A 16-year old girl arriving in the emergency room for seizures

- No significant medical past except orthopaedic surgery for bilateral genu valgum without any obvious etiology at the age of 14 years
- Bone deformations
- Bone pains for more than one year
- No fever
- No head trauma
- Biochemicals
  - Glucose normal, negative search for toxics
  - Sodium 128 mmol/L
  - Total calcium 1.25 mmol/L
  - Phosphorus 2.7 mmol/L
  - Creatinine 1059 µmol/L
  - Hemoglobin 96 g/L
  - PTH 700 pg/L

Roland-Gosselin, Arch Pediatr 2013

- Progressive growth impairment
- The diagnosis should have been (at least) discussed earlier ++++
- No biochemicals performed by the GP!
- No biochemicals performed by the orthopaedic surgeon even in the absence of obvious etiology for bilateral genu valgum!
- No biochemicals performed by the anesthesiologist before surgery!

Roland-Gosselin, Arch Pediatr 2013

A 16-year old girl arriving in the emergency room for seizures

Hypocalcemic seizure in a context of undiagnosed ESRD

Bilateral slipped capital femoral epiphysis
Secondary hyperparathyroidism
"Historical" renal osteodystrophy
It was too late for the final height!

Roland-Gosselin, Arch Pediatr 2013

The complex interplay between bone and kidney

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>Total cohort</th>
<th>Height &lt;- 2 SD</th>
<th>Clinical manifestations of bone disease</th>
<th>Pathological fractures</th>
<th>Aseptic bone oedema</th>
<th>Mild disabling bone disease</th>
<th>Severe disabling bone disease</th>
<th>Invetering bone disease (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42 (16.9%)</td>
<td>51 (20.6%)</td>
<td>35 (14.4%)</td>
<td>52 (21.0%)</td>
<td>56 (22.5%)</td>
<td>54 (21.7%)</td>
<td>44 (17.8%)</td>
</tr>
</tbody>
</table>

Groothoff et al., Kidney International 2002

Fracture risk in CKD children

- CKD 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)

Denburg, JASN 2015

Causes of bone impairment in pediatric CKD

- Growth failure, impaired GH-IGF1 axis
- Inadequate intake of calories and proteins / nutrition
- Muscle deficits
- Hypogonadism / delayed puberty
- Acidosis
- Inflammation
- Vitamin D deficiency
- Hyperparathyroidism
- Long-term use of corticosteroids and other drugs

Drugs inducing bone toxicity

- Calcineurin inhibitors
  - Increased RANKL expression
  - Activation of osteoclastic activity
  - VDR inhibition
- mTor inhibitors
  - Animal models +++, clinical data
  - Direct toxicity on growth plate
- Anti-epileptic drugs
  - Secondary rickets
- Anti-acid drugs
  - Hyphosphatemia
  - Impaired mineralization
- Long-term use of heparin
  - This list is not exhaustive!

Hofbauer, 2001
Fukunaga 2004
Lee, Am J Nephrol 2011

Acidosis and bone metabolism

- Stimulation of osteoclastic differentiation
- Stimulation of osteoclastic resorption
- Inhibition of osteoblastic differentiation

Kato, BioScience Trends 2013
Kraut, Kidney International 1986

Evaluating bone quality and quantity in clinical practice and research

Alvarez-Garcia, Kidney 2010
Gonzalez, Ped Neph 2011

Kraut, Kidney International 1986
Lee, Am J Nephrol 2011
How to evaluate bone status in pediatric CKD in daily practice?

- **Growth**
- **Biomarkers**
  - Calcium, phosphorus
  - PTH, 25(OH)D, ALP
  - FGF23, Klotho, sclerostin, etc.? (But variability: age, puberty, gender)
- **Dual X-ray absorptiometry: DXA**
- **The reference standard: bone biopsy**
- **New 3D imaging techniques**
  - pQCT, HR-pQCT, MRI
  - For research only!

In daily practice: dual X-ray absorptiometry?

- **Advantages**
  - "Gold standard" for assessing bone mineral density
  - Minor irradiation: 2.7 to 3.6 μSv
  - Not expensive and easily available
  - Evaluation of body composition
- **Limitations**
  - Bidimensional technique: major technical concern in pediatrics
  - Systematic underestimation of BMD in children with poor growth
  - No distinction between cortical and trabecular bone
  - No evaluation of geometry and microarchitecture
  - BUT prediction of fracture risk in CKD adults

The gold standard: bone biopsy at the iliac crest

- **Limitations**
  - Procedure
    - Needle: Bordier versus Jamshidi
    - Interpretation
- **Indications**
  - K/DIGO 2009: detailed list of indications
  - K/DIGO 2016: when the management can be modified by the results
- **Perspectives**
  - EUROD initiative
  - CKD-MBD working group of the ERA-EDTA
  - Chair: P Evenepoel
  - Mainly for adult patients
  - An opportunity for European children???

Theorically, histomorphometry is required to define the type of renal osteodystrophy

<table>
<thead>
<tr>
<th>Type of Renal Osteodystrophy</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>
Renal osteodystrophy in pediatric nephrology

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

Clinical consequences of pediatric renal osteodystrophy

- Adynamic bone = Low PTH =
  - Mainly due to vitamin D analogs and calcium salts
  - Growth retardation + Calculifications +++
- Ostearthrosis = High PTH =
  - Growth retardation + Fractures +++

A recent 3D bone imaging technique: HR-pQCT

- High Resolution Peripheral Quantitative Computed Tomography
- Resolution 82 μm
- Irradiation = DXA (5 μR)
- Acquisition time: 3 minutes
- Radius and tibia
- Bone mineral density
  - Total, cortical, trabecular
- Bone microarchitecture
  - Trabecular parameters
  - Cortical thickness / porosity
- Biomechanical evaluation
  - FEA: finite element analysis
  - Stiffness and failure load

Is there an interest for non-invasive 3D imaging techniques?

- 171 patients aged 5-21 years with CKD stage 2-5D at enrollment
- 99 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

Is there an interest for non-invasive 3D imaging techniques?

<table>
<thead>
<tr>
<th>CKD patients</th>
<th>Healthy peers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.0 (10.2-17.4)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>77 (41-157)</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>81 (59-394)</td>
</tr>
<tr>
<td>25-OHD (nmol/L)</td>
<td>76 (32-130)</td>
</tr>
<tr>
<td>Ca (mmol/L)</td>
<td>2.61 (2.40-2.77)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.45 (1.36-1.55)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>606 (295-1180)</td>
</tr>
<tr>
<td>Density</td>
<td>0.78 (0.69-0.84)</td>
</tr>
</tbody>
</table>
| Trabecular structure
  - BV/TV (%) | 2.17 (0.86-3.38) | 2.23 (0.97-3.81) |
  - TH (mm²) | 1.72 (1.38-2.62) | 1.79 (1.48-2.45) |
  - TH (mm³) | 0.09 (0.06-0.12) | 0.10 (0.07-0.12) |
  - TH (µm)  | 0.49 (0.36-0.65) | 0.47 (0.33-0.64) |
  - TH (mm³/µm²) | 0.20 (0.12-0.37) | 0.20 (0.13-0.32) |

No differences for cortical porosity and biomechanical properties (FEA)

| Salusky and Kuizon, 2004 | Yokoyama et al. JASN 2018 | Bacchetta Ped Neph 2011 |

Is there an interest for non-invasive 3D imaging techniques?
When interpreting results of clinical studies on pediatric renal osteodystrophy... Remember that PTH levels depend on geography!

Searching the optimal PTH target...

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

- European guidelines 2006
  - Keep PTH levels within 2-3 times the upper normal limit: 120-180 pg/mL

- K-DIGO 2006
  - PTH 2-9 times above the upper normal limit: 120-540 pg/mL

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

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

CKD-MBD - a systemic disease

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

CKD-MBD - a balance between bone and vessels

- Renal osteodystrophy
- Fracture risk
- Growth retardation
- Bone pains and deformations
- Vascular calcifications
- Pathophysiology
- Same biomarkers than bone

GFR < 60 mL/min per 1.73 m²
Bone and vessels in children with CKD
Is there a relationship?

- 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

« In a growing skeleton: ‘the better the bone, the worse the vessel’

So... do we give too much calcium to CKD children (at least in Lyon)?

- 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)
- TBial pQCT: lower calcium levels independently associated with baseline and progressive cortical deficits
- Recent data from CKD: 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
- No specific pediatric data

Management of renal osteodystrophy in pediatric CKD

- Decreased phosphorus intake
- Phosphate binders
- Decreased urinary excretion of phosphorus
- 25 OH vitamin D analogs
- Decreased tubular vitamin D 1-hydroxylation
- Hyperphosphatemia
- Decreased intestinal absorption of calcium
- Hyperparathyroidism
- Hypocalcemia
- Calcimetics Parathyroidectomy
- Decreased inhibition of PTH synthesis
- Decreased expression of VDR and CaR in the parathyroid

markers of bone metabolism are influenced by GH therapy in pediatric CKD

- European study 4C
  - 556 children
  - CKD
  - eGFR 10-60
  - Age 6-18 years
  - 41 mGH
  - 41 matched controls

rhGH therapy improves mineralization, whatever the type of the underlying osteodystrophy

- Study from USA
  - Randomized trial: 33 children, PD
  - Low Turnover LTD, n= 14, mGH 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

Markers of bone metabolism are influenced by GH therapy in pediatric CKD
Genetic renal diseases and specific bone impairment

Nephropathic cystinosis and bone

- Clinical signs
  - Pathological fractures
  - Bone pains
  - Deformities
- Unknown pathophysiology: 4 hypotheses
  - Copper deficiency
  - Bone consequences of severe hypophosphatemic rickets during infancy
  - Cysteamine toxicity
  - Abnormal thyroid metabolism
  - Role of chronic hypoparathyroidism?

Conclusion and perspectives

CKD-MBD in pediatric CKD...
Which management in 2017?

- A global management
  - Denutrition
  - Anemia
  - Acidosis
- A management focused on mineral metabolism
  - Nutritional intake: phosphorus
  - Native vitamin D deficiency: target > 30 ng/mL (75 nmol/L) => European guidelines on their way (R Shroff)
  - Phosphate binders
    - Calcium carbonate
    - Sevelamer
    - Lanthanum
    - New binders currently evaluated => sucroferric oxyhydroxide
  - Vitamin D analogs => European guidelines on their way (R Shroff)
  - Calcimimetics
    - Cinacalcet
  - Dialysis intensification
    - Parathyroidectomy
- A management targeting not only growth but also bone
  - Recombinant growth hormone therapy
Take-home messages

- CKD-MBD: Bone and vessels
- A close interaction between these two compartments
- A growing skeleton
- The question of calcium supplementation in pediatric CKD remains open
- Exact threshold that would become too much?
- International trials required!

- On the long-term
- Bone pain, fracture, deformations
- Vascular calcifications, but also...
- Quality of life
- Social and professional reintegration
- Improved self-esteem