Kidney-Bone and Beyond: An Academic Career

Isidro B. Salusky, M.D.
Distinguished Professor of Pediatrics
Chief, Division of Pediatric Nephrology
Director, Clinical Translational Research Center
Associate Dean of Clinical Research
David Geffen School of Medicine at UCLA
With Hectorol® (doxercalciferol) Therapy

Normal Metabolic Pathway

In Kidney Failure

No Active Vitamin D Hormone

With Hectorol® (doxercalciferol) Therapy

Major Active Vitamin D Hormone

Minor Active Vitamin D Hormone

VITAMIN D₂

1,25 D₂

1,24 D₂
Ca = calcium; CVD = cardiovascular disease; P = phosphorus.

Courtesy of Kevin Martin, MB, BCh.
Progressive loss of kidney function

↓ 1α-Hydroxylase

↓ VDR Expression

↓ CaSR Expression

Partial 1,25(OH)₂D resistance

Normal

Diffuse

Progressive loss of 1,25(OH)₂D has a profound effect on the structure and function of the parathyroid glands

Spectrum of Renal Osteodystrophy

Calcium, Vitamin D

Low turnover

Adynamic
Osteomalacia

Normal bone formation

Mixed lesion

Al^{3+}

Mild
Osteitis fibrosa

High turnover

Vascular Calcification Process
Therapeutic Options for the Treatment of Renal Osteodystrophy

Phosphate Binders

Aluminum Ca-Salts

Active Vitamin D Analogues

Oxacalcitrol - Japan
Paracalcitrol - USA Stage 5
Doxercalciferol - USA Stage 3-5

Calcimimetic Drugs

Cinacalcet
Table 1. Characteristics of the Children and Young Adults with Chronic Renal Insufficiency Who Were Treated with Dialysis and Calcium Carbonate or Aluminum Hydroxide.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>AGE (yr)</th>
<th>SEX</th>
<th>PRIMARY RENAL DISEASE</th>
<th>Z Score*</th>
<th>INITIAL</th>
<th>FINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium carbonate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17.8</td>
<td>M</td>
<td>Alport's syndrome</td>
<td>-2.35</td>
<td>-2.34</td>
<td></td>
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<tr>
<td>2</td>
<td>15.9</td>
<td>F</td>
<td>Rapidly progressive glomerulonephritis</td>
<td>-3.14</td>
<td>-3.21</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18.2</td>
<td>F</td>
<td>Hemolytic uremic syndrome</td>
<td>-3.14</td>
<td>-3.06</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15.0</td>
<td>F</td>
<td>Renal dysplasia</td>
<td>-3.79</td>
<td>-3.52</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21.0</td>
<td>F</td>
<td>Obstructive uropathy</td>
<td>-0.33</td>
<td>-0.33</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10.1</td>
<td>M</td>
<td>Alport's syndrome</td>
<td>-4.97</td>
<td>-4.95</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11.0</td>
<td>F</td>
<td>Focal glomerulosclerosis</td>
<td>-3.78</td>
<td>-4.02</td>
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<tr>
<td>8</td>
<td>19.0</td>
<td>F</td>
<td>Reflux nephropathy</td>
<td>+0.06</td>
<td>+0.14</td>
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<tr>
<td>9</td>
<td>13.4</td>
<td>F</td>
<td>Dysplastic kidneys</td>
<td>-3.43</td>
<td>-3.09</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>13.2</td>
<td>F</td>
<td>Obstructive uropathy</td>
<td>-2.91</td>
<td>-2.96</td>
<td></td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>15.5±3.7</td>
<td></td>
<td></td>
<td></td>
<td>-2.78±1.55</td>
<td>-2.73±1.55</td>
</tr>
<tr>
<td><strong>Aluminum hydroxide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>7.8</td>
<td>M</td>
<td>Renal dysplasia</td>
<td>-4.16</td>
<td>-4.20</td>
<td></td>
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<tr>
<td>12</td>
<td>19.0</td>
<td>M</td>
<td>Alport's syndrome</td>
<td>-1.02</td>
<td>-1.02</td>
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<tr>
<td>13</td>
<td>11.3</td>
<td>M</td>
<td>Membranoproliferative glomerulonephritis</td>
<td>-0.71</td>
<td>-1.31</td>
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<tr>
<td>14</td>
<td>17.5</td>
<td>F</td>
<td>Chronic glomerulonephritis</td>
<td>-2.88</td>
<td>-2.96</td>
<td></td>
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<tr>
<td>15</td>
<td>14.0</td>
<td>F</td>
<td>Membranoproliferative glomerulonephritis</td>
<td>-0.16</td>
<td>-0.21</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>14.0</td>
<td>F</td>
<td>Systemic lupus erythematosus</td>
<td>-2.12</td>
<td>-2.19</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>14.9</td>
<td>F</td>
<td>Polycystic kidney disease</td>
<td>-1.18</td>
<td>-1.58</td>
<td></td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>14.1±3.7</td>
<td></td>
<td></td>
<td></td>
<td>-1.75±1.39</td>
<td>-1.92±1.33</td>
</tr>
</tbody>
</table>

*Values are the Z scores for height adjusted for chronologic age and sex.
Change in Plasma Al levels During the Course of the Study

![Bar chart showing plasma aluminum levels over 12 months]

**Figure 2.** Mean (±SE) Basal Plasma Aluminum Concentrations in 17 Children and Young Adults with Chronic Renal Insufficiency Treated with Dialysis and Aluminum Hydroxide (N = 7; Open Bars) or Calcium Carbonate (N = 10; Hatched Bars).

Asterisks indicate a significant change from the respective initial values (P<0.05).

Salusky IB et al NEJM 1990
Change in Plasma Aluminum Levels after DFO

Figure 3. Mean (± SE) Increments in Plasma Aluminum Concentrations after Single Intravenous Infusions of Deferoxamine (40 mg per Kilogram) before and after Treatment with Aluminum Hydroxide (N = 7; Open Bars) or Calcium Carbonate (N = 10; Hatched Bars) in Children and Young Adults with Chronic Renal Insufficiency Treated with Dialysis.
Therapeutic Options for the Treatment of Renal Osteodystrophy

Phosphate Binders

- **Sevelamer**: Ca free – Metal Free
- **Lanthanum Ca**: Ca free - Metal +

Active Vitamin D Analogue

- Oxacalcitrol - Japan
- Paracalcitol - USA
- Doxercalciferol - USA

Calcimimetic Drugs

- Cinacalcet
Reduced Kidney Function and SHPT

- Reduced Renal Mass
  - Decreased Serum 1,25(OH)₂D (Active Vitamin D Calcitriol)
  - Increased Serum Phosphate

Hypocalcemia

Increased PTH Secretion

- Decreased Vitamin D Receptors
- Decreased Ca-Sensing Receptors

Parathyroid Glands

Progression of CKD and Indices of Bone Metabolism

# Clinical Features of Childhood ROD

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height $&lt;-2$ SD</td>
<td>153 (61.9%)</td>
</tr>
<tr>
<td>Clinical manifestations of bone disease</td>
<td>91 (36.8%)</td>
</tr>
<tr>
<td>Deformities</td>
<td>63 (25.5%)</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>33 (13.4%)</td>
</tr>
<tr>
<td>Aseptic bone necrosis</td>
<td>32 (13.0%)</td>
</tr>
<tr>
<td>Mild disabling bone disease</td>
<td>26 (10.5%)</td>
</tr>
<tr>
<td>Severe disabling bone disease</td>
<td>18 (7.3%)</td>
</tr>
<tr>
<td>Invalidating bone disease (all)</td>
<td>44 (17.8%)</td>
</tr>
</tbody>
</table>

Groothoff JW *KI* 63 (2003) 266–275
## STUDY DESIGN

<table>
<thead>
<tr>
<th></th>
<th>Calcitriol</th>
<th>Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CaCO$_3$</td>
<td></td>
<td>Sevelamer</td>
</tr>
<tr>
<td>1-$\alpha$ D$_2$</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CaCO$_3$</td>
<td>Sevelamer</td>
</tr>
</tbody>
</table>
Effects of Therapy on Bone Turnover

Bone Formation Rate (um²/mm²/day)

- Initial
- Final

- $1\alpha(OH)D_2 + CaCO_3$
- $1\alpha(OH)D_2 + Sevelamer$
- $1,25(OH)_2D_3 + CaCO_3$
- $1,25(OH)_2D_3 + Sevelamer$

* $p<0.001$

Wesseling K. et al KI 2010
Bone Gene Expression in Calcified Plaque

Bostrom K et al JCI 1993
Extra-Skeletal Calcification in Chronic Renal Failure

Courtesy of Kevin Martin, M.D.
Intimal Atherosclerotic Plaque
Process of Vascular Calcification

1. Loss of inhibition
   - MGP
   - OPN
   - Fetuin/α2-HS-glycoprotein
   - Pyrophosphate
   - Others

2. Hyperphosphatemia
   Hypercalcemia
   Ca x Pi

3. Induction of Bone formation
   - Vascular osteoblast/chondrocyte-like cells
   - Matrix vesicles

4. Circulating nucleational complexes
   Bisphosphonates
   OPG

Remodeling bone
Apoptotic bodies

(Giachelli et al 2004)
Coronary Artery Calcification in Young Dialysis Patients

Calcification scores doubled in patients with positive initial scan when rescanned at 20 months

*Determined by EBT.
Risk Factors Associated With Increased Risk for Cardiac Calcification in Young Dialysis Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coronary Calcification (n=14)</th>
<th>No Calcification (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca from calcium binders (mg/day)*</td>
<td>6456 ± 4278</td>
<td>3325 ± 1490</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum P (mg/dL)</td>
<td>6.9 ± 0.9</td>
<td>6.3 ± 1.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Ca × P product (mg²/dL²)*</td>
<td>65.0 ± 10.6</td>
<td>56.4 ± 12.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 3</td>
<td>15 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean duration of dialysis (years)</td>
<td>14 ± 5</td>
<td>4 ± 4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Modifiable.

Serum calcium was not significant.

Risk of Cardiovascular Calcification Is Increased in Dialysis Patients

*Determined by EBT.

CAD = coronary artery disease; CV = cardiovascular.

Arterial Media Calcification in ESRD


[Image of X-ray scans labeled A and B]
Cardiovascular disease (CVD) mortality
general population versus ESRD patients


GP=general population

Age (years)

Annual CVD mortality (%)

25-34  35-44  45-54  55-64  65-74  75-84  >85

GP male
GP female
GP black
GP white
dialysis male
dialysis female
dialysis black
dialysis white

GP=general population

"Amazing — you have the heart of a 375-year-old man."
Vascular Calcification in Patients With CKD

- Patients with Stage 5 CKD are at high risk for vascular calcification
- Vascular calcifications are present in almost 50% of patients with stage 4 CKD and new dialysis patients
- Vascular calcification can be quantified
- Vascular calcification is associated with modifiable risk factors
  - Ca intake from calcium-based binders
  - S-P, S-Ca and Ca × P product
  - Therapy with vitamin D
- Vascular calcification results in arterial stiffening and increased pulse pressure and adynamic bone disease

New Definition of ROD: 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
Therapeutic Options for the Treatment of Renal Osteodystrophy

**Phosphate Binders**

- **Sevelamer**: Ca free - Metal Free
- **Lanthanum Ca**: Ca free - Metal +

**Active Vitamin D Analogues**

- Oxacalcitrol - Japan
- Paracalcitrol - USA
- Doxercalciferol - USA
  - Stage 3-5
  - Stage 5

**Calcimimetic Drugs**

- Cinacalcet
FGF-23 and Rickets

Hypophosphatemia
Renal phosphate wasting
Low (or inappropriately normal) 1,25D
Normal serum Ca levels
Increased FGF-23 values

ADHR (Autosomal Dominant Hypophosphatemic rickets)
TIO (Tumor Induced Osteomalacia)
XLH (X-linked hypophosphatemia)
ARHP (Autosomal Recessive Hypophosphatemia)
FGF-23 is Produced in Osteocytes and Regulates Phosphorus and Vitamin D
Traditional Bone Histomorphometry
Connections between blood vessels and osteocyte-lacunocanaliculi

Novel Regulators of Phosphate and Bone Metabolism

<table>
<thead>
<tr>
<th>MARKER</th>
<th>EXPRESSION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phex</td>
<td>Early and late osteocytes</td>
<td>Phosphate metabolism</td>
</tr>
<tr>
<td>OF45/MEPE</td>
<td>Late osteoblast through osteocytes</td>
<td>Inhibitor of bone formation/regulator of phosphate metabolism</td>
</tr>
<tr>
<td>DMPI</td>
<td>Early and mature osteocytes</td>
<td>Phosphate metabolism and mineralization</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>Late embedded osteocyte</td>
<td>Inhibitor of bone formation</td>
</tr>
<tr>
<td>FGF23</td>
<td>Early and mature osteocytes</td>
<td>Induces hypophosphatemia</td>
</tr>
</tbody>
</table>

Increased Serum Pi, PTH and FGF23 by GRF in 447 CKiD Children

Portale A et al CJASN 2013
Bone FGF-23 Expression (50x)

Healthy Control

CKD (Stage 2)

Pereira RC et al Bone 2009 in press
Bone DMP1 Expression (200x)

Healthy Control

CKD (Stage 2)

Pereira RC et al Bone 2009 in press
FGF23 Associated with LVH in Patients with CKD

(Faul C et al. JCI 2012)
cFGF-23 Quartiles and Mortality in Dialysis Patients (Gutierrez et al. NEJM 2008)
Temporal aspects of disordered mineral metabolism in CKD

1. Increased FGF-23 is the earliest alteration in mineral metabolism in CKD
2. Gradually increasing FGF-23 levels cause early decline in 1,25D levels
3. This frees PTH from feedback inhibition, leading to SHPT
4. All these changes occur long before increases in serum P levels are evident

GFR (mL/min/1.73 m²)

Dialysis

Time post-transplant (months)

cFGF-23, C-terminal Fibroblast Growth Factor-23

Collaborators

UCLA

Immutopics

Loma Linda Med. Ctr.

Mass. General Hospital

Support