CKD-MBD in children

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London, UK
Disclosures

Speaker: Gambro, Baxter, Genzyme, Amgen

Educational / Research support: Gambro
Children are not small adults

- Children have higher Ca and P requirements
- Total skeletal Ca increases from ~25g at birth to ~1000g in an adult
- 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>
</tbody>
</table>

Calcium balance is positive throughout childhood
Paediatric CKD-MBD studies

- No RCTs
  - Registry reports
  - Longitudinal studies in pre-dialysis and dialysis

- No ‘hard’ end-points for vascular studies
  - Surrogate measures of vascular disease
  - *Ex vivo* changes in vessels

‘Clean population’
- no pre-existing CVD
- rarely have diabetes or underlying inflammatory disease
- some studies have selected children without uncontrolled HT or dyslipidaemia
Outline

- CKD-MBD evolution in children
- Paediatric CVD and MBD
  - single / multicentre studies
  - Registry reports
  - Longitudinal studies on progression of vascular and bone disease
- Vessel and bone biopsy data
CKD-MBD in children

Hemodialysis 0–19 years
- Cardiac (32%)
- Infections (11%)
- Withdrawal (5%)
- Malignancy (3%)
- Hyperkalemia (2%)
- All other (47%)

Peritoneal dialysis 0–19 years

Transplant 0–19 years

USRDS 2011 report
Vascular changes begin pre-dialysis

586 children; age 1-16 years
eGFR 30-90 mL/min/1.73 m²

700 children; age 6 – 18 years
eGFR 10 – 45ml/min/1.73m²
Increased cIMT in pre-dialysis CKD

- 100 children with a median GFR 43 ml/min/1.73 m²
- Increased cIMT was associated with HT and dyslipidemia

Brady et al; CJASN 2012
Increased cIMT & PWV pre-dialysis

Intima Media Thickness

Pulse Wave Velocity

N = 700
eGFR 10 – 45ml/min/1.73m²

Slide courtesy of Prof Schaefer
# Predictors of cIMT and PWV

## IMT SDS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta</th>
<th>Partial R²</th>
<th>Model R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP SDS</td>
<td>0.17</td>
<td>0.029</td>
<td>0.029</td>
<td>0.0005</td>
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<tr>
<td>S-Phosphate</td>
<td>0.55</td>
<td>0.028</td>
<td>0.056</td>
<td>0.0005</td>
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<tr>
<td>S-Calcium</td>
<td>-1.03</td>
<td>0.022</td>
<td>0.078</td>
<td>0.0016</td>
</tr>
<tr>
<td>25OH Vitamin D</td>
<td>-0.02</td>
<td>0.014</td>
<td>0.092</td>
<td>0.012</td>
</tr>
</tbody>
</table>

## PWV SDS

<table>
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<tr>
<th>Predictor</th>
<th>Beta</th>
<th>Partial R²</th>
<th>Model R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP SDS</td>
<td>0.42</td>
<td>0.126</td>
<td>0.126</td>
<td>&lt;.0001</td>
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<tr>
<td>25OH Vitamin D</td>
<td>-0.025</td>
<td>0.032</td>
<td>0.158</td>
<td>0.0002</td>
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<tr>
<td>S-Phosphate</td>
<td>0.52</td>
<td>0.014</td>
<td>0.171</td>
<td>0.0115</td>
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<tr>
<td>iPTH</td>
<td>0.006</td>
<td>0.007</td>
<td>0.179</td>
<td>0.0675</td>
</tr>
</tbody>
</table>

*Slide courtesy of Prof Schaefer*
Studies in dialysis patients
High P levels in 45% of PD patients

KDOQI CKD-MBD Guideline Adherence Rates

- All: Above (45), Within (64), Below (10)
- < 1: Above (16), Within (30), Below (24)
- 1 to 5: Above (30), Within (60), Below (24)
- 5 to 11: Above (30), Within (63), Below (8)
- 12+: Above (81), Within (19), Below (16)

International Pediatric Peritoneal Dialysis Network
PTH levels in PD patients

Median serum iPTH level (pg/ml)

Netherlands | France | Greece | Poland | Germany | UK | Canada | Korea | Czech Rep | India | Turkey | Italy | China | USA | Chile | Uruguay | Brazil | Argentina

KDIGO 2009, KDOQI 2003, EPDWG 2003
<table>
<thead>
<tr>
<th>Authors / Journal</th>
<th>Number of dialysis pts</th>
<th>Vascular measures</th>
<th>Clinical / biochemical associations with cIMT</th>
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<tr>
<td>Oh / Circulation 2002</td>
<td>39</td>
<td>cIMT CAC</td>
<td>- dialysis duration</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
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<td>- mean PTH levels</td>
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<td>cIMT PWV CAC</td>
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<td></td>
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<td></td>
<td>- total &amp; LDL cholesterol</td>
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<td>PWV</td>
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PTH is associated with calcification

**Intima Media Thickness (mm)**

- **Controls**
  - PTH < 2xULN: 0.38 ± 0.01
  - PTH > 2xULN: 0.39 ± 0.01

- **PTH < 2xULN**: 0.4 ± 0.01
- **PTH > 2xULN**: 0.58 ± 0.02

- **p < 0.0001**
- **R² = 0.65**

**Pulse wave velocity (m/sec)**

- **Controls**
  - PTH < 2xULN: 5.6 ± 1.8
  - PTH > 2xULN: 5.8 ± 1.2

- **PTH < 2xULN**: 8.6 ± 2.3
- **PTH > 2xULN**: 8.6 ± 2.3

- **p = 0.03**

**Calcification score**

- **Total**
  - PTH < 2 ULN: 5 (12%)
  - PTH > 2 ULN: 12 (27%)

- **Calcification score**
  - PTH < 2 ULN: 7.8 (0 – 98)
  - PTH > 2 ULN: 85.3 (0 – 2039)

- **p < 0.01**
- **p = 0.001**

**Shroff et al, JASN 2007**
CAC in children and young adults

**Predictors of CAC**

- age
- dialysis duration
- serum P
- PTH
- hs-CRP
- Higher Ca intake from binders
Effects of vitamin D supplementation
Vitamin D supplements (Ergo/cholecalciferol) in pre-dialysis CKD

Intima Media Thickness

Vitamin D vs. No Vitamin D

*<0.008

Pulse Wave Velocity

Vitamin D vs. No Vitamin D

*<0.0001

Slide courtesy of Prof Schaefer
Ergocalciferol in CKD2-4 delays the onset of secondary hyperparathyroidism

Number at risk
Ergocalciferol: 20 20 19 17 16 12 9
Placebo: 20 20 15 13 12 8 5

25-hydroxyvitamin D (nmol/L)

- Baseline: p < 0.0001
- 3 months: p = 0.15
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Bimodal effect of 1,25 dihydroxy D
Association with FGF23

Wan and Shroff; NDT 2012
Progression of vascular disease
P levels determine progression of coronary calcification

Goodman et al; NEJM 2000

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>β</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final CACS</td>
<td>Final Ca×P product</td>
<td>0.880</td>
<td>0.736</td>
<td>0.004</td>
</tr>
<tr>
<td>CAC progression</td>
<td>Final albumin</td>
<td>-0.811</td>
<td>0.601</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Evolution of cIMT and PWV

IMT Progression within 1 Year of Follow-up

PWV Progression within 1 Year of Follow-up

Slide courtesy of Prof Schaefer
An arterial biopsy model

Shroff et al, Circulation 2008; JASN 2010; JASN 2013
Ca accumulation in vessels begins in pre-dialysis CKD

Histological changes in the vessels were only seen in dialysis patients

No inflammation

Shroff et al; Circulation 2008
Calcification is associated with Ca x P levels

Mean time-integrated Ca x P product (mMol²/L²)

Ca load in the vessel (µg/µL)

p = 0.007
r² = 0.41

pre-dialysis  n = 10
Dialysis      n = 24
Ca load correlates with carotid IMT

Pulse wave velocity
In 2 /31 patients

Coronary calcification on CT scan
In 2 /31 patients

Shroff et al; Circulation 2008

Ca load in the vessel (µg/µL)

Pre-dialysis n=9
Dialysis n=22

P=0.01
R²=0.42

0.0 0.3 0.4 0.5 0.6 0.7
Carotid Intima Media Thickness (mm)
Calcification progression is determined by vessel calcium load

**Associations with cIMT progression**
- Baseline vessel Ca load \( r = 0.47 \)
- Baseline 25-OH D level \( r = -0.22 \)
- Mean time-averaged P \( r = 0.61 \)
- \( \Delta \) PTH \( r = 0.17 \)
- \( \Delta \) Fetuin-A levels \( r = 0.11 \)

**No associations with**
- Serum calcium
- FGF-23 or s-klotho
- Osteoprotegerin

\[ p = 0.004 \]
\[ r = 0.47 \]
Conclusions – vascular studies

• Vascular changes begin in pre-dialysis CKD stage 3b (or earlier) and progress rapidly on dialysis

• Serum phosphate is associated with progression of vascular disease (cIMT and calcification)

• 4C and CKiD studies may soon provide markers of CVD progression
Bone disease in children with CKD

KDIGO 2009

We recommend that infants with CKD 2-5D have their lengths measured at least quarterly, while children with CKD 2-5D should be assessed for linear growth at least annually (1B)
Bone disease in PD patients

- High Ca*P
- Osteodystrophy
- Limb deformities
- Osteopenia
- Tissue calcification
- Bone pain

% patients

0 5 10 15 20 25

PTH (pg/ml)

0-100 100-200 200-300 300-500 500-1000 >1000

% patients with complications

0 10 20 30 40 50 60

IPPN Registry data - Borzych et al. Kidney Int 2010

n = 900 children on PD

- Longitudinal growth
- Clinical & radiological symptoms

Ca↑

Ca↓
## 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>198 ± 16</td>
<td>286 ± 38</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 = 39)</td>
<td>9.2 ± 0.2</td>
<td>6.2 ± 0.2</td>
<td>340 ± 31</td>
<td>587 ± 58</td>
</tr>
<tr>
<td></td>
<td>Abnormal (n = 53)</td>
<td>8.8 ± 0.1</td>
<td>6.5 ± 0.2</td>
<td>506 ± 39</td>
<td>924 ± 67</td>
</tr>
</tbody>
</table>

↓ serum calcium and ↑ PTH in patients with defective mineralization, irrespective of bone turnover.
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
Tibia QCT - ↓ Ca and ↑ PTH are associated with decline in cortical BMD

**Cross-sectional**  
- 171 patients, age 5-21 yrs  
- CKD 2-5D

<table>
<thead>
<tr>
<th></th>
<th>( \beta ) (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>

FGF23, underlying renal disease and acidosis were not significant.

**Longitudinal**  
- After 12 months  
- 89 patients

**Decline in cortical BMD Z-scores:**
- Higher baseline 1,25(OH)_2D  
- ↑ΔPTH

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

Lower cortical BMD – increased fracture risk (HR 1.75)

*Denburg, et al. JCEM 2013*
Limitations of DXA in CKD

- 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

- recommends against routine DXA BMD testing in CKD3-5
- BMD does not differentiate the type of renal osteodystrophy
- Whole body BMC Z-scores were correlated with pQCT cortical area Z-scores ($R = 0.77$, $p < 0.0001$) rather than cortical BMD.
- Greater linear growth was associated with greater increases in WB-BMC Z-scores ($p = 0.01$).
- Greater glucocorticoid exposure was associated with greater declines in WB-BMC Z-scores ($p < 0.001$).

Tsampalieros, et al; Am J Transplant 2013
Renal Transplant: Lumbar Spine DXA

Baseline age <13 yrs

Months Since Transplantation

Changes in LS-BMD correlated with changes in pQCT trabecular BMD (R = 0.47)

Decrease in LS-BMD
- ↓ PTH levels
- ↑ Steroid exposure

Tsampalieros, et al; Am J Transplant 2013
Conclusions – bone studies

- Abnormal bone mineralisation occurs early (CKD2) and is associated with low serum calcium and high PTH.

- Non-invasive assessment by qCT and DXA may be useful tools in evaluating children with CKD.
In the context of paediatric CKD-MBD

Do we need new guidelines? ✓
Do we need to change existing recommendations / grading of existing recommendations? ✓

Separate paediatric guidelines or
More precisely address paediatric management within any new guidelines?