Bone disease in children with CKD

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Outline

• Normal bone turnover
• Clinical and histological studies
• Biomarkers – PTH as a marker of bone disease?
• Bone – vascular link
• Cochrane review
• What the guidelines say
Normal bone turnover

Bone remodeling cycle

Ca requirement of growing bones

- Children have high Ca and P requirements
- Total skeletal Ca increases from ~25g at birth to ~1000g in an adult
- ~25% of total skeletal mass is laid down during the 2-year interval of peak height velocity
- Buffering capacity of the growing skeleton

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Calcium threshold (mg/day)</th>
<th>Balance per day (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1090</td>
<td>503±91</td>
</tr>
<tr>
<td>2-8</td>
<td>1390</td>
<td>246±126</td>
</tr>
<tr>
<td>9-17</td>
<td>1480</td>
<td>396±164</td>
</tr>
<tr>
<td>18-30</td>
<td>957</td>
<td>114±133</td>
</tr>
</tbody>
</table>

Calcium balance is positive throughout childhood
Bone imaging

**DEXA**

**pQCT**

Limitations of DEXA

- Confounding by short stature
- 2D measurement of superimposed cortical and trabecular bone
- Superimposed vascular calcifications
- Failure to distinguish between PTH effects on trabecular and cortical bone

**KDIGO 2009** and **ISCD 2007** - recommend **against** routine DEXA BMD testing in CKD

Bone histomorphometry

<table>
<thead>
<tr>
<th>Disease</th>
<th>Turnover</th>
<th>Mineralization</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomalacia</td>
<td>Low</td>
<td>Abnormal</td>
<td>Low / normal</td>
</tr>
<tr>
<td>Adynamic bone</td>
<td>Low</td>
<td>Normal</td>
<td>Low / normal</td>
</tr>
<tr>
<td>Moderate hyperparathyroidism</td>
<td>Moderate</td>
<td>Normal</td>
<td>Normal / High</td>
</tr>
<tr>
<td>Mixed renal osteodystrophy</td>
<td>High</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Osteitis fibrosa</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
</tr>
</tbody>
</table>

Moe et al, Kidney International 2006
Bone strength

- Bone strength is a function of:
  - bone density (g/cm³) – measured by DEXA or pQCT
  - bone quality (microarchitecture, turnover, matrix collagen and mineralization, geometry and microdamage repair) – assessed by histology

Histomorphometry is required to define the type of renal osteodystrophy

What can we measure non-invasively?

- **Bone density**
  - Material density
  - Compartment density
  - Areal density

- **Bone quality**
  - Cortical dimensions (QCT)
  - Micro-architecture (mMRI and HR-pQCT)
  - Cortical porosity (HR-pQCT)
  - Mineralization (Solid State Phosphorus MRI?)
  - Turnover (PET scan?)
  - Micro-damage repair
Bone disease in children with CKD

N=249 young adults with ESRD between 0 and 14 years, at least 10 years follow-up

<table>
<thead>
<tr>
<th>Bone mass</th>
<th>↓50% risk of fracture after menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 30-35</td>
<td>+10% peak bone mass</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height &lt; -2 SD</td>
<td>153 (63.9%)</td>
</tr>
<tr>
<td>Clinical manifestations of bone disease</td>
<td>94 (36.1%)</td>
</tr>
<tr>
<td>Deformities</td>
<td>85 (32.3%)</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>80 (31.5%)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>70 (27.3%)</td>
</tr>
<tr>
<td>Fracture risk</td>
<td>60 (24.1%)</td>
</tr>
<tr>
<td>Serum calcium level</td>
<td>50 (19.9%)</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>40 (15.7%)</td>
</tr>
<tr>
<td>Serum phosphorus level</td>
<td>30 (11.7%)</td>
</tr>
<tr>
<td>Serum parathyroid hormone level</td>
<td>20 (7.8%)</td>
</tr>
</tbody>
</table>

Bone disease in children with CKD

Groothoff J et al., KI 2003

Hip Fractures in Adults

4.5-fold higher risk of hip fractures in adult dialysis patients compared to the general population

1-year hip fracture mortality:
- 50% in dialysis patients
- 20% in the general population
Fractures in children and young adults

Prospective study
537 children
Mild - moderate CKD (83% in CKD stages 2-3)
- 4 year follow-up

2-3 fold higher fracture risk in boys and girls with CKD compared to their healthy peers

Denburg, et al.  ASN 2012

Fractures in the CKiD cohort

Denburg, et al.  JASN 2016

Tibia QCT - ↓ Ca and ↑ PTH are associated with decline in cortical BMD

<table>
<thead>
<tr>
<th>β</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (per 1 mg/dl)</td>
<td>0.31 (0.08, 0.54)</td>
<td>0.01</td>
</tr>
<tr>
<td>25(OH)D (per 10 ng/ml)</td>
<td>0.18 (0.01, 0.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>1,25(OH)2D (per 10%)</td>
<td>-0.07 (-0.10, -0.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PTH (per 10%)</td>
<td>-0.02 (-0.04, -0.01)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Decline in cortical BMD Z-scores:
- Higher baseline 1,25(OH)2D
- ↑ΔPTH

↑Δ Calcium - ↑ cortical BMD (especially in growing children)

1 SD decrease in BMD → 2-fold increase in fracture risk (Hazard Ratio per SD decrease in BMD 1.75; p=0.009)
### CKD patients fracture at a greater BMD

<table>
<thead>
<tr>
<th></th>
<th>No CKD</th>
<th>CKD</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (95% CI) per SD lower Femoral Neck BMD T-score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.45 (2.13, 2.82)</td>
<td>2.32 (1.79, 3.01)</td>
<td>0.72</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.14 (1.80, 2.55)</td>
<td>2.69 (1.96, 3.69)</td>
<td>0.70</td>
</tr>
<tr>
<td>PTH &amp; Vit D</td>
<td>2.15 (1.80, 2.57)</td>
<td>2.74 (1.99, 3.77)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Yenchek, et al. CJASN

### PTH influences changes in bone structure

103 patients aged 5-21 years
CKD (26 on dialysis)
Baseline and 12 months later


### Bone biopsies - ↓ Ca and ↑ PTH are associated with defective mineralization

Bone biopsies in 52 children with CKD 2-4
Age - 2 to 21 years

Wesseling-Perry et al; cJASN 2012

Defective mineralization present in:
- 29% of patients with stage 2
- 42% with stage 3
- 79% with stage 4/5 CKD

Abnormal mineralization
↓ serum calcium
↑ PTH
FGF-23: NS
Acidosis: NS

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Abnormal mineralization
↓ serum calcium
↑ PTH
FGF-23: NS
Acidosis: NS
### Associations with abnormal mineralization

<table>
<thead>
<tr>
<th>Turnover (BFR/BS)</th>
<th>Mineralization (OV/BV + OMT)</th>
<th>Serum Calcium (mg/dl)</th>
<th>Serum Phosphorus (mg/dl)</th>
<th>Alkaline Phosphatase (IU/L)</th>
<th>PTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n = 7)</td>
<td>Normal (n = 5)</td>
<td>9.6 ± 0.4</td>
<td>8.2 ± 0.6</td>
<td>197 ± 26</td>
<td>116 ± 15</td>
</tr>
<tr>
<td></td>
<td>Abnormal (n = 2)</td>
<td>8.1 ± 2.0</td>
<td>8.2 ± 2.2</td>
<td>250 ± 160</td>
<td>282 ± 162</td>
</tr>
<tr>
<td>Normal (n = 62)</td>
<td>Normal (n = 39)</td>
<td>9.6 ± 0.1</td>
<td>6.0 ± 0.2</td>
<td>158 ± 16</td>
<td>236 ± 36</td>
</tr>
<tr>
<td></td>
<td>Abnormal (n = 23)</td>
<td>8.9 ± 0.2</td>
<td>5.9 ± 0.3</td>
<td>243 ± 41</td>
<td>477 ± 68</td>
</tr>
<tr>
<td>High (n = 92)</td>
<td>Normal (n = 59)</td>
<td>9.2 ± 0.2</td>
<td>6.2 ± 0.2</td>
<td>340 ± 31</td>
<td>567 ± 58</td>
</tr>
<tr>
<td></td>
<td>Abnormal (n = 33)</td>
<td>8.8 ± 0.1</td>
<td>6.5 ± 0.2</td>
<td>556 ± 39</td>
<td>924 ± 67</td>
</tr>
</tbody>
</table>

↓ serum calcium and ↑ PTH in patients with defective mineralization, irrespective of bone turnover.

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### Bone disease in PD patients

#### PTH levels and MBD

- **IPPN Registry data - Borzych et al. Kidney Int 2010**

#### Longitudinal growth
- Clinical & radiological symptoms
- **Ca**
MINERAL DysREGULATION seen with:
- abnormal serum phosphorus levels were observed in 25% (14% hypo- and 11% hyperphosphatemia)
- abnormal serum calcium in 30% (19% hypo-, 11% hypercalcemia)
- hyperparathyroidism in 41% of the patients

A longer time since transplantation was associated with a lower risk of having mineral levels above target range.

Serum phosphorus levels above the recommended targets were associated with an increased risk of graft failure independently of eGFR.

Bone disease persists after renal transplantation

Bonthuis et al; cJASN 2015
High circulating FGF23 is associated with improved skeletal mineralisation

Role of osteocytes in bone physiology

- Transgenic mice overexpressing a normal human SOST gene
  - Osteopenia
  - Blocking SOST with a specific AB => osteoanabolic effect

- Human inactivating mutations of SOST
  - Progressive generalized osteosclerosis
  - Increased bone volume

Synthesis of SCLEROSTIN
Osteoblastic inhibition

Synthesis of RANK-L
Osteoclastic activation
Sclerostin levels ↑ as GFR ↓

- Sclerostin levels correlate positively with BMD and micro-architecture

- 76 HD adults vs 46 healthy controls
- In 37: DXA and HR-pQCT in addition to bone biomarkers
- Multivariable analysis:
  PTH and gender as predictors of SOST levels

<table>
<thead>
<tr>
<th></th>
<th>HH</th>
<th>OC</th>
<th>HD</th>
<th>Q5 (5th percentile)</th>
<th>Q95 (95th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>23.9 ± 19.6</td>
<td>23.9 ± 23.6</td>
<td>23.9 ± 21.6</td>
<td>23.9 ± 18.9</td>
<td>23.9 ± 21.6</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>74.7 ± 47.9</td>
<td>74.7 ± 47.9</td>
<td>74.7 ± 47.9</td>
<td>74.7 ± 47.9</td>
<td>74.7 ± 47.9</td>
</tr>
<tr>
<td>Calcium-Phosphorus</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Sclerostin (ng/mL)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>80%</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Sclerostin levels as a marker of vascular calcifications in HD patients

- N=53 HD, 25-80 yrs

- Higher circulating sclerostin levels associated with decreased mortality in prevalent HD patients

Bone – vascular link?
Calcium is ‘bad’

Ca accumulation in pre-dialysis & dialysis vessels

Predictors of CAC
- age
- dialysis duration
- serum P
- PTH
- hs-CRP
- Higher Ca intake from binders

Oh et al., Circulation 2002
Goodman et al., NEJM 2000
Civilibal et al., Pediatr Nephrol 2006
Shroff et al., JASN 2007
Shroff et al; Circulation 2008
Shroff et al; JASN 2010
In adults with CKD
The worse the bone, the worse the vessel

Osteoporosis was a significant predictor of CAC progression ($β=4.6; 95\% \text{ CI, 1.8 to 7.5}; P=0.002$).

N = 213 HD patients

- Cross-sectional study (local ancillary from the 4C cohort)
- 32 teenagers pre-dialysis CKD
- Bone assessment: HR-pQCT
- Vascular evaluation: ABPM

The greater the trabecular thickness and density:
- The greater the ABPM, and notably the diastolic and the mean BP

Bacchetta, IPNA 2013 poster P-SAT-355

In children with CKD
Bone ↔ vessel association?

Bone ↔ vessel cross-talk in CKD?

Are bone talking to vessels?
Phosphate / FGF23 / SOST

Are vessels talking to bone?
Osteogenic conversion of vascular smooth muscle cells

Do other tissues play a role in this cross-talk?
Hepatocytes and fetuin; Inflammation; renal tubular cells and Klotho

Do our treatments influence this cross-talk?
Phosphate-binder, vitamin D, calcium
Conclusions

• Bone disease, assessed by changes in PTH levels, is improved by all vitamin D preparations.
  - no consistent differences between routes of administration, frequencies of dosing or vitamin D preparations demonstrated.

• Sevelamer compared with calcium-containing binders:
  - phosphorus values were reduced to similar extents
  - fewer episodes of hypercalcaemia

All studies were small with few data available on patient-centred outcomes (growth, bone deformities) and limited data on biochemical parameters or bone histology resulting in considerable imprecision of results thus limiting the applicability to the care of children with CKD.

Guidelines on paediatric CKD-MBD management
Future studies

1. Develop sensitive methods to assess:
   - bone strength (mineralisation and quality)
   - vascular disease
   - Biomarkers of bone and vascular disease

2. Simultaneous study of bone and vessels to examine effects of:
   - Ca-based and Ca-free phosphate binders
   - new(er) phosphate binders
   - native and active vitamin D analogues

3. Calcium balance studies

Conclusions

• Abnormal bone mineralisation occurs early in CKD and is associated with low serum calcium and high PTH

• Non-invasive assessment by qCT and DEXA may be useful tools in evaluating children with CKD

• ‘Optimise’ Ca and PTH levels for optimal bone and cardiovascular health