Management of Bone Disease

Dieter Haffner
Department of Pediatric Kidney, Liver and Metabolic Diseases

Medizinische Hochschule Hannover
Renal Osteodystrophy in Children

Growth plate in experimental uremia

Toluidinblue staining; 100x
Renal Osteodystrophy in Children
CKD-Mineral and Bone Disorder

Ectopic vascular calcifications
X-ray of the left hand in a 16 year old boy with severe renal bone disease:

- Subperiostal erosions (middle phalanges)
- Brown tumor in the 2. digit
- „ricket-like“ lesions
- Vascular calcifications at the forearm
Fibroblast growth factor 23 „Phosphatonin“ is elevated in early CKD: The counterplayer of vitamin D

FGF23 increases P-excretion and reduces active vitamin D
- by inhibiting alpha-1-hydroxylase activity in the kidney
- by stimulating 24-hydroxylase
- by inhibiting P-absorption

Etiology of CKD-MBD

- GFR↓, phosphate load↑, hyperphosphatemia
- FGF23 synthesis in bone ↑, active vitamin D↓, hypocalcemia
- Secondary hyperparathyroidism
- native vitamin D↓
Other causes of renal bone disease

- Metabolic acidosis
- Malnutrition
- Disturbances of GH axis
- Corticosteroid therapy (osteoporosis)
- Hypophosphatemia (diet, phosphate binders)
- Reduced physical activity, muscle deficits
Assessment of CKD-MBD

- Clinical assessment: signs of rickets, leg bowing, pain (every visit)
- Serum Ca, P, AP, iPTH (1-6 monthly)
- Serum 25(OH)D (6-12 monthly)
- X-ray of left wrist (at yearly intervals in advanced CKD)
- Bone histomorphometry: invasive
- DXA of no use at all
- Clinical studies: pQCT, PWV, cIMT, FGF23 & other novel biomarkers of bone and mineral metabolism
Bone metabolism in early CKD

- Increased bone formation rates
- Mineralization defects
- Increased PTH levels
- Increased FGF23 levels

**Figure 1.** Prevalence of increased bone formation rates (black bars), mineralization defects (white bars), increased PTH levels (striped bars), and increased FGF-23 values (black polka-dotted bars) in pediatric patients with CKD. The mineralization defect was defined as an abnormal accumulation of osteoid (osteoid volume) in combination with a delay osteoid maturation time. Increased PTH values and FGF-23 values were defined as values above the range determined in healthy individuals.
Treatment of CKD-MBD

AIMS:

✓ Normal bone turnover
✓ Prevent skeletal deformities, bone & joint pain, fractures
✓ Maintain normal growth
✓ Prevent tertiary HPT
✓ Prevent ectopic calcifications
✓ Decrease CV mortality
Treatment of CKD-MBD

CHALLENGES:
✓ Assessment of bone turnover requires bone biopsy
✓ Sensitivity & specificity of surrogate parameters of bone turnover like PTH are limited
✓ Skeletal resistance to PTH with progressing CKD
✓ Poor growth may persist despite normalization of bone turnover
Treatment of renal bone disease - CKD-MBD

CKD stage 2 3 4 5D ➔ dialysis/transplantation

Native Vitamin D supplementation
- Diet
  - Phosphate Binders
- Active Vitamin D
- Calcimimetics
- Parathyroidectomy
If plasma phosphate is elevated, phosphate intake should be limited

- Dietary training of patient and parents by a dietician!
- Phosphate from natural sources is less resorbed than artificially added phosphate!

Table 1  Weight-related suggested daily dietary phosphate intake for children with chronic kidney disease (CKD)

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Phosphate allowance (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>&lt;400</td>
</tr>
<tr>
<td>10–20</td>
<td>&lt;600</td>
</tr>
<tr>
<td>20–40</td>
<td>&lt;800</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&lt;1,000</td>
</tr>
</tbody>
</table>

Rees and Schroff, Pediatr Nephrol 2010
Age dependent phosphate and calcium levels, and Ca x P product

Ca x P product < 5.25 mmol$^2$/l$^2$ (<12 yrs.); < 4.44 mmol$^2$/l$^2$ (>12 yrs.)

Holliday, Textbook: Pediatric Nephrology 1998
www.kidney.org/professionals/KDOQI/guidelines/
Phosphate Education Program (PEP)

5 PU

1 PU

4 PU

2 PU
Self-adjustment of phosphate binder dose to meal phosphorus content (PEP)

Fig. 1. Basic principle of the PEP concept. A typical meal is depicted. Patients are instructed to eye-estimate the inorganic phosphorus content of the various meal components using PU. Total meal PU is derived from summing up PUs of each meal component. In conjunction with the PEP concept, PB are only prescribed in relation to PU, i.e. 1 PB pill per PU (1 PB/1 PU). For an exemplary meal of 5 PU, as depicted, the patient will consume 5 PB pills.
PEP improves hyperphosphatemia management in pediatric CKD patients

Fig. 2. Follow-up of serum phosphate levels at baseline and during the 24-week follow-up after PEP training. Individual serum phosphate levels of 16 study subjects are shown before PEP training and during 24 weeks afterwards, subdivided into four intervals of 6 weeks (n = 16 in Week 3–12; n = 13 in Week 13–18; n = 11 in Week 19–24). The mean levels for each interval are indicated as a line. The upper threshold for target serum PO levels (1.78 mmol/l) is given as a dotted line; significance (P < 0.05) versus baseline data as asterisks.

Ahlenstiel et al, Nephrol Dial Transplant 2010
Consumption of PB per meal before and after introduction of PEP

Fig. 4. Consumption of phosphate binders per meal before and after introduction of the PEP concept. The number of phosphate binder pills per meal at baseline (open bars) and during the second to the fourth month after PEP training (solid bars) was derived from dietary diaries of 14 paediatric patients (37 dietary diaries before PEP training versus 37 afterwards). Data is given as mean ± SD; significance (P < 0.05) versus baseline data as asterisks.
## Table 20. Recommended Calcium Intake for Children with CKD Stages 2 to 5 and 5D

<table>
<thead>
<tr>
<th>Age</th>
<th>DRI</th>
<th>Upper Limit (for healthy children)</th>
<th>Upper Limit for CKD Stages 2-5, 5D (Dietary + Phosphate Binders*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>210</td>
<td>ND</td>
<td>≤420</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>270</td>
<td>ND</td>
<td>≤540</td>
</tr>
<tr>
<td>1-3 y</td>
<td>500</td>
<td>2,500</td>
<td>≤1,000</td>
</tr>
<tr>
<td>4-8 y</td>
<td>800</td>
<td>2,500</td>
<td>≤1,600</td>
</tr>
<tr>
<td>9-18 y</td>
<td>1,300</td>
<td>2,500</td>
<td>≤2,500</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not determined.

* Determined as 200% of the DRI, to a maximum of 2,500 mg elemental calcium.
Evolution of Phosphate Binders

1970

Aluminium-cont. PB

- effective
toxic
encephalopathy
osteomalacia

1980

Calcium-cont. PB

- effective
resorption
hypercalcemia
inexpensive

1990

Sevelamer-HCl carbonate

- effective
no calcium
no resorption
LDL cholesterol ↓
hypercalcemia ↓
(acidosis)
expensive

2000

- more effective
no calcium
resorption
accumulation
expensive

2006

Lanthanum carbonate

- more effective
no calcium
resorption
accumulation
expensive

2009

- effective
anion exchange resin
no calcium
LDL cholesterol ↓

2012

Colestilan

Ongoing Industry Trials in Pediatric CKD
Choice of Phosphate-binders

- **P binding capacity:**
  - Ca-carbonate: 1g – 39 mg P
  - Ca-acetate: 1g – 45 mg P
  - Sevelamer: 1g – 80 mg P
  - Lanthanum: 1g – 110 mg P

- **First choice: Ca-containing P binders:**
  - Total Ca intake ≤ 2.5 g/day (including diet)
  - Serum Ca < 2.55 mmol/l
  - Ca neutral dialysate (Ca⁺⁺ 1.25 mmol/l)
In case of hyperphosphatemia, the dialysis efficacy should be optimised

PD
- Increase dwell volume to 1000-1400 ml/m² BSA
- APD: avoid a too short dwell time
- APD: a daytime dwell should be added
- APD: prolong time on dialysis

HD
- Optimize blood flow, short daily or nocturnal dialysis
Short daily HD is associated with lower plasma FGF23 levels when compared with conventional HD in adult patients.

**Figure 1**: Serum FGF23 in conventional hemodialysis and in those treated with short daily hemodialysis. Serum FGF-23 was significantly higher in those treated with conventional hemodialysis (median 2521 RU/mL) versus those treated with short daily hemodialysis (median 823 RU/mL). Box plots demonstrate 25th, 50th and 75th percentiles with error bars spanning 10–90th percentiles. *P < 0.01.*
Supplementation for vitamin D deficiency/insufficiency in CKD 2-5D

Table 3  Recommended supplementation for vitamin D deficiency/insufficiency in children with CKD, used with permission from [85]

<table>
<thead>
<tr>
<th>Serum 25(OH)D (ng/ml)</th>
<th>Definition</th>
<th>Ergocalciferol (D$_2$) or cholecalciferol (D$_3$) (oral dosing)</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Severe vitamin D deficiency</td>
<td>8,000 IU daily (or 50,000 IU/week) for 4 weeks; then 4,000 IU daily (or 50,000 IU every alternate week) for 2 months</td>
<td>3</td>
</tr>
<tr>
<td>5–15</td>
<td>Mild vitamin D deficiency</td>
<td>4,000 IU daily for 12 weeks (or 50,000 IU every alternate week for 12 weeks)</td>
<td>3</td>
</tr>
<tr>
<td>16–30</td>
<td>Vitamin D insufficiency</td>
<td>2,000 IU daily (or 50,000 IU every 4 weeks)</td>
<td>3</td>
</tr>
</tbody>
</table>

CKD, Chronic kidney disease

- Start vitamin D supplementation before use of active vitamin D in CKD 2-3 if vitamin D levels are decreased
- Target: 25(OH)D > 30 ng/ml (75nMol/L)
- Stop if levels are above 50 ng/ml (120nMol/L)

www.kidney.org/professionals/KDOQI/guidelines/
Klaus Ped Nephrol 2006; Schroff et al, Pediatr Nephrol 2010
Vitamin D supplementation and development of secondary hyperparathyroidism

- Effective in CKD2-3
- Ineffective in CKD4

Figure 3. Time to development of secondary hyperparathyroidism in ergocalciferol and placebo-treated patients.

The type of renal bone disease depends on therapeutic interventions.
## Renal Osteodystrophy in Children

### Target PTH levels

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>iPTH (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KDOQI:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>35-70</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>35-70</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>70-110</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15, dialysis</td>
<td>200-300</td>
</tr>
<tr>
<td><strong>Europe:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>120-180</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15, dialysis</td>
<td>120-180</td>
</tr>
</tbody>
</table>

www.kidney.org/professionals/KDOQI/guidelines/
Klaus et al, Pediatr Nephrol 2006
Absence of CKD-MBD complications and absence of hypercalcemia optimal PTH: **100-300 pg/ml** (ROC analysis)

**Figure 2** | Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extrasosseous calcifications, radiological osteomalacia and/or osteopenia)
Predictors of LVH in 507 Children on CPD

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic hypertension</td>
<td>2.11 (1.40-3.19)</td>
<td>0.0004</td>
</tr>
<tr>
<td>High BMI SDS</td>
<td>2.33 (1.34-4.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>PTH &gt;200 pg/ml</td>
<td>1.77 (1.22-2.57)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.04 (1.01-1.07)</td>
<td>0.025</td>
</tr>
<tr>
<td>CAKUT diagnosis</td>
<td>0.65 (0.44-0.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>Automated PD</td>
<td>0.55 (0.33-0.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>Urine output (L/m²/day)</td>
<td>0.59 (0.36-0.96)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Bakkaloglu et al. cJASN 2011
Figure 4 | Time-averaged mean plasma intact parathyroid hormone (iPTH) concentrations and change in standardized height in 214 pre- and early pubertal children followed prospectively for at least 12 months. Full circles indicate patients receiving recombinant growth hormone. SDS, standard deviation score.
Treatment with calcitriol/ alfacalcidol

- Indication: persistent elevated PTH levels despite vitamin D suppl.
- In CKD 4-5D: active & native vitamin D may be started in parallel
- Oral daily Tx; application in the evening (hypercalcemia)
- Alfacalcidol is ineffective in severe liver disease!
- Starting dose of calcitriol:
  - Weight < 10 kg: 0.05 – 0.1 μg/day
  - Weight 10 – 20 kg: 0.1 – 0.15 μg/day
  - Weight > 20 kg: 0.25 μg/day (max. 1 μg)
- Apply minimal PTH suppressive dosage!
- Check: Ca, P, AP, PTH!
Randomized study in 33 short dialysis pts. : GH vs. non-GH
Bone biopsy at baseline and after 8 months

Results:
• **Bone formation rate** per bone surface during GH Tx:
  – increased in pts. with low bone turnover
  – decreased in pts. with high bone turnover
  – was unchanged in pts. with normal bone turnover

• Bone formation rates were higher with GH Tx, irrespective of underlying bone histologic features

• GH Tx resulted in greater increase in height SDS irrespective of underlying bone histologic features
Parathyroidectomy

- Severe, therapy-refractory sHPT: radiological signs, hypercalcemia, Ca x P product $>> 5.25$ mmol$^2$/l$^2$
- Parathyroid gland $> 0.5$ cm$^3$ or diameter $> 1.0$ cm
- Subtotal PTX and/or autotransplantation
Calcimimetics

- Increases Ca sensing receptor sensitivity to ionized calcium
- Dose dependent suppression of PTH up-to 80%
- May increase therapeutic window for vitamin D / Ca based P binder therapy
- Not licensed in pediatric patients
Cinacalcet in children with severe sHPT

7 children on dialysis; cinacalcet: 0.25 mg/kg once daily
PTH secretion
Phosphate load
Calcium intake
Active vitamin D
Klotho deficiency
Activated RAAS
Iron deficiency
Inflammation

Osteocytes

Circulation

Klotho-dependent
Klotho-dependent and Klotho-independent
Klotho-independent

Stimulation of phosphate excretion and inhibition of CYP27b1
Inhibition of PTH secretion
Inhibition of CYP27b1 in monocytes
Impairment of neutrophil recruitment
Modulation of balance between NO and ROS
Alteration of neuronal morphology and synaptic density
Induction of myocyte hypertrophy via activation of FGFR4

Non-functioning kidney
Hyperplastic parathyroid gland
Impairment of host defense
Endothelial dysfunction
Atherosclerosis
Cognitive dysfunction
Left ventricular hypertrophy

FGF23
Increased expression
Increased levels

PMN
PBMC
Active vitamin D
Open questions

• Calcium balance across pediatric age range: Therapeutic window for calcium-based vs calcium free P binders in dialyzed children

• Should we use P binders in normophosphatemic pre-dialysis CKD patients?

• Value of FGF23 monitoring

• Optimal dosing of native & active vitamin D

• Efficacy of native & active vitamin D in improving bone & CV health in pediatric CKD patients

➤ adequately designed pediatric trials on CKD-MBD Tx
The challenge: Optimal clinical care!
Thank you very much for your attention!