CKD-MBD

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Goals

• Understand the new definition that ties vascular calcification, mineral disorders and bone abnormalities together - CKD-MBD
• Understand new concepts on bone adaptation to CKD
• Be familiar with the therapies directed toward preventing extraskeletal calcification and low bone turnover syndrome
Disclosures

I am either a consultant, on the speaker bureau, on the advisory board or conduct clinical trials for Abbott, Ortho Biotech, Amgen, Genzyme, ASH Medical, Diasorin, Shire or DaVita.

This talk is unsponsored.
ESTABLISHED ASSOCIATION BETWEEN VASCULAR CALCIFICATION AND RENAL FAILURE

1968
Renal Osteodystrophy linkage to vascular calcification is not new

“Consideration is also given to the manifestations of soft-tissue calcification, both of the vascular and subcutaneous type, and to the effects of treatment”

1985 - Uremic Arterial Disease

- Rabbit model of 9 months renal failure
- All major systemic arteries affected
- Medial degeneration without lipid accumulation
- No coronary stenosis
- Medial calcification in non-cholesterol-fed rabbits
- Uremic arterial disease different than atherosclerosis

1987 Aortic and Mitral valve Calcification in ESRD

- Echocardiography in 87 patients
- 35 to 70 years old
- Maintenance dialysis 7.5 years
- 24 patients: aortic valve calcification
- 31 patients: mitral annular calcification

1990 - Pulse Wave Velocity -
Aorta and large artery compliance in ESRD

- 90 control and 92 hemodialysis patients
- Matched for age and MAP
- Aortic calcification - plain films and echo
  - PWV $1113 \pm 319$ cm/sec in HD
  - $965 \pm 216$ cm/sec in Control ($P=0.0016$)
- Pulse Pressure
  - HD $76.6 \pm 23.7$ mg Hg
  - CS $63.9 \pm 22$ mg Hg ($p=0.007$)

2001 - Longitudinal Study linking calcification with mortality

Linkage of vascular calcification and bone


LDLR-/- 5/6 Nephrectomized Mice with Metabolic Syndrome

LDLR-/- mice

- High fat, cholesterol diets, and normal kidneys
  - Decreased bone turnover, vascular calcification and hyperphosphatemia
- Added 5/6 nephrectomy
  - LBT worsened
- Treating with BMP-7
  - Corrected LBT, hyperphosphatemia and vascular calcification
- Decreased VC by reducing the serum P0\textsubscript{4} with a phosphate binder

BMP-7 and VC in LDLR-/- mice

Vascular calcium deposition is blocked in fat-fed, uremic, LDLR-/- mice treated with BMP-7

*Figure 2. Chemical assessment of effect of BMP-7 on vascular calcification by treatment group. Total aortic calcium content measured in a 10% formic acid eluate of crushed. Data are mean ± SD. Trend is significant by ANOVA, *P* = 0.008. *Fat-fed uremic animals treated with vehicle have significantly higher levels than chow-fed sham controls. (*P* < 0.01, by Dunnetts post hoc test.) Fat-fed uremic animals treated with BMP-7 are indistinguishable statistically from control (chow sham animal).
How the LDLR related to Bone Formation?
Mechanism of LDLR-/- VSMC Calcification

Working model: osteogenic regulation of vascular calcification

- High fat diets → ↑BMP2
- Diabetes
- ? Oxidative stress
- ↑ canonical Wnt/Dkk1 ratio
- ↑ Local LRP5/6 signaling
- ↑ Nuclear β-catenin

Osteogenic differentiation of CVCs

- Organic phosphates
  - PO₄³⁻
  - PO₄³⁻

↑ Serum [Ca] × [PO₄] product (passive process)

↑ ALP

Ca²⁺ → 2 × PO₄³⁻ → CaPO₄ mineral deposition

- ENPP1
- TCF/LEF → Osx

PPI

UPREGULATED

Pyrophosphate-generating (PPI-generating) enzyme Blocks VC

Difference between blood vessel and bone is the MSX2 in adventitial fibroblasts.

- **BMP2**
- **MSX2**
- **LRP5/6 + WNT**
- **RUNX2 (Cbfα1)**

**WNT**
- (WNT signaling does not occur because there is no LDL Co-receptor)
- In LDLR -/- mice skeletonization decreases

**Osteoblastic vascular calcification**
Vascular Smooth Muscle Cell

- Alkaline Phosphatase
- Noncollagenous Protein Production (Osteocalcin, Osteopontin, Matrix Gla Protein, BMP-2a, Alkaline Phosphatase)
- Apoptosis
- Calcification
- Collagen Rich ECM
- Osteoblast Differentiation

Bone Morphogenetic Protein Receptors

**BMP-7**

- TGFβ superfamily
- Induces SMAD
- 14 BMPS (BMP-2 induces vascular calcification)
- 20q13 (long arm, 13th band of chromosome 20)
- Holt-Oram - ↑BMP-7
  - Nonapposable thumb, ASD
- BMP-7 downregulated early in kidney failure
- Maintains VSMC differentiation - blocks transformation to osteoblast

**SIGMA-ALDRICH**

![Diagram showing BMP receptors and their interactions with Smad proteins, indicating the regulation of mesenchyme precursor to osteoblast differentiation.]
BMP ACTIONS

BMP2/BMP 7 - Needed for Osteoblast Differentiation
BMP7 - Blocks Vascular calcification
BMP-7 has great potential

- Blocks tubular epithelial cell de-differentiation,
- Blocks mesenchymal transformation and apoptosis
- Preserves glomerular integrity
- Inhibits injury-mediated mesangial matrix accumulation.
- Eliminates peritrabecular fibrosis
- Decreases bone resorption and restores normal rates of bone formation
- Increases the skeletal deposition of ingested phosphorus and calcium, preventing vascular calcification in CKD restoring osteocalcin expression to normal tissue-restricted sites.

Concept of the roles of the BMPs in Pathogenesis and Treatment of Vascular Calcification in Chronic Kidney Disease

Circ. Res. 2005;97;105-114
Renal Osteodystrophy no longer works

- Strong relationship between mineral metabolism and CKD morbidity
- Osteodystrophy
  - Implies a bone disorder
  - 24 to 37 year old diaysis patients have the cv death rate 70 to 80 year olds
  - 99% of patients die of cardiovascular disease prior to reaching dialysis
- KDIGO establishes new classification in 2005
Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD-MBD and Renal Osteodystrophy

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

Definition of Renal Osteodystrophy
• Renal osteodystrophy is an 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 histomorphometry of bone biopsy.

CHRONIC KIDNEY DISEASE—MINERAL AND BONE DISORDER

CKD-MBD
CKD-MBD

The broad syndrome that develops as a systemic disorder of mineral and bone metabolism caused by CKD

**Laboratory**
- Calcium
- Phosphorus
- PTH
- Vitamin D

**Calcification**
- X-ray
- EBCT
- Plethysmography

**Renal Osteodystrophy**
- Turnover
- Mineralization
- Volume
- Linear Growth
- Strength

**CVD Fractures Mortality**
- Laboratory Abnormalities
- Bone Abnormalities
- Vascular Calcification

**Calcification**

**Laboratory**

**Renal Osteodystrophy**
LBC - Evaluation in CKD

• **Laboratory**
  – PTH, Calcium, Phosphorus, alkaline phosphatase (total or bone specific), serum bicarbonate, vitamin D level

• **Bone Biopsy Only if**
  – High PTH and low alkaline phosphatase
  – Unexplained bone pain and fractures

• **Calcification -**
  – Soft Tissue Imaging
  – Pulse Pressure
Vascular Calcification: Confounding Disease Processes

- Atherosclerosis
- CKD-MBD
- Osteoporosis
Case Study

- 54 year old African American Man on hemodialysis for 4 years. Hypertensive 20 years. Diabetes 10 years. L upper arm AVF.
  - Kt/V 1.3, BP 157/70 mm Hg,
  - Serum Phosphorus 6.1 mg/dL
  - iPTH 321 pg/L (Bayer Alexis Method)
  - Serum Calcium 10.2 mg/dL
  - Serum Albumin 4.1 g/dL
  - Sevelamer 800 mg, 3 with each meal
  - Doxercalciferol 3 mcg/treatment
  - Cinacalcet 30 mg each day
Bone Biopsy - TMV

1. OM - Osteomalacia
2. MUO - Mixed uremic osteodystrophy
3. AD - Adynamic bone disease
4. HPT - Hyperparathyroid-related
5. OF - Osteitis Fibrosa

Low Bone Turnover

Photo courtesy Stuart Sprague
High Bone Turnover

Photo courtesy Stuart Sprague
iPTH levels between African Americans and Caucasians

- 76 ESRD patients (Caucasian = 48, African Americans = 28)
- histomorphometric measurement and iPTH levels
- Age, duration of dialysis, and calcium and phosphorus levels were similar between the two groups.
- iPTH levels
  - African American group - 534 pg/mL ± 79 vs. Caucasian 270 pg/mL ± 46 (P < 0.01).
- iPTH levels with low bone turnover
  - African Americans 460 pg/mL ±115 vs
  - Caucasians 168 pg/mL ± 41
- Alkaline phosphatase levels
  - African American group 162mg/dL ± 31 vs.
  - Caucasian 144 mg/dL ± 43, (P < 0.01).
- Correlations between PTH levels and activation frequency
  - r = 0.60, P < 0.01 in Caucasians
  - r = 0.22, P = NS in African Americans.

How aggressive should we be in managing PTH levels?

![Graph showing RR Mortality vs. iPTH (pg/mL) for cardiac and non-cardiac mortality. The graph highlights the K/DOQI reference range with a red circle around an RR of 1.65 for iPTH levels above 800 pg/mL.](image)
**Compare PTH assay to K/DOQI standard**

<table>
<thead>
<tr>
<th>Assay</th>
<th>PTH (ng/L) 1</th>
<th>PTH (ng/L) 2</th>
<th>PTH (ng/L) 3</th>
<th>Median Bias (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegro intact PTH</td>
<td>150</td>
<td>300</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>N-tact PTH IRMA</td>
<td>83</td>
<td>160</td>
<td>517</td>
<td>-44.9 (-68.0; -26.2)</td>
</tr>
<tr>
<td>PTH IRMA Immunotech</td>
<td>188</td>
<td>369</td>
<td>1216</td>
<td>23.9 (-6.1; 108.3)</td>
</tr>
<tr>
<td>ELISA-PTH</td>
<td>149</td>
<td>290</td>
<td>948</td>
<td>-1.6 (-24.3; 47.2)</td>
</tr>
<tr>
<td>Total intact PTH IRMA</td>
<td>134</td>
<td>262</td>
<td>857</td>
<td>-14.5 (-41.5; 23.5)</td>
</tr>
<tr>
<td>DSL PTH IRMA</td>
<td>323</td>
<td>638</td>
<td>2108</td>
<td>123.0 (53.1; 188.9)</td>
</tr>
<tr>
<td>DSL PTH ELISA</td>
<td>264</td>
<td>523</td>
<td>1734</td>
<td>79.6 (-8.0; 180.9)</td>
</tr>
<tr>
<td>Elecsys PTH</td>
<td>161</td>
<td>311</td>
<td>1011</td>
<td>7.3 (-13.8; 80.3)</td>
</tr>
<tr>
<td>Immulite 2000 intact PTH</td>
<td>212</td>
<td>410</td>
<td>1334</td>
<td>37.8 (3.8; 130.8)</td>
</tr>
<tr>
<td>PTH-ACS 180</td>
<td>185</td>
<td>374</td>
<td>1256</td>
<td>18.8 (-9.9; 69.4)</td>
</tr>
<tr>
<td>PTH Adviacentaur</td>
<td>168</td>
<td>342</td>
<td>1154</td>
<td>9.5 (27.6; 55.6)</td>
</tr>
<tr>
<td>Intact PTH advantage</td>
<td>174</td>
<td>339</td>
<td>1109</td>
<td>14.6 (-10.4; 72.2)</td>
</tr>
<tr>
<td>LIAISON N-tact PTH</td>
<td>111</td>
<td>223</td>
<td>748</td>
<td>-23.4 (-68.2; -1.9)</td>
</tr>
<tr>
<td>Ca-PTH IRMA</td>
<td>84</td>
<td>165</td>
<td>543</td>
<td>-44.8 (-65.6; -22.8)</td>
</tr>
<tr>
<td>Biointact PTH advantage</td>
<td>109</td>
<td>214</td>
<td>704</td>
<td>-27.6 (-53.0; 12.5)</td>
</tr>
</tbody>
</table>

**NOTE.** Comparison of PTH assay concentrations in comparison to the Allegro assay at 3 concentrations (150 ng/L, 300 ng/L, and 1,000 ng/L). (Reproduced with permission.37)
5/6 Nephrectomized Mice

- Chow fed
  - Developed secondary hyperparathyroidism
- Phosphate restricted and treated with calcitriol
  - Adynamic bone disease
  - Depressions in osteoblast number, perimeters, bone formation rates, and mineral apposition rates

African Americans may be more resistant to PTH and have higher levels.
Suppressing the iPTH to accepted levels could lead to low bone turnover disease

Kidney International (2003) 64, 737-742
Pathological Fractures

• Dialysis Patients in their 40s
  – 80 fold higher risk of hip fracture

• Hip fracture
  – Double mortality

• Low or high PTH level
  – a risk factor for hip fracture
Vascular Calcification

- **Associations with dialysis patients**

- **Mortality associated with EBCT**

- **65% patients starting HD have vascular calcification. Patients with zero calcification at onset of HD do not progress**
Peripheral Vascular Disease

- Plain film femoral artery calcification related to increased all cause mortality
- Increased pulse wave velocity
- Increased pulse pressure
- Inverse relation to bone mineralization
  - Bone mineralizes at ages 25 to 25, then decreases,
  - accentuated in CKD
- Common in CKD
  

- Low bone turnover - greatest risk of vascular calcification
- Non calcium binders - may have role in decreasing calcification, increasing trabeculation
- Some patients never get vascular calcification

Abdominal Aorta X-ray Score

- Plain lateral x-ray of the lumbar spine
  - Aortic calcification >7
  - CACs on EBT > 1000
  - Aortic valve of 75.9
  - (p < 0.001)
- CAC Score > 100 (Valve)
  - Sensitivity 53%
  - Specificity 70%
- CAC Score > 100 (Xr >7)
  - Sensitivity 67%
  - Specificity 91%

How aggressive should we be in managing Phosphorus levels?
Laboratory Evidence

10% higher risk at phosphorus concentrations of 6.4 to 7.5 mg/dL
18% higher risk at phosphorus concentration of 6.6 to 7.8 mg/dL
25% higher risk at phosphorus concentrations of 6.0 to 7.0 mg/dL
28% higher risk at phosphorus concentrations of 6.5 to 7.0 mg/dL
53% higher risk at phosphorus concentrations of 6.0 to 7.0 mg/dL
54% higher risk at phosphorus concentrations greater than 6.0 mg/dL 83% higher risk in CKD patients with P concentrations of 4.5 to 4.9 mg/dL.

4 AJKD 31:607, 1998
7 JASN 15:2208, 2004
8 KI 67:1179, 2005
9 JASN 16:1788, 2005
10 JASN 15:770, 2004
11 KI 70:351, 2006
12 JASN 16:520, 2005
Phosphorus in non dialysis

• Association with early atherosclerosis in patients with presumed normal kidney function (p=0.0003; N=294)

• CARE: Normal cr, PO₄ ≥ 3.5 gm/dL - adjusted mortality hazard ration of 1.27 (CI 1.02 to 1.59 p=0.03 for trend).

• 8 VAMCs: (n=96,619 patients), 7021 non dialysis patients had creatinine levels > 1.2 mg/dL.
  – Serum P0₄ than 3.5 mg/dL associated with a significantly increased risk of death
  – Mortality rate increased linearly with 0.5 mg/dL serum P0₄ increments
Phosphorus

- Directly influences the development of parathyroid hyperplasia and PTH secretion
- Indirectly influences vitamin D resistance.
  - Enhances expression of a potent growth promoter, TGFα (transforming growth factor alpha) and its receptor, EGFR, the epidermal growth factor receptor.
  - TGFα/EGFR expression and downstream signaling lead to severe parathyroid hyperplasia and vitamin D resistance.
- Lends insight into how vitamin D is less effective in controlling hyperparathyroidism when severe hyperphosphatemia is present.

Nodular parathyroid growth: Role of vitamin D resistance
Adriana S Dusso
FGF-23 FACTS

• What
  – In FGF Family
  – FIBROBLAST GROWTH FACTOR 23;
  – 3 exons, 10 kb of genomic sequence
  – 251-amino acids contains an N-terminal 24-amino acid signal sequence

• When
  – FGF23 gene encodes mutant factor
    • autosomal dominant hypophosphatemic rickets
  – Tumor induced osteomalacia
  – +/- knockout mice
    • hyperphosphatemia and increased 1 alpha hydroxylase activity

• Where
  – lies in 54 kb telomeric of FGF6 12p13 (short arm, 13th band)

• Why
  – Essential for phosphorus metabolism
  – Essential for adaptation of hyperphosphatemia induced by CKD
  – Present in normal circulation

• How
  – Decreased Na dependent phosphate uptake in kidney cells
  – Decreases 1 alpha hydroxylase activity
  – Binds to Klotho - high affinity - Klotho essential for its function
  – Klotho generates receptor from FGF1

• Breakdown
  – cleaved between arg179 and ser180,

• Measured
  – sandwich ELISA for human FGF23, using 2 monoclonal antibodies to FGF23.

PHOSPHORUS STIMULATES FGF23 IN CKD

Source: Entrez Gene
Elevated Serum Phosphorus

- 30% ingested phosphorus excreted in the gastrointestinal tract, remaining 70% eliminated by the kidney.
- Phosphorus stimulates FGF-23 in CKD
  - This increase tubular excretion of $P_{04}$, maintaining levels.
  - Decreases $1,\alpha$ Hydroxylase - which decreases active vitamin D
  - Increased PTH synthesis
    - *J Clin Endocrinol Metab* 2006
- Serum $P_{04}$ would rise sooner in CKD were it not for FGF-23
- Keeps serum phosphorus levels normal during moderate to severe CKD
- Phosphorus retention begins when these compensatory mechanisms are overcome by the decrease in kidney function (GFR 20-25 mL/min/1.73m$^2$).
- PTH corrects with dietary protein restriction (supplemented 0.3 g/kg/bw) in early CKD
Established relationships between $\text{P}0_4$ and PTH

$\uparrow\text{PO}_4$ → $\uparrow\text{FGF-23}$ → $\downarrow\text{1α OHase}$ → $\downarrow\text{1,25 D}_3$ → $\downarrow\text{Ca}^+$ → $\uparrow\text{PTH}$

$\uparrow\text{CBFA1}$ → $\uparrow\text{TGFβ}$ → $\uparrow\text{EGFR}$ → $\downarrow\text{VIT D RECEPTOR}$ → $\text{VASC CALCIF}$ → $\text{VSMC CHANGE}$

Fadem, SZ and Moe, SM  
Adv Chr Kidney Dis 14:44-35, 2006
Dietary P04 control

- 800 to 1,000 mg/day limits protein to below requirements
  - [http://nutrinfo.org](http://nutrinfo.org) – Source: USDA
- Phosphorus - an additive to processed foods
  - Restructured meats, spreads, puddings and caramelized colas,
  - “Fast foods” and less expensive foods - burdensome to families
  - Polyphosphates and pyrophosphates are rapidly absorbed.
- Crossover study of graduate students,
  - Diet free of phosphate additives reduced the load by an average of 1,154 mg per day,
  - Maintained protein content
  
  *J Nutr* 1977;107:42-50
- Plant foods require phytase for phosphorus breakdown
  - Absent in humans
  - Phosphate absorption less complete
  
  *Semin Dial* 2003;16:186-8
A summary of therapy

• 1970s - Suppress PTH with oral vitamin D and control Serum P04 with aluminum
• Aluminum Toxicity lead to Calcium binders
• 1980s iv calcitriol lead to hypercalcemia
• 1990s vitamin D analogs
  – P04 mortality and Vascular calcification studies
• Late 1990s Sevelamer
• 2000s Lanthanum, Cinacalcet

Nephrol Dial Transplant 19:1902-1906, 2004
Contrib Nephrol 102:110-124, 1993
Am J Kidney Dis 33:694-701, 1999
N Eng J med 350:1516-1525, 2004
Lower P$_{04}$ without raising Ca

**Median Percentage Change in Coronary Scores at 52 Weeks**

- **Calcium**: 25%*
- **Sevelamer**: 6%*

**Median Percentage Change in Coronary And Aorta Scores at 2 Years**

- **Cors Aorta Calcium**: 82%*
- **Cors Aorta Sevelamer**: 20%*
- **Aorta Calcium**: 61%*
- **Aorta Sevelamer**: -7%*

*Within treatment $P<0.0001$; between treatment groups $P=0.02$.
Patients with a baseline score $>30$.

* Between treatment groups $P<0.0001$ (Patients with a baseline score $>30$)

*Chertow, GM, Burke, SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002;62:245-252*
Changes in Thoracic Vertebral Bone Density After 2 Years of Randomization

![Bar Chart]

*Np<0.05

Sevelamer and Calcium Carbonate decrease kidney calcification in 5/6 nephrectomy rats

Figure 5. Effects of sevelamer and CaCO₃ on kidney foci of calcification. Mean of foci of calcification in remnant kidney tissue uremic (5/6-nephrectomized) rats undergoing one of the following experimental protocols for 3 mo: uremic control + high-phosphorus diet (U-HP) (closed bar); uremic + HP diet + 3% sevelamer (U-HP+S) (open bar); uremic + HP diet + 3% calcium carbonate (U-HP+C) (dashed bar). Results represent the mean and SEM from four sections/rat in five rats per group. P values were obtained by ANOVA and Bonferroni tests. Magnification, ×20.
Binder Studies

• **CARE Study - 8 week blinded study**
  – Calcium acetate more efficacious in controlling serum $P_{04}$ than sevelamer
    • Kidney International 65:1914-1926, 2004

• **RIND Study 18 month trial**
  – 60 incident patients randomized to calcium binders
    - had progressive calcification
  – 54 to sevelamer HCL
    • Kidney International 68:1815-1824, 2005

• **LANTHANUM 6 weeks**
  – Significant drop in $P_{04}$ in one week - 2250 mg/day
    • Clinical Nephrology 65:191-202, 2006
Vitamin D

- Vitamin D, especially the new analogs, confers a protective effect on patient survival
- Reasons
  - Inflammation
  - Renin-angiotensin system
  - Myocardium
  - Muscle
  - Bone (may also decrease bone pain)

Prog Biophys Mol Biol 2006;92:4-8.
Vitamin D and Blood Pressure

• NHANES III survey
  • Representative sample of the US population between 1988 and 1994.
  • 12,644 participants with 25OHD levels and Blood Pressure measurements,
  • Systolic blood pressure was 2.7 mmHg lower (P=0.0005)
    – vitamin D levels ≥ 85.7 nmole/L compared with the lowest quintile <40.4 nmole/L when adjusted for BMI, age, sex and ethnicity.
  • Diastolic blood pressure changes were significant, but not when adjusted for BMI (p=0.013).

• Down-regulates renin production
Vitamin D Deficiency

• Calcidiol, 25(OH)D₃, low due to
  – Urban living
  – Cultural dress
  – Lack of sun exposure
  – Lack of physical activity
  – CKD population

• Limited studies evaluating the effects of supplementation with ergocalciferol or cholecalciferol

• Measure vitamin D₃ in CKD

• Treat with OTC Ergocalciferol
Exercise

• Weight bearing on bone mass - Astronauts
  – NASA Space Program
  – Trabecular bone loss was similar in space travel to that in prolonged bed rest.

• Weight-bearing exercise in postmenopausal women
  – slow or decrease a decline in bone mineral density
  – Increase trochanteric bone mineral content,
  – Reducing the risk of falls (15889312)

• Exercise in CKD - need for additional studies
### Nocturnal Dialysis

**mmol (P < 0.01)**

<table>
<thead>
<tr>
<th>Dietary Phosphorus Absorbed</th>
<th>10 and 30 mmol/day (310-930 mg/day)</th>
<th>100 to 210 mmol/week (3100 - 6510 mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Hemodialysis</td>
<td>25.3 ± 7.5 (784.3 mg/L)</td>
<td>75.8 ± 22.5 (1,516 mg/L)</td>
</tr>
<tr>
<td>Nocturnal Hemodialysis</td>
<td>26.9 ± 9.8 (833.9 mg/L)</td>
<td>161.6 ± 59.0 (5,010 mg/L)</td>
</tr>
</tbody>
</table>

*Weekly intake in ESRD around 1 gm/day
Only 40-80% absorbed
By fourth month patients were on no binders
Dietary Phosphorus intake doubled

Conversion from nephron.com*

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**Nocturnal hemodialysis may slow vascular calcification**

PTH caveats

• Higher PTH levels and adynamic bone disease in African Americans
• PTH may be a normal adaptation mechanism in CKD, and we may not want to over treat it
• DOPPS data does not show the strong association between PTH with mortality in K/DOQI range
• The measurement of PTH does not relate to the original Nichols Allegro assay with current Bayer Centaur or Roche Elecys assays
• Newer agents such as cinacalcet enable PTH suppression without hypercalemia
• Therefore, a high serum calcium level in a patient on cinacalcet who has a lowered PTH level could have low bone turnover disease, particularly if African American
Appendix

Aluminum hydroxide
Calcium Carbonate
Calcium Acetate
Sevelamer
Lanthanum
Ferric citrate
Magnesium
Nicotinamide
Combination binder therapy
Ergocalciferol/Hydroxycholecalciferol
Calcitriol
Doxercalciferol
Paricalcitol
Cinacalcet

Appendix -2

M. S. Parisi, B. Oliveri, J. Somoza et al., Clin Nephrol 59 (6), 471 (2003).
CKD-MBD

• Parathyroid Hormone
  – Epidemiology
  – Accuracy
  – Management

• Bone Disease
  – CKD Adaptation
  – Assessment
  – Management

• Vascular Calcification
  – Association with CKD-MBD
  – Assessment (Plain Films)
  – Management

• Phosphorus Control
  – Consequences
  – Management (Diet, Meds, Dialysis)

• Vitamin D
  – Vitamin D Deficiency
  – Vitamin D and Survival
  – Vitamin D in over suppression
Take Away

- Vascular calcification plays a key role in CKD mortality
- Vascular calcification starts early
- We may be doing a disservice to patients by not emphasizing early phosphorus control and over suppressing PTH levels

- We should be offering nocturnal dialysis to more patients
- Vitamin D has non-skeletal functions that are ignored not only in CKD but in the general population
FIG. 1. Differentiation of bone cells of three lineages and its regulation by transcription factors