Renal bone disease in pediatrics

Justine Bacchetta, MD, PhD

Reference Center for Rare Diseases of Calcium and Phosphate Metabolism
Reference Center for Rare Renal Diseases, Lyon, France
Disclosures

- **Consultancy and speaker**
  - Kyowa Kirin
  - Amgen
  - Pfizer
  - Alexion
  - Bayer
  - Lilly
  - Vifor

- **Research grants**
  - Kyowa Kirin
  - Amgen
  - Horizon
  - Novartis
  - Crinex

- **Travel grants**
  - Kyowa Kirin
Outline of the talk

• Epidemiology of bone disease in pediatric CKD

• Evaluating bone «quality» and «quantity» in clinical practice and research in children with CKD

• Renal osteodystrophy: the tip of the iceberg for CKD-MBD and cardiovascular comorbidities

• Management of CKD-MBD in pediatric CKD

• Genetic renal diseases and specific bone impairment
Calcium and phosphate metabolism: everything is modified by CKD!

Consequences on bone and vessels
Bone and mineral disorders
CKD-MBD

Stimulating effect / Inhibiting effect

Adapted from Bacchetta, EMC 2015
Renal osteodystrophy: only a component of CKD-MBD

Hypocalcemia
Hyperphosphatemia
HyperPTH
Decreased 1-25 D
Prurit
Skin necrosis
Keratitis
Corneal calcifications

GFR < 60 mL/min per 1.73 m²

Renal osteodystrophy
Growth retardation
GH resistance
Proximal myopathy
Vascular calcifications
Two main challenges for pediatric nephrologists...
At least in the field of CKD-MBD!

Cardiovascular disease

Growth retardation and fracture risk
Epidemiology of bone disease in pediatric CKD
Bone disease in CKD children

N=249 young adults with ESRD between 0 and 14 years, born before 1979

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total cohort</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 et al., Kidney International 2003*
Fracture risk in CKD children

- CKiD cohort, 537 CKD children
- Median age at baseline 11 years, 16% past of fracture
- Median follow-up 3.9 years, 43 boys and 24 girls with fracture
- Fracture risk: 2 to 3 fold higher than in general populations (113/10000 persons/year)

Figure 1. Final multivariable Cox regression model: correlates of incident fracture.
\(^{a}\)HR for males \(\geq 15\) years versus females \(\geq 15\) years = (3.94 \(\times 0.67\)) = 2.6. \(^{b}\)PTH natural log transformed.
Causes of bone impairment in pediatric CKD

- **The factors we cannot control**
  - Growth failure, impaired GH-IGF1 axis
  - Muscle deficits
  - Hypogonadism / delayed puberty
  - Long-term use of corticosteroids and other drugs
  - Underlying renal disease (oxalosis, cystinosis, etc)

- **The factors we can control (at least try!)**
  - Acidosis
  - Inflammation
  - Vitamin D deficiency
  - Hyperparathyroidism
  - Inadequate intake of calories and proteins / nutrition
  - Long-term use of corticosteroids => sparing strategies
Drugs inducing bone toxicity

- **Calcineurin inhibitors**
  - Increased RANKL expression
  - Activation of osteoclastic activity
  - VDR inhibition

- **mTor inhibitors**
  - Animal models +++, clinical data
  - Impaired growth
  - Direct toxicity on growth plate

- **Anti-epileptic drugs**
  - Secondary rickets

- **Anti-acid drugs**
  - Hypophosphatemia
  - Impaired mineralization

- **Long-term use of heparin**

- **This list is not exhaustive!**

Alvarez-Garcia, Kidney 2010
Gonzalez, Ped Neph 2011
Hofbauer, 2001
Fukunaga 2004
Lee, Am J Nephrol 2011
Acidosis and bone metabolism

- Stimulation of osteoclastic differentiation
- Stimulation of osteoclastic resorption

Kato, BioScience Trends 2013c

Acidosis and bone metabolism

- Inhibition of osteoblastic differentiation

Resorption activity depending on pH

Harambat Kidney Int 2017

Bicar<22 as a risk factor for CKD progression in the 4C cohort

Kraut, Kidney International 1986
Kato, BioScience Trends 2013c

ALP staining
Evaluating bone « quality » and « quantity » in clinical practice and research in children with CKD
How to evaluate CKD-MBD in pediatric CKD in daily practice?

- **Growth / nutrition**
- **Biomarkers**
  - Calcium, phosphate
  - PTH, 25OH-D
  - ALP
- **Bone imaging**
  - Wrist X-ray?
  - Targeted X-ray?
  - Dual X-ray absorptiometry: DXA?
- **Cardio-vascular evaluation**
  - BP, Ambulatory BP monitoring
  - Cardiac US
- **Research tools**
  - FGF23, sclerostin, other bone biomarkers
  - Bone MRI, pQCT, HR-pQCT, US...
  - Bone biopsy
  - Carotid IMT, PWV
The child with CKD also has a growing skeleton!

Children: Ca balance = positive for skeletal accrual

Mean daily calcium accretion rate in healthy pubertal boys and girls: 359 and 284 mg

Importance of dietary assessment, DRI depending on age

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.
KDIGO 2009/2017: one **CRUCIAL** point to keep in mind for the evaluation of CKD-MBD

It is recommended that therapeutic decisions are based on trends rather than on a single laboratory value, taking into account all available CKD-MBD measurements

<table>
<thead>
<tr>
<th>14-year old boy</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD CAKUT</td>
<td>Calcium (mmol/L)</td>
<td>2.29</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>Phosphorus (mmol/L)</td>
<td>1.56 2.15</td>
<td>1.67 2.03</td>
</tr>
<tr>
<td></td>
<td>25 OH (nmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTH (15-65 pg/mL)</td>
<td>500</td>
<td>688</td>
</tr>
<tr>
<td></td>
<td>PTH (pg/mL)</td>
<td>1200</td>
<td>920</td>
</tr>
</tbody>
</table>
Simple biomarkers: reference values for phosphate must be adapted to age +++

=> Z-score of phosphate depending on age ++++

Ardeshirpour Pediatr Endocrinol Rev 2007
Changes of biomarkers with declining renal function

Chang HU, NDT 2012
Pavik, NDT 2012
PTH levels depend on geography!
### PTH levels can be completely different depending on the assay

<table>
<thead>
<tr>
<th>Name of assay</th>
<th>Generation</th>
<th>Reference value</th>
<th>PTH (ng/L)</th>
<th>PTH (ng/L)</th>
<th>PTH (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegro Intact PTH</td>
<td>2(^{nd})</td>
<td>10-65</td>
<td>150</td>
<td>300</td>
<td>1000</td>
</tr>
<tr>
<td>N-Tact PTH IRMA</td>
<td>2(^{nd})</td>
<td>13-54</td>
<td>83</td>
<td>160</td>
<td>517</td>
</tr>
<tr>
<td>DSL PTH IRMA</td>
<td>2(^{nd})</td>
<td>9-55</td>
<td>323</td>
<td>638</td>
<td>2108</td>
</tr>
<tr>
<td>Ca-PTH IRMA</td>
<td>3(^{rd})</td>
<td>5-39</td>
<td>84</td>
<td>165</td>
<td>543</td>
</tr>
<tr>
<td>Biointact PTH advantage</td>
<td>3(^{rd})</td>
<td>8-50</td>
<td>109</td>
<td>214</td>
<td>704</td>
</tr>
</tbody>
</table>
PTH levels: different guidelines... different targets...

- **K-DOQI 2005**
  - PTH 3-5 times above the upper normal limit: \(200-300\) pg/mL

- **European guidelines 2006**
  - European Pediatric Dialysis Working Group
  - Keep PTH levels within 2-3 times the upper normal limit: \(120-180\) pg/mL

- **K-DIGO 2017**
  - PTH 2-9 times above the upper normal limit: \(120-540\) pg/mL

- **Limited clinical evidence**
- Data from IPNN in PD: optimal range 1.7-3 times above the upper normal limit: \(100-200\) pg/mL

_Haffner Pediatr Nephrol 2013_
High PTH levels are associated with...

- Longitudinal growth (>500 pg/mL)
- Vascular calcifications
- Anemia
- Left ventricular hypertrophy
- Cardiovascular disease
- Mortality

- Data from the IPPN registry
  - More than 1800 children
  - 87 centers
  - 31 countries
Pediatric renal osteodystrophy and PTH levels

Adynamic bone
« Low PTH state »
Mainly due to vitamin D analogs and calcium salts
Growth retardation +++
Calcifications +++
Fractures +++

Osteitis fibrosa
« High PTH state »

Growth retardation +
Calcifications +++

Salusky and Kuizon, 2004
Patients with adynamic bone disease clearly have lower PTH levels than those with SHPT/OF...

- « Old study » from UCLA
- 55 patients in PD
- 68 BB
- 13±5 years
- IP high doses vitD analogs

- To predict adynamic bone disease
- PTH < 200 pg/mL
  - Sensibility 100%
  - Specificity 79%
- PTH < 150 pg/mL AND Ca > 2.5 mmol/L
  - Sensibility 100%
  - Specificity 92%

Salusky Kidney Int 1994

Moe et al, Kidney International 2006
...But PTH alone is not a good predictor of the underlying renal osteodystrophy

- The combined use of total ALP and PTH levels may improve our ability to detect the underlying type of renal osteodystrophy

- Cohort of 161 pediatric patients
- Maintenance peritoneal dialysis

**PTH levels < 400 pg/mL + total ALP levels < 400 IU/L**

The highest correct prediction rate for **Normal bone turnover and normal mineralization**

- Levels of PTH were higher and serum calcium levels were lower in patients with defective mineralization, irrespective of bone turnover

Renal osteodystrophy in pediatric nephrology

- 52 US pediatric patients with CKD
  - Range 2 to 21 years
- Early onset of mineralization abnormalities despite normal Ca and phosphate levels
- Late onset of turnover abnormalities
- Preserved bone volume
  - FGF23
  - Then PTH
  - Then phosphate

Wesseling-Perry et al, cJASN 2012
SHPT is a predictor of cortical impairment using 3D non-invasive bone imaging techniques

- **156 CKD II-III children**
  - 69 II-III: 42 (2-521) pg/mL for PTH
  - 51 IV-V: 140 (8 to 770) pg/mL
  - 36 dialysis: 267 (10 to 1139) pg/mL
  - Aged 5-21 years

- **831 healthy controls**
- **Tibia pQCT**

- **SHPT associated with**
  - Significant reduction in cortical vBMD and area
  - Increased cortical porosity
  - **Greater trabecular vBMD in younger participants**: anabolic effect of PTH?
pQCT as a predictor of the risk of fracture

- 171 patients aged 5-21 years with CKD stage 2-5D at enrollment
- 89 patients one year later
- Tibia pQCT

- **Predictors of Cortical vBMD Z-scores at baseline**
  - Lower calcium
  - Lower 25-D
  - **Higher PTH**
  - Higher 1-25 D
  - Independently associated with lower cortical vBMD at baseline

- **Cortical vBMD Z-score at baseline: associated with increased fracture risk during follow-up**
  - Hazard ratio for fracture 1.75 (95%CI: 1.15-2.67, p=0.009) per SD lower baseline cortical vBMD
  - Similar results than in adults with DXA...
The gold standard: bone biopsy at the iliac crest

‘Standard’ histomorphometry
Immuno-chemistry
Micro-radiography

FTIRM  *Fourier Transform InfraRed Microspectroscopy*
ERKNet poll during a Webinar, September 2018

Do you perform BB in the CKD children followed in your centre?

• Yes => 0%

• No=> 100%
Renal osteodystrophy: the tip of the iceberg for CKD-MBD and cardiovascular comorbidities
Our main challenge: cardiovascular disease as the leading cause of mortality in CKD

Our main challenge: cardiovascular disease as the leading cause of mortality in CKD children.

Figure 1. Leading causes of death in general pediatric population and in children on renal replacement therapy. Data are presented as percentages. Data for dialysis and transplant patients are from the USRDS (2011). Data for general pediatric population are from Mathews et al. (2011).
CKD-MBD
A balance between bone and vessels

Renal osteodystrophy
Fracture risk
Growth retardation
Bone pains and deformations

Growing skeleton
The better the bone
The worse the vessels

Cardiovascular disease
Vascular calcifications
Cardio-vascular morbi-mortality

Adults
The better the bone
The better the vessels

Ziolkowska, Ped Nephrology 2008; Preka Pediatr Nephrol 2018
Cejka, Bone 2014 / Malluche JASN 2015
What should be the exquisite balance of calcium in pediatric CKD?

- Not giving enough calcium supplements may be deleterious for bone in pediatric CKD
- **Histomorphometry:** defective skeletal mineralization associated with lower calcium levels.
- **Histomorphometry:** 160 children on PD; serum calcium concentrations inversely related to mineralization (but not turnover)
- **Tibial pQCT:** lower calcium levels independently associated with baseline and progressive cortical deficits
- **Recent data from CKiD:** phosphate binder treatment (predominantly calcium-based) associated with a significant lower fracture risk
- All these data thus provide a strong rationale for giving calcium supplementation in pediatric CKD, at least for bone quality and quantity.

- Giving too much calcium supplements may also be deleterious for vessels
- Meta-analysis in adults: increased mortality risk with calcium-based phosphate binders
- Pediatric data are scarce

Management of CKD-MBD in pediatric CKD
25 OH vitamin D supplementation
Target 75–120 nmol/L

End-stage renal disease

Decreased urinary excretion of phosphorus

Hyperphosphatemia

Hyperparathyroidism

Decreased tubular vitamin D 1-hydroxylation

Decreased intestinal absorption of calcium

Hypocalcemia

Decreased phosphate intake
Phosphate binders

Dialysis intensification

Vitamin D analogs
Calcimimetics
Parathyroidectomy

Calcium nutritional intake/
Calcium supplementation / Calcium in the dialysate

Vitamin D analogs

rhGH

Bacchetta CTI 2020
Increased phosphate intake

End-stage renal disease

Decreased urinary excretion of phosphorus

Hyperphosphatemia

Hyperparathyroidism

Decreased tubular vitamin D 1-hydroxylation

Decreased intestinal absorption of calcium

Hypocalcemia

Vitamin D analogs
ESPN 2017

25 OH vitamin D supplementation
ESPN 2017

Nutritional task force 2020

Calcimimetics
ESPN 2019

rhGH
ESPN 2019

Calcium nutritional intake/ Calcium supplementation / Calcium in the dialysate
Nutritional task force 2020
For clinical practice in children: the philosophy of the 2006 European guidelines remains interesting

- **R1:** follow-up
- **R2:** acidosis correction
  - Nutrition
  - Dialysis intensification
  - Sodium bicarbonate / citrate
- **R3:** phosphate control
  - Target depending on age +++
  - As soon as GFR < 40 mL/min/1.73 m²
  - Cardiovascular risk factor
- **R4:** first nutrition for phosphate control
- **R5:** then dialysis intensification
- **R6:** and last aluminum-free binders
  - Calcium-based first
  - If hyperCa: non Ca non Al binders: *the role of the new ferric citrate to concomitantly decrease phosphate and treat iron deficiency deserves further studies*

Klaus, Ped Nephrol 2006, European guidelines; Hanunel Ped Neph 2018
It is crucial to assess nutritional calcium and phosphate intake in pediatric CKD-MBD: enough calcium and not too much phosphate...

Table 7  Summary of SDI (suggested dietary intake) for calcium and phosphate in children with CKD2-5D

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>SDI calcium (mg)</th>
<th>SDI phosphate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–&lt; 4 months</td>
<td>220</td>
<td>120</td>
</tr>
<tr>
<td>4–&lt; 12 months</td>
<td>330–540</td>
<td>275–420</td>
</tr>
<tr>
<td>1–3 years</td>
<td>450–700</td>
<td>250–500</td>
</tr>
<tr>
<td>4–10 years</td>
<td>700–1000</td>
<td>440–800</td>
</tr>
<tr>
<td>11–17 years</td>
<td>900–1300</td>
<td>640–1250</td>
</tr>
</tbody>
</table>

For children with poor growth, reference to the SDI for height age may be appropriate. This is the age that corresponds to their height when plotted at the 50th centile on a growth chart.
Focus on phosphate: beware of hidden phosphates in the diet, and particularly in food additives

<table>
<thead>
<tr>
<th>Name of additive</th>
<th>Food where the additive can be found</th>
<th>Function of the additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthophosphoric acid (E338)</td>
<td>Cola</td>
<td>Acidification</td>
</tr>
<tr>
<td>Sodium orthophosphate (E339)</td>
<td>Pizza, food preparation as « preparation bags» for desserts</td>
<td>Anti-oxidation, acidification, texture</td>
</tr>
<tr>
<td>Potassium orthophosphate (E 340)</td>
<td>Cappuccino, soja drink, dessert cream</td>
<td>Acidification regulation, texture, water retention</td>
</tr>
<tr>
<td>Calcium orthophosphate (E 341)</td>
<td>Dairy products</td>
<td>Anti-oxidation, stabilization, firming agent</td>
</tr>
<tr>
<td>Magnesium orthophosphate (E 343)</td>
<td>Butter, ice cream, breakfast cereals, appetizers</td>
<td>Anti-oxidation, anti-agglomeration, thickening agent, emulsifier</td>
</tr>
<tr>
<td>Diphosphate (E 450)</td>
<td>Soft cheese</td>
<td>Modification of the repartition between fat and proteins in the cheese</td>
</tr>
<tr>
<td>Triphosphate (E 451)</td>
<td>Chocolate powder</td>
<td>Water retention</td>
</tr>
<tr>
<td>Polyphosphate (E 452)</td>
<td>Ham</td>
<td>Emulsifier, binding agent, modified starch</td>
</tr>
<tr>
<td>Other food additives containing phosphate: E 442, E 626–635, E 101, E 1410, E 1412, E 1413, E 1414, E 1415 and E 541</td>
<td>Cacao and chocolate desserts/chocolate-based sweets</td>
<td></td>
</tr>
</tbody>
</table>
Focus on phosphate: beware of hidden phosphates in the diet

<table>
<thead>
<tr>
<th>Food</th>
<th>Portion (g)</th>
<th>Phosphate quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaufort, Parmesan, dry goat cheese</td>
<td>30</td>
<td>240</td>
</tr>
<tr>
<td>Cheese with cooked pressed dough</td>
<td>30</td>
<td>192</td>
</tr>
<tr>
<td>Gouda, Edam, Morbier</td>
<td>30</td>
<td>156</td>
</tr>
<tr>
<td>Comté, Mimolette</td>
<td>30</td>
<td>204</td>
</tr>
<tr>
<td>Soft cheese (Camembert)</td>
<td>30</td>
<td>132</td>
</tr>
<tr>
<td>Soft cheese (St Marcellin ou St Félicien)</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>Fresh goat cheese</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>Cream cheese (Petit suisse)</td>
<td>100</td>
<td>126</td>
</tr>
<tr>
<td>Yogurt</td>
<td>125</td>
<td>115</td>
</tr>
<tr>
<td>Cooked fish</td>
<td>100</td>
<td>226</td>
</tr>
<tr>
<td>Cooked chicken</td>
<td>100</td>
<td>223</td>
</tr>
<tr>
<td>Cooked meat</td>
<td>100</td>
<td>213</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>212</td>
</tr>
<tr>
<td>Egg</td>
<td>100 = 2 œufs</td>
<td>204</td>
</tr>
<tr>
<td>Crustaceans</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Pulses and legumes (cooked)</td>
<td>100</td>
<td>140</td>
</tr>
<tr>
<td>Muesli</td>
<td>50</td>
<td>157</td>
</tr>
<tr>
<td>Brazil nuts</td>
<td>30 g = a handful</td>
<td>197</td>
</tr>
<tr>
<td>Walnuts, cashews, almond</td>
<td>20 g = a handful</td>
<td>90</td>
</tr>
<tr>
<td>Hazelnut, Pecan nut</td>
<td>20 = a handful</td>
<td>54</td>
</tr>
<tr>
<td>Nut spread</td>
<td>15 = a tea spoon</td>
<td>28</td>
</tr>
<tr>
<td>Chocolate (milk or dark)</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Cola</td>
<td>200 mL = a glass</td>
<td>20</td>
</tr>
</tbody>
</table>
For clinical practice in children: the philosophy of the 2006 European guidelines remains interesting

- **R7**: avoid 25-D deficiency (outdated by the 2017 guidelines)

- **R8**: avoid hyperPTH
  - Active vit D analogs (outdated by the 2017 guidelines)

- **R9**: PTH target: 2-3 upper normal limit in ESRD

- **R10**: if increased PTH levels and phosphate < 2 mmol/L
  - Active vit D analogs
  - Very few data for calcimimetics (in the mean time 2017 European approval by EMA for cinacalcet in pediatric dialysis)
  - => outdated by the 2019 guidelines

*Klaus, Ped Nephrol 2006, European guidelines*
For clinical practice in children: the philosophy of the 2006 European guidelines remains interesting

- **R11: no rhGH in case of severe hyperparathyroidism**
  - Before rhGH: nutrition and acidosis correction $\Rightarrow$ outdated by the 2019 guidelines

- **R12: in case of hyperCa**
  - Stop vit D analogs
  - Stop Ca-based binders
  - Decrease the calcium concentration in the dialysate

- **R13: PxCa product**
  - To keep it below $5 \text{mmol}^2/L^2$ $\Rightarrow$ outdated

- **R14: parathyroidectomy**
  - Rarely performed
KDIGO2017: what has changed?

- Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium
  - Suggested to lower elevated phosphate levels toward the normal range
  - Suggested to maintain serum calcium in the age-appropriated normal range
  - In adults suggested to restrict the dose of Ca-based binders
  - In children reasonable to base the choice of phosphate-lowering treatments on serum calcium levels
  - Suggested to limit dietary phosphate intake and to consider phosphate source (e.g., animal, vegetal and additives) to make dietary recommendations
rhGH therapy improves mineralization, whatever the type of the underlying osteodystrophy

- **Study from USA**
  - Randomized trial: 33 children, PD
  - Low Turnover LTO, n= 14, rhGH or nothing
  - High Turnover HTO, n= 19, GH + calcitriol IP or calcitriol IP
  - rhGH for 8 months

- **Study from Austria and Poland**
  - 18 children, hemodialysis
  - rhGH for one-year
  - Paired analysis before/after
  - Baseline: high prevalence of low bone turnover

---

*Bacchetta, cJASN, 2013*

*Nawrot-Wawrzyniak, AJKD 2013*
The 2019 European consensus paper on the use of cinacalcet in children above 3 years undergoing hemodialysis: only if calcium is above 2.40 mmol/L (9.6 mg/dL)

<table>
<thead>
<tr>
<th>In a child &gt;3 years of age</th>
<th>Requirements before initiating cinacalcet therapy</th>
<th>Titration phase</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameters</td>
<td>Optimization of conventional management of CKD-MBD</td>
<td>Evaluation of potential side effects at every visit</td>
<td>Evaluation of potential side effects at every visit</td>
</tr>
<tr>
<td></td>
<td>Evaluation of calcium intake from diet, medications and dialysate Calculation of QTc interval</td>
<td>Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects Evaluation of calcium intake from diet, medications and dialysate</td>
<td>Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects Evaluation of calcium intake from diet, medications and dialysate</td>
</tr>
<tr>
<td></td>
<td>Evaluation of comorbidities of interest (seizures, cardiac arrhythmia, liver disease) Explanation to parents Calcium level ≥2.40 mmol/L</td>
<td>Realization of an ECG in case of hypocalcaemia</td>
<td>Realization of an ECG in case of hypocalcaemia; if ECG performed for another reason and increased QTc interval, cinacalcet withdrawal</td>
</tr>
<tr>
<td>Biological parameters</td>
<td>Weekly evaluation of calcium and phosphate levels</td>
<td>Cinacalcet withdrawal if calcium levels &lt;2 mmol/L</td>
<td>At least monthly evaluation of calcium and phosphate levels, target range for calcium within the normal range for age and in any case &gt;2.2 mmol/L Cinacalcet withdrawal if calcium levels &lt;2 mmol/L and decrease/wrathall if calcium levels between 2 and 2.2 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Weekly evaluation of PTH levels, 12–24 h after cinacalcet administration</td>
<td>Cinacalcet withdrawal if PTH levels &lt;100 pg/mL</td>
<td>At least monthly evaluation of PTH levels, 12–24 h after cinacalcet administration, target range 100–200 pg/mL Cinacalcet withdrawal if PTH levels &lt;100 pg/mL</td>
</tr>
<tr>
<td>Therapeutic parameters</td>
<td>Verification of concomitant therapies that can interfere with cinacalcet</td>
<td>Starting dose of ≤0.2 mg/kg/day, increments by 0.2 mg/kg/day to a maximum of 2.5 mg/kg/day. Dose titration intervals should be at least 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Bacchetta et al, NDT 2019
Concomitant drugs that are contra-indicated with cinacalcet

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example of drug that is contra-indicated in association with cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential to increase QTc</td>
<td>Ondansetron</td>
</tr>
<tr>
<td></td>
<td>Albuterol</td>
</tr>
<tr>
<td></td>
<td>Salbutamol</td>
</tr>
<tr>
<td>Inhibitors of CYP3A4</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
</tr>
<tr>
<td></td>
<td>Flecanide</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Inhibitors of CYP2D6</td>
<td></td>
</tr>
</tbody>
</table>

This list is not exhaustive: before prescribing cinacalcet or new therapies to patients already receiving cinacalcet, physicians in charge of the patients are responsible for checking the potential interferences and contra-indications.

Risk of increased QT interval

Bacchetta et al, NDT 2019
Perspectives: low doses of D-analogs and low doses of calcimimetics?

• In line with the KDIGO 2017 in adults
• Experimental evidence

Direct anabolic effects of calcimimetics on osteoblasts
- Promotion of differentiation and mineralization in human mesenchymal stem cells
- Increased osteoblast number and bone formation in normal and uremic rats

Direct effects of calcimimetics on osteoclasts
- Moderate inhibition of osteoclastic differentiation (in a lesser extent than 1-25-D)
- Inhibition of bone resorption activity

No synergistic effect when co-treating human PBMCs/OCs with both 1.25-D and KP2326
- Use of decreased doses of 1.25-D with low-doses of calcimimetics could control SHPT
- Without substantially affecting osteoclastogenesis
- And therefore decreasing the risk of adynamic osteodystrophy?

Obviously we need more experimental and clinical data to support this hypothesis

Bernardor and Bacchetta, submitted; Diaz-Tocados and al. Kidney Int, 2019
Genetic renal diseases and specific bone impairment
Primary hyperoxaluria 1 and bone: oxalate osteopathy
Nephropathic cystinosis and bone

• **Clinical signs => 70% of patients!**
  - Pathological fractures
  - Bone pains
  - Deformities
  - Teenage/young adult

• **Unknown pathophysiology: 6 hypotheses**
  - Copper deficiency
  - Bone consequences of severe hypophosphatemic rickets during infancy
  - Cysteamine toxicity
  - Abnormal thyroid metabolism
  - Role of chronic hypoparathyroidism?
  - Direct effect of CTNS mutation on bone cells
The concept of CMBD: cystinosis bone disease 2019 international guidelines

**1- Renal Fanconi syndrome**
- resulting in rickets due to
  - Hypophosphatemia
  - Metabolic acidosis
  - 1,25-D deficiency
  - Hypocalcemia

**2- Deficiency in nutrition and micronutrition**
- Malnutrition
- Copper deficiency

**3- Hormonal disturbances**
- Hypothyroidism
- Hypogonadism
- Hypoparathyroidism
- GH and IGF1 resistance

**4- Myopathy**

**Cystinosis metabolic bone disease (CMBD)**
- Short stature
- Osteomalacia
- Bone deformities
- Bone pain
- Osteoporosis

**Children:**
- Rickets

**Adults:**
- Long bone fractures
- Incidental vertebral fractures
- Scoliosis
- Low bone mass
- Cortical impairment

**5- Intrinsic and treatment associated bone lesions**
- Intrinsic osteoblast/osteoclast defect due to CTNS mutation
- Cysteamine toxicity

**6- Mineral and bone disorders due to CKD (CKD=MBD)**
- Hyperphosphatemia
- Secondary hyperparathyroidism
- 1,25-D deficiency
- Hypocalcemia
- 25OH-D deficiency

**7- CKD=MBD post transplantation**
- Glucocorticoid and CNI treatment
- Hypophosphatemia due to persistent Fanconi syndrome
- Mineral and bone disorders related to transplant dysfunction

**FIGURE 4** Current understanding of the abnormalities leading to cystinosis metabolic bone disease (CMBD). Virtually all individuals with classical, nephropathic cystinosis suffer from CMBD, related to the renal Fanconi syndrome in infancy and progressive chronic kidney disease (CKD) later in life inducing CKD-associated mineral and bone disorders (CKD-MBD). Malnutrition and copper deficiency, but also hormonal disturbances, myopathy, and transplantation may worsen the clinical picture. The cystinosin defect also induces intrinsic bone defects such as osteoblastic and osteoclastic dysfunction. The impact of cysteamine on bone deserves further studies, but high doses of cysteamine may contribute to CMBD. Taken together, all these mechanisms can lead to bone deformities and pains, osteoporosis, fractures, cortical impairment, and short stature in teenagers and young adults.

Hohenfellner, J Inherit Metab Dis 2019
# 2019 International Guidelines for CMBD: Evaluation

**Table 2: Recommended Tests for CMBD**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Methods and frequency</th>
</tr>
</thead>
</table>
| Growth           | - Calculate genetic target height based on parental height  
|                  | - Plot height/length and weight on growth charts in infants (monthly) and preschool children (3 monthly) and older children (6 monthly)  
|                  | - Calculate annual height velocity  
|                  | - Measure head circumference every 3 months in infants and small children  
| Bone metabolism  | - Measure serum iPTH, calcium, phosphate, ALP, and bicarbonate levels every 1 to 6 months depending on the clinical status and CKD stage  
|                  | - Consider iliac crest bone biopsies, with tetracycline labeling in cases of unclear severe bone disorder  
| Bone deformities | - Check for rickets and scoliosis by physical examination and/or radiographs (e.g., X-ray of the knees and/or the wrist), with regular follow-up  
| Growth hormone   | - Evaluate IGF-1 serum levels prior to starting treatment with GH to rule out GH deficiency  
|                  | - Obtain X-ray of the left wrist in children aged >5 years to assess bone age and prove growth potential (i.e., open epiphyses) prior to initiation of GH treatment  
| Thyroid function | - Check TSH and thyroxine levels annually, more frequently if following treatment  
|                  | - Perform ultrasound of the thyroid to exclude other thyroid disease  
| Gonadal function | - For male patients at pubertal age: monitor levels of FSH, LH, testosterone, inhibin B, and prolactin annually after age 14 years  
|                  | - For female patients at pubertal age (14 years): determine first menstrual cycle and monitor levels of FSH, LH, estradiol, anti-mullerian hormone, and prolactin annually  
| Muscle function  | - Obtain mechanographic testing, for example, grip strength  
| Other            | - WBC cystine levels to assess disease control  

Abbreviations: ALP, alkaline phosphatase; CKD, chronic kidney disease; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; iPTH, intact serum parathyroid hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

*Hohenfellner, J Inherit Metab Dis 2019*
### 2019 international guidelines for CMBD: management

#### TABLE 3  Treatment of CMBD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| **Phosphate**                 | • Starting dose of 30–40 mg/kg/d based on elemental phosphorus in 3 to 5 doses equally spaced throughout the day  
• Treatment needs to be individualized in order to control rickets and a wider range of 20-80 mg/kg/d may be used. Minimal effective dosage should be used  
• Dosage should be adjusted to the stage of CKD |
| **Citrate/bicarbonate**       | • Treat acidosis with alkali (citrate or bicarbonate) administered 3-4 times daily  
• Aim to return bicarbonate levels to normal levels (22-25 mEq/L);  
• Levels >20 mEq/L may not be achieved in all patients |
| **Calcium/active and native vitamin D** | • Starting dose of calcitriol or alfalcacidol 0.1 to 0.75 µg depending on patient size and severity of rickets  
• Maintain at lowest possible dose to successfully treat rickets and keep PTH in the CKD stage-dependent target range (see below)  
• Supplementation with native vitamin D (eg, cholecalciferol) if 25 OH vitamin-D levels are reduced  
• Oral calcium supplements in case of persistent hypocalcemia based on albumin corrected calcium levels |
| **GH**                        | • Indication: height below the 3rd percentile and height velocity below the 25th percentile in the presence of open epiphyses  
• Dosage: 0.045 to 0.05 mg/kg body weight per day by subcutaneous injections in the evening  
• Calcium, phosphorus, PTH, fasting glucose, and HbA1c levels should be monitored.  
• GH treatment should generally be stopped after kidney transplantation and may be reinstituted in case of persistent growth failure at least 12 months after transplantation. |
| **Parathyroid levels**        | • For CKD stages 1 to 2, maintain PTH levels within the normal range  
• For CKD stages 3 to 5, maintain PTH levels as recommended for other renal diseases by dietary measures, active/native vitamin D, calcimimetics, and/or oral phosphate binders |
| **Sex hormone replacement therapy** | • Per pediatric endocrinologist, for pubertas tarda and hypergonadotrophic hypogonadism  
• Testosterone patch or intramuscular |
| **L-Thyroxine**               | • In case of hypothyroidism to normalize free T4 and TSH |
| **Cysteamine**                | • Ensure optimal dose adjustment and control of cystinosis |

Abbreviations: CKD, chronic kidney disease; GH, growth hormone; HbA1c, glycated hemoglobin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
The ‘amazing OSTEOCYTE’, a key player in bone physiology

Sclerostin synthesis
Osteoblastic inhibition

RANK-L synthesis
Osteoclastic activation
Sclerostin as an inhibitor of the Wnt signaling

Baron, Nature Medicine 2013
Table 1 | Demographics and parameters of mineral metabolism in ESRD patients with and without ADPKD

<table>
<thead>
<tr>
<th>Demographics and laboratory parameters</th>
<th>ADPKD (n = 99)</th>
<th>Non-ADPKD (n = 419)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56.9 ± 8.8</td>
<td>54.2 ± 13.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>49.5</td>
<td>63.3</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7 ± 4.0</td>
<td>24.9 ± 4.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Dialysis vintage (M)</td>
<td>31.8 (17.0–42.3)</td>
<td>31.8 (18.6–50.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Renal diagnosis, %</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>0</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis/vasculitis</td>
<td>0</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Hypertensive/large vessel disease</td>
<td>0</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Cystic/hereditary/congenital diseases</td>
<td>100</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Etiology unknown or missing</td>
<td>0</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.1</td>
<td>21.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>CVD, %</td>
<td>27.3</td>
<td>42.3</td>
<td>0.005</td>
</tr>
<tr>
<td>PTX, %</td>
<td>7.1</td>
<td>14.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Fracture, %</td>
<td>6.1</td>
<td>5.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcium, mg/dl</td>
<td>9.2 ± 0.6</td>
<td>9.2 ± 0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
<td>4.7 ± 1.5</td>
<td>4.4 ± 1.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Magnesium, mg/dl</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>bPiTH, ng/l</td>
<td>133.8 (69.1–220.9)</td>
<td>121.7 (66.4–236.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>25(OH)D3, ng/l</td>
<td>37.7 (25.1–49.2)</td>
<td>35.5 (23.6–48.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>1,25(OH)D3, ng/ml</td>
<td>22.3 (20.2–34.1)</td>
<td>26.7 (17.9–32.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>FGF23, ng/l</td>
<td>3323 (1083–9548)</td>
<td>2040 (606–7573)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sclerostin, ng/ml</td>
<td>2.20 (1.68–3.16)</td>
<td>1.84 (1.28–2.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>OPG, pmol/l</td>
<td>9.97 (8.0–12.3)</td>
<td>10.2 (7.3–14.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>sRANKL, pmol/l</td>
<td>0.075 (0.063–0.14)</td>
<td>0.097 (0.063–0.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>sRANKL/OPG</td>
<td>0.009 (0.006–0.016)</td>
<td>0.010 (0.005–0.021)</td>
<td>0.2</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>3.60 (1.50–8.30)</td>
<td>3.30 (1.30–7.50)</td>
<td>0.6</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>1.71 (0.87–2.77)</td>
<td>1.35 (0.63–2.37)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>tAR × UN</td>
<td>0.27 (0.02–0.56)</td>
<td>0.28 (0.06–1.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>BSAP, ng/ml</td>
<td>17.4 (13.2–27.0)</td>
<td>22.6 (16.1–35.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH, ng/ml</td>
<td>77.5 (49.8–117.1)</td>
<td>83.6 (35.7–147.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>TRAP5b, U/l</td>
<td>4.65 (3.13–6.57)</td>
<td>5.46 (3.84–7.59)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

ADPKD, autosomal-dominant polycystic kidney disease; BMI, body mass index; bPiTH, bihibiki parathyroid hormone; BSAP, bone-specific alkaline phosphatase; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; IL-6, interleukin-6; OPG, osteoprotegerin; PTH, parathyroid hormone; sRANKL, soluble receptor activator of nuclear factor-κB ligand; TRAP5b, tetratrate-resistant acid phosphatase 5b.
ADPKD and new insights into the pathophysiology of CKD-MBD

ADPKD: PC1 and/or PC2 defect: abnormal primary cilia also in osteocytes and osteoblasts

Early stages of CKD
Low bone turnover and osteopenia, probably as a consequence of increased SOST

ESRD
ADPKD mitigates BMD loss induced by SHPT by suppressing bone turnover
Suppressed bone turnover
Preserved cortical BMD
High SOST and FGF23 levels, low bAP levels
Ciliopathies associated with skeletal developmental defects

Table 1 | Ciliopathies associated with skeletal developmental defects

- Alstrom syndrome
- Jeune asphyxiating thoracic dystrophy
- Bardet-Biedl syndrome
- Ellis-van Creveld syndrome
- Joubert syndrome
- Mainzer-Saldino syndrome
- Meckel-Gruber syndrome
- Nephronophthisis
- Oral-facial-digital syndrome
- Polycystic kidney disease
- Senior-Loken syndrome
- Simpson-Golabi-Behmel syndrome

Primary cilia were noted in rat osteocytes in 1974!
ADPKD and new insights into the pathophysiology of CKD-MBD

SOST antibodies are being developed for osteoporosis, but we will have to be cautious in CKD+++
Altered osteocyte biology in CKD

Systemic signals:
- Circulating WNT inhibitors?

- Altered WNT signaling in bone
- Impaired osteocyte maturation

FGF23

- Defective skeletal mineralization
- Impaired bone formation
- Bone fragility

Left ventricular hypertrophy
Immune dysfunction

SOST
Conclusion and perspectives
Racial-ethnic differences in pediatric CKD-MBD

From biochemicals: higher PTH in African-Americans, magnification of this effect in girls

From biopsy: African-Americans have a greater cortical thickness and a decreased cortical porosity; Caucasians have a greater prevalence of mineralization defects
Back in the real life of a CKD patient...
Phosphate is a/the vascular toxin/silent killer

Vascular calcifications

Scialla, Kidney International 2013
Shroff, Pediatric Nephrology 2013
Phosphate and longevity

Klotho -/- mice

Conversion mg/dL: 0.323 mmol/L

y = -1.5418Ln(x) + 10.02
R² = 0.8942

Kuro-O Mech Ageing Dev 2010
Take-home messages

- CKD-MBD: Bone and vessels
- A close interaction between these two compartments

- On the long-term
  - Bone pain, fracture, deformations, vascular calcifications, but also...
  - Quality of life, social and professional (re)integration, self-esteem

- The assessment of CKD-MBD is of utmost importance in pediatric CKD
  - Biological markers are crucial
  - Bone imaging techniques are interesting for research protocols
  - We need to improve our evaluation of vessels for daily practice...

- Child with CKD = a growing skeleton
  - The question of calcium supplementation in pediatric CKD remains open
  - Exact threshold that would become too much?

- Guidelines
  - To improve our daily management
  - Many of them have been recently updated/written
Why thinking simple when you can think complicated?

Keep phosphate under control and do not forget calcium intake!

Justine.bacchetta@chu-lyon.fr