing receptor
- Decrease PTH, Ca and P
- **Lower cardiovascular risk profile**
  - by lowering PTH?
  - by direct effects on vessels and adipocytes?
# Treatment Guidelines

<table>
<thead>
<tr>
<th>Serum Ca</th>
<th>Serum P&lt;sub&gt;i&lt;/sub&gt;</th>
<th>Serum PTH</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or low</td>
<td>High</td>
<td>&gt; 350 pg/ml</td>
<td>Reduce dietary P&lt;sub&gt;i&lt;/sub&gt; and begin P&lt;sub&gt;i&lt;/sub&gt; binders (CaCO&lt;sub&gt;3&lt;/sub&gt;) Begin daily calcitriol when Pi normalized</td>
</tr>
<tr>
<td>High</td>
<td>Normal or low</td>
<td>&lt; 150 pg/ml</td>
<td>Stop Ca-containing Pi binders Stop Calcitriol Use low-Ca dialysate Consider Renagel</td>
</tr>
<tr>
<td>Normal or high</td>
<td>High</td>
<td>&gt; 500 pg/ml</td>
<td>Hold calcitriol Scan for PT adenoma Increase Pi binders: Ca acetate, consider Renagel, temporary aluminium hydroxide Consider calcimimetics Consider parathyroidectomy</td>
</tr>
</tbody>
</table>