Renal bone disease in pediatrics
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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!

Renal osteodystrophy: only a component of CKD-MBD

Two main challenges for pediatric nephrologists...
At least in the field of CKD-MBD!
Epidemiology of bone disease in pediatric CKD

Groothoff et al., Kidney International 2003
N=249 young adults with ESRD between 0 and 14 years, born before 1979

<table>
<thead>
<tr>
<th>Total cohort</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Height &lt; -2 SD</td>
<td>135 (64.0%)</td>
</tr>
<tr>
<td>Clinical manifestations of bone disease</td>
<td>69 (32.0%)</td>
</tr>
<tr>
<td>Deformities</td>
<td>91 (37.0%)</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>33 (13.4%)</td>
</tr>
<tr>
<td>Aseptic bone necrosis</td>
<td>32 (13.3%)</td>
</tr>
<tr>
<td>Mild disabling bone disease</td>
<td>26 (10.5%)</td>
</tr>
<tr>
<td>Severe disabling bone disease</td>
<td>18 (7.2%)</td>
</tr>
<tr>
<td>Enlaiding bone disease (40)</td>
<td>44 (17.6%)</td>
</tr>
</tbody>
</table>

Denburg, JASN 2015

- 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)

- 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!

Acidosis and bone metabolism

- Stimulation of osteoclastic differentiation
- Stimulation of osteoclastic resorption

- Inhibition of osteoblastic differentiation

Bicar<22 as a risk factor for CKD progression in the 4C cohort
Evaluating bone « quality » and « quantity » in clinical practice and research in children with CKD

The child with CKD also has a growing skeleton!

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 ESRD

<table>
<thead>
<tr>
<th>Age</th>
<th>DH</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6mo</td>
<td>210</td>
<td>2.29</td>
<td>2.26</td>
<td>2.29</td>
</tr>
<tr>
<td>1-12mo</td>
<td>210</td>
<td>2.15</td>
<td>2.23</td>
<td>2.26</td>
</tr>
<tr>
<td>1-9y</td>
<td>600</td>
<td>1.96</td>
<td>1.80</td>
<td>1.96</td>
</tr>
<tr>
<td>9-12y</td>
<td>800</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>&gt;12y</td>
<td>3,000</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
</tbody>
</table>

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

Simple biomarkers: reference values for phosphate must be adapted to age +++

Changes of biomarkers with declining renal function
**PTH levels depend on geography!**

Borzych, Kidney International 2010

**Table: 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>2nd</td>
<td>10-65</td>
<td>150</td>
<td>300</td>
<td>1000</td>
</tr>
<tr>
<td>N-Tact PTH IRMA</td>
<td>2nd</td>
<td>13-54</td>
<td>81</td>
<td>160</td>
<td>517</td>
</tr>
<tr>
<td>DSL PTH IRMA</td>
<td>2nd</td>
<td>9-55</td>
<td>121</td>
<td>638</td>
<td>2108</td>
</tr>
<tr>
<td>Ca-PTH IRMA</td>
<td>3rd</td>
<td>5-39</td>
<td>84</td>
<td>165</td>
<td>543</td>
</tr>
<tr>
<td>Biointact PTH advantage</td>
<td>3rd</td>
<td>8-50</td>
<td>109</td>
<td>214</td>
<td>704</td>
</tr>
</tbody>
</table>


**Legend:**
- **Allegro Intact**: 2nd generation assay with a reference value range of 10-65 ng/L.
- **N-Tact PTH IRMA**: 2nd generation assay with a reference value range of 13-54 ng/L.
- **DSL PTH IRMA**: 2nd generation assay with a reference value range of 9-55 ng/L.
- **Ca-PTH IRMA**: 3rd generation assay with a reference value range of 5-39 ng/L.
- **Biointact PTH advantage**: 3rd generation assay with a reference value range of 8-50 ng/L.

**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.
- **Osteitis fibrosa**: High PTH state, growth retardation, calcifications, fractures.

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 vitamin D analogs

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

Salusky Kidney Int 1994

**Graph:**
- X-axis: Growth retardation (%)
- Y-axis: Osteitis, Mild SHPT, Normal, Adynamic
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

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

The gold standard: bone biopsy at the iliac crest

- ‘Standard’ histomorphometry
- Immunochemistry
- Micro-radiography
- FTIRM

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

Mitsnefes, JASN 2012

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

Adults
The better the bone
The worse the vessels

Cardiovascular disease
Vascular calcifications
Cardio-vascular morbidity/mortality

Zukowska, 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
Decreased phosphate intake
- Phosphate binders
- Dialysis intensification
- Vitamin D analogs
- Calcimimetics
- Parathyroidectomy
- Calcium nutritional intake/
  Calcium supplementation / Calcium in the dialysate

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

It is crucial to assess nutritional calcium and phosphate intake in pediatric CKD-MBD: enough calcium and not too much phosphate...

Focus on phosphate: beware of hidden phosphates in the diet, and particularly in food additives

| Table 3: Main food additives containing phosphate | 25 OH vitamin D supplementation
|-------------------------------------------------|-----------------------------
| Name of additive | Phosphoric acid (E 391)
|------------------|-----------------------------
| Sodium phosphate (E 339) | Acids
| Potassium phosphate (E 338) | Antioxidants, stabilizers, thickeners
| Casein phosphopeptide (E 341) | Calcium phosphate, dextrin, corn starch
| Soy phosphopeptide (E 342) | Dietary fibers, thickeners, humectants
| Calcium monohydrogen phosphate (E 345) | Citric acid, citric acid salts, pectin derivatives
| Calcium gluconate (E 346) | Diuretics
| Magnesium phosphate (E 347) | Edible gums, emulsifiers, stabilizers
| Ferric citrate (E 348) | Food coloring, flavor enhancers
| Phosphate (E 450) | Fumaric acid, lemon juice, sodium citrate
| Polyphosphates (E 451) | Glucose, fructose, maltodextrins
| Other food additives containing phosphate | Monosodium glutamate, aspartame, saccharin, sucrose, sorbitol, sucrose polyester

Focus on phosphate: beware of hidden phosphates in the diet

For clinical practice in children: the philosophy of the 2006 European guidelines remains interesting
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 → 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 mmol/L² ⇒ outdated
- R14: parathyroidectomy
  - Rarely performed

Klaus, Ped Nephrol 2006, European guidelines

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

Bacchetta, cJASN, 2013

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

Bacchetta et al, NDT 2019

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)

Bacchetta et al, NDT 2019

Concomitant drugs that are contra-indicated with cinacalcet

- 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

- 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


Nephropathic cystinosis and bone

Primary hyperoxaluria 1 and bone: oxalate osteopathy

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2019 international guidelines for CMBD: evaluation

Hohenfellner J Inherit Metab Dis 2019

The concept of CMBD: cystinosis bone disease

2019 international guidelines

Hohenfellner J Inherit Metab Dis 2019

Human nephron j. inherit. Metab. Dis. 2019

The 2019 International guidelines for CMBD: Evaluation

Hohenfellner J Inherit Metab Dis 2019

FIGURE 1. Cystinosis bone disease (CMBD) represents the most common genetic skeletal disorder. CMBD features characteristic skeletal deformities, decreased bone mass, and increased fracture risk.

Table 1. Cystinosis bone disease: Diagnosis and management

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Table 2. Cystinosis bone disease: Treatment and management

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<td>Early and aggressive treatment using D-modifiers and D-analogs</td>
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Hohenfellner J Inherit Metab Dis 2019

FIGURE 2. The 2019 International Guidelines for CMBD: Evaluation of Cystinosis Bone Disease (CMBD).}

Hohenfellner J Inherit Metab Dis 2019

The concept of CMBD: cystinosis bone disease

2019 international guidelines

Hohenfellner J Inherit Metab Dis 2019

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FIGURE 2. The 2019 International Guidelines for CMBD: Evaluation of Cystinosis Bone Disease (CMBD).
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

ADPKD and new insights into the pathophysiology of CKD-MBD

Ciliopathies associated with skeletal developmental defects

Table 1] Ciliopathies associated with skeletal developmental defects

<table>
<thead>
<tr>
<th>Ciliopathy</th>
<th>Skeletal developmental defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alstrom syndrome</td>
<td>Neuronal dystrophy, retinopathy, auditory dysfunction</td>
</tr>
<tr>
<td>Jeune syndrome</td>
<td>Hypothalamic-pituitary dysfunction, immunodeficiency, skeletal abnormalities</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Macrosomia, visceromegaly, growth and endocrine abnormalities</td>
</tr>
<tr>
<td>Ellis-van Creveld syndrome</td>
<td>Short stature, short limbs, heart defects, bone anomalies</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Cerebellar hypoplasia, retinopathy, skeletal anomalies</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>Severe renal anomalies, central nervous system malformations, skeletal abnormalities</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>Polycystic kidney disease, liver abnormalities</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>Retinitis pigmentosa, dwarfism, skeletal anomalies</td>
</tr>
<tr>
<td>Snydromes-Golabi-Barnd syndrome</td>
<td>Intellectual disability, growth retardation, skeletal anomalies</td>
</tr>
</tbody>
</table>

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

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

Phosphate and longevity

Guinea pig
Gerbil
Dialysis patient

Rhinoceros
Elephant
Centenarian
Human
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 reintegration, 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

Keep phosphate under control and do not forget calcium intake!

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