Bone impairment in pediatric CKD

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Long Beach, CA, 2017

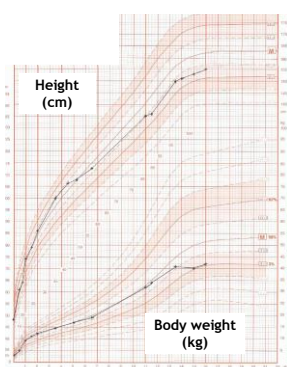
Annual Dialysis Conference
presented by the University of Missouri Division of Nephrology

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

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



- 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

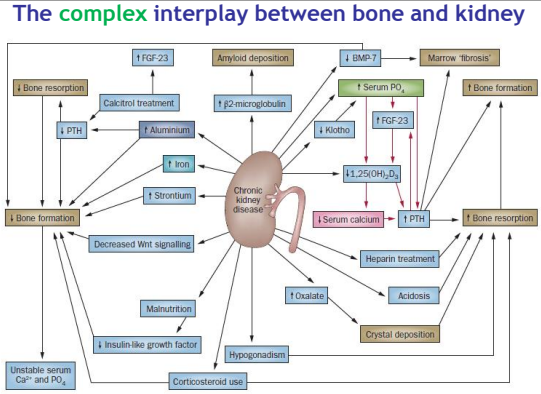
A 16-year old girl arriving in the emergency room for seizures

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!

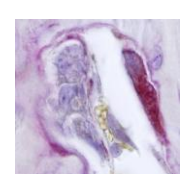
Roland-Gosselin, Arch Pediatr 2013

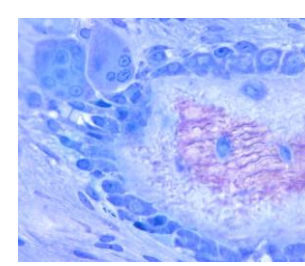
The complex interplay between bone and kidney



Ott, Nature Reviews Nephrology 2013

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

	Total cohort[a]
Height <−2 SD	153 (61.9%)
Clinical manifestations of bone disease	91 (36.8%)
Deformities	63 (25.5%)
Pathological fractures	33 (13.4%)
Aseptic bone necrosis	32 (13.0%)
Mild disabling bone disease	26 (10.5%)
Severe disabling bone disease	18 (7.3%)
Invalidating bone disease (all)	44 (17.8%)

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)

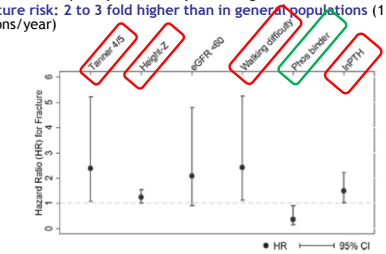


Figure 1. Final multivariable Cox regression model: correlates of incident fracture. [a]HR for males ≥15 years versus females ≥15 years=(3.94*0.67)=2.6. [b]PTH natural log transformed.

Denburg, JASN 2015

Causes of bone impairment in pediatric CKD

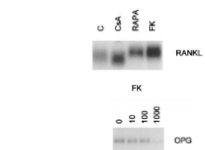
- Growth failure, impaired GH-IGF1 axis
- Inadequate intake of calories and proteins / nutrition
- Muscle deficits
- Hypogonadism / delayed puberty

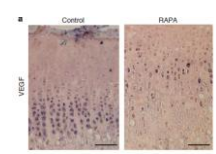
- Acidosis
- Inflammation
- Vitamin D deficiency
- Hyperparathyroidism

- 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
  - 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!



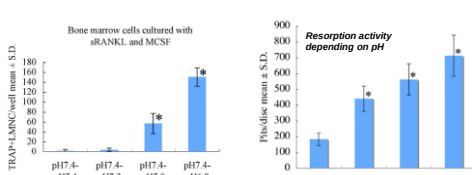


Alvarez-Garcia, Kidney 2010
Gonzalez, Ped Neph 2011

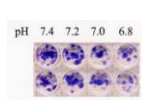
Hofbauer, 2001
Fukunaga 2004
Lee, Am J Nephrol 2011

Acidosis and bone metabolism

- Stimulation of osteoclastic differentiation
- Stimulation of osteoclastic resorption

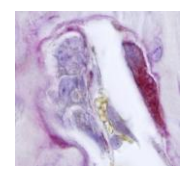


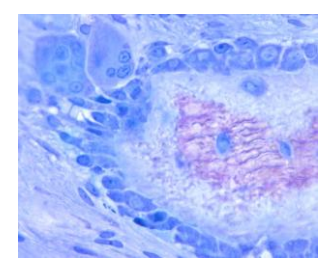
- Inhibition of osteoblastic differentiation



Kraut, Kidney International 1986
Kato, BioScience Trends 2013c

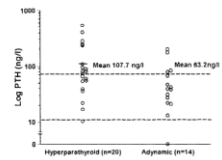
Evaluating bone quality and quantity in clinical practice and research

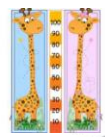


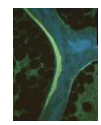


How to evaluate bone status in pediatric CKD in daily practice?

- **Growth**
- **Biomarkers**
  - Calcium, phosphorus
  - PTH, 25OH-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!*



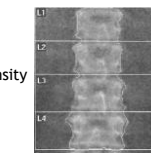




Bacchetta J et al, J Ren Nut 2009 / Hernandez JD et al, Clin J Am Soc Nephrol 2008

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

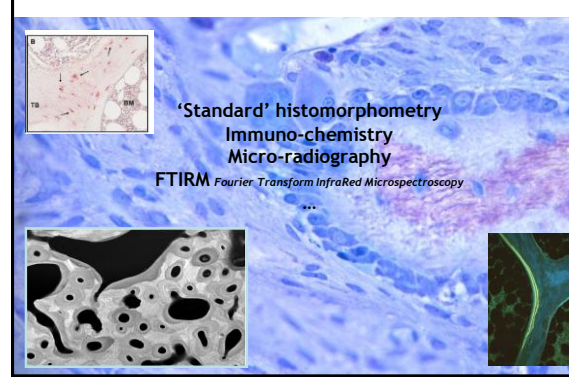
Mehls, Pediatr Nephrol 2010; ISCD consensus papers 2014

In daily practice: dual X-ray absorptiometry?

- **Daily practice**
  - **Adults**, KDIGO 2009: DXA no longer recommended
  - Adults, KDIGO 2016: DXA recommended
  - **In CKD children: DXA no longer recommended in 2011**
  - **2013 ISCD position in pediatrics**
    - Height-adjusted Z-scores
    - Total body less head and posterior-anterior spine
    - **DXA when the patient may benefit from interventions** to decrease their elevated risk of a clinically significant fracture and when the DXA results will influence that management

Mehls, Pediatr Nephrol 2010; ISCD consensus papers 2014

The gold standard: bone biopsy at the iliac crest



The gold standard: bone biopsy at the iliac crest


Trocart de Meunier (8mm Ø)

- **Limitations**
  - Procedure
  - Needle: Bordier *versus* Jamshidi
  - Interpretation

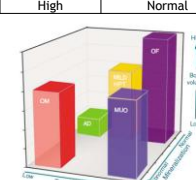

Trocart de Jamshidi ou Bell, (4 mm Ø, 8G)

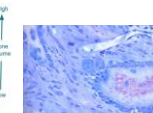
- **Indications**
  - K-DIGO 2009: detailed list of indications
  - K-DIGO 2016: **when the management can be modified by the results**
- **Perspectives**
  - **EUROD initiative**
  - CKD-MBD working group of the ERA-EDTA
  - Chair: P Evenepoel
  - Mainly for adult patients
  - An opportunity for European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

Evenepoel, NDT submitted: unpublished data from MH Lafage-Proust

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

TMV KDIGO2006	Turnover	Mineralization	Volume
Osteomalacia	Low	Abnormal	Low / normal
Adynamic bone	Low	Normal	Low / normal
Moderate hyperparathyroidism	Moderate	Normal	Normal / High
Mixed renal osteodystrophy	High	Abnormal	Normal
Osteitis fibrosa	High	Normal	High



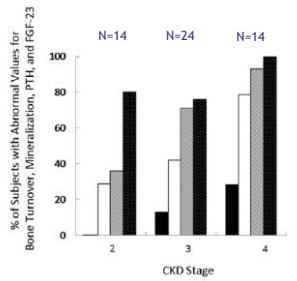


Moe et al, Kidney International 2006

Renal osteodystophy 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



Turnover / Mineralization / PTH / FGF23

Wesseling-Perry et al, cJASN 2012

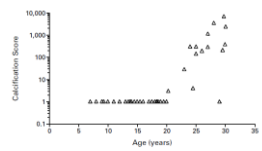
Clinical consequences of pediatric renal osteodystrophy

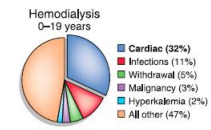
Adynamic bone
« Low PTH »

Mainly due to vitamin D analogs and calcium salts
Growth retardation +++
Calcifications +++
Fractures +++

Osteitis fibrosa
« High PTH »

Growth retardation +
Calcifications +++





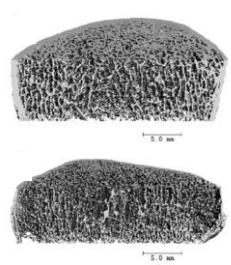
Salusky and Kuizon, 2004
Goodman NEJM 2000
Mistnefes 2012

A recent 3D bone imaging technique: HR-pQCT

- **High Resolution Peripheral Quantitative Computed Tomography**

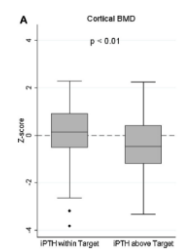
- Resolution 82 µm³
- Irradiation ≈ DXA (5 µSv)
- Acquisition time: 3 minutes
- Radius and tibia

- **Bone mineral density**
  - Total, cortical, trabecular
- **Bone microarchitecture**
  - Trabecular parameters
  - Cortical thickness / porosity
- **Biomechanical evaluation**
  - FEA: finite element analysis
  - Stiffness and failure load



Bacchetta Ped Neph 2011

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



Targets
70 pg/mL II-III
110 IV and 300 V-D

- **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**

- **Secondary hyperparathyroidism associated with**
  - **Significant reduction in cortical vBMD and area**
  - Greater endosteal circumference
  - Reflect of PTH effect on cortical bone: increased cortical porosity and loss of endocortical bone
  - **Greater trabecular vBMD in younger participants**: anabolic effect of PTH?

Wetzsteon et al JBMR 2011

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

- 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

Denburg JCEM 2013

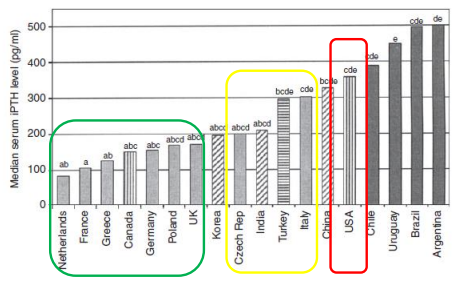
Is there an interest for non-invasive 3D imaging techniques?

	CKD patients	Healthy peers
		Matched on age, gender and Tanner stage
N	32	
Age (years)	12.9 [10.2-17.9]	12.6 [10.0-17.8]
eGFR (ml/min/1.73 m²) *	33 [11-72]	102 [73-135]
PTH (pg/mL) *	81 [9-359]	18 [9-34]
25-OH D (nmol/L)	70 [32-116]	60 [31-123]
Geometry		
- Tt.Ar [mm²] *	588 [337-968]	626 [442-956]
- Ct.Ar [mm²] *	66 [35-121]	82 [26-170]
- Ct.Th [mm²]	0.69 [0.33-1.32]	0.80 [0.28-1.48]
- Tb.Ar [mm²]	506 [265-886]	543 [360-804]
Density		
- Tt.vBMD [mg/cm³]	265 [186-365]	259 [217-369]
- Tb.vBMD [mg/cm³]	201 [126-268]	187 [151-250]
- Ct.vBMD [mg/cm³]	740 [621-898]	733 [607-913]
Trabecular structure		
- BV.TV	0.17 [0.11-0.22]	0.16 [0.13-0.21]
- Tb.N [mm⁻¹]	1.72 [1.38-2.62]	1.79 [1.58-2.43]
- Tb.Th [µm]	0.09 [0.06-0.12]	0.09 [0.07-0.12]
- Tb.Sp [µm]	0.49 [0.30-0.65]	0.47 [0.33-0.54]
- Tb.Sp.SD [µm]	0.20 [0.12-0.35]	0.20 [0.13-0.23]

No differences for cortical porosity and biomechanical properties (FEA)

Vierge M, IPNA 2016 / Preka, in preparation

When interpreting results of clinical studies on pediatric renal osteodystrophy… Remember that PTH levels depend on geography!



Borzych, Kidney International 2010

PTH levels are associated with…

- Longitudinal growth
- Vascular calcifications
- Anemia
- Left ventricular hypertrophy
- Cardiovascular disease

- Data from the IPPN registry
  - More than 1800 children
  - 87 centers
  - 31 countries

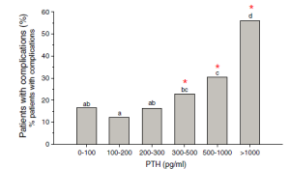


Fig. 3 Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extraosseous calcifications, radiological osteomalacia and/or osteopenia) stratified by time-averaged mean parathyroid hormone (PTH) levels. Groups sharing same letters do not differ significantly; (Fig. adapted from 39; used with permission)

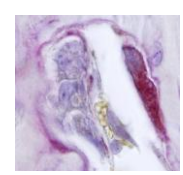
Haffner Pediatr Nephrol 2013

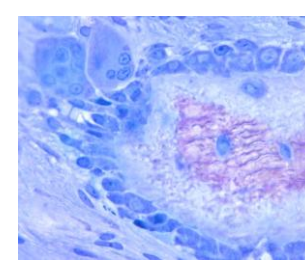
Searching the optimal PTH target…

- **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 2006**
  - 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

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





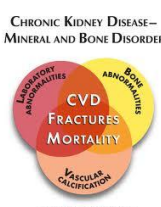
CKD-MBD
A systemic disease

Hypocalcemia
Hyperphosphatemia

HyperPTH
Decreased 1-25 D

Prurit
Skin necrosis

Keratitis
Corneal calcifications



CKD-MBD

Renal osteodystrophy

Growth retardation
GH resistance

Proximal myopathy

Vascular calcifications

GFR < 60 mL/min per 1.73 m²

CKD-MBD
A balance between bone and vessels

Renal osteodystrophy
Fracture risk
Growth retardation
Bone pains and deformations

Adults
The better the bone
The better the vessels

Vascular calcifications
Pathophysiology
Same biomarkers than bone
Vitamin D, PTH, FGF23…

Groothoff et al., Kidney International 2003 Goodman et al, New England Journal of Medicine 2000 Cejka, Bone 2014 / Malluche JASN 2015

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
- Two major determinants for blood pressure (mean and diastolic, night, day, and 24-hour) by multivariable analyses: serum calcium and trabecular thickness

=> In a growing skeleton: 'the better the bone, the worse the vessel'

Ziolkowska, Ped Nephrology 2008; Preka IPNA 2016, manuscript in preparation

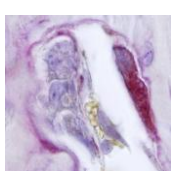
So… do we give too much calcium to CKD children (at least in Lyon)?

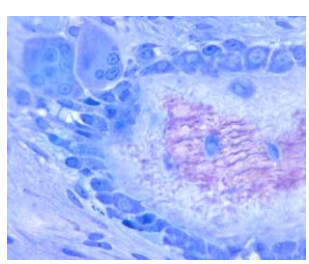
- Not giving enough calcium supplements may be deleterious for bone in pediatric CKD
- **Histomorphometry**: defective skeletal mineralization associated with lower calcium levels.
- **Histomorphometry**: 160 children on PD; serum calcium concentrations inversely related to mineralization (but not turnover)
- **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
- No specific pediatric data

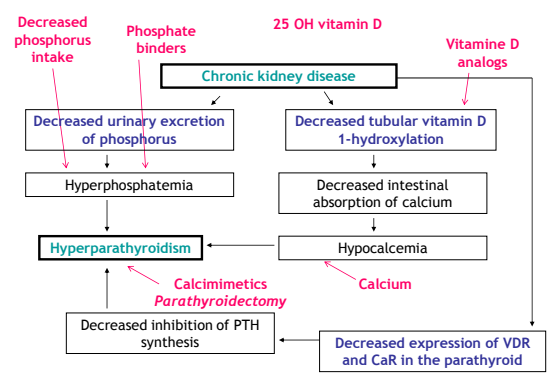
Wesseling-Perry cJASN 2012; Denburg JCEM 2013; Wesseling-Perry Kidney 2011; Bakkaloglu cJASN 2010; Denburg JASN2016; Jamal Lancet 2013

Management of renal osteodystrophy in pediatric CKD



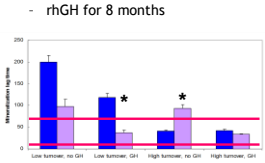


The cornerstones of CKD-MBD management



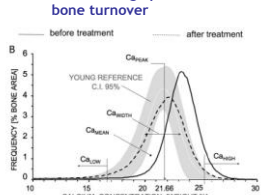
rhGH therapy improves mineralization, whatever the type of the underlying osteodystrophy

- 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



Nawrot-Wawrzyniak, AJKD 2013

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 rhGH
  - 41 matched controls

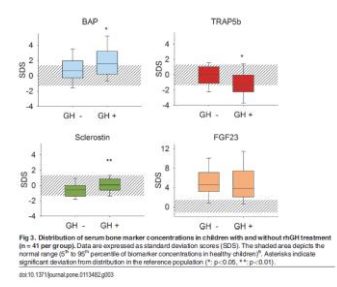
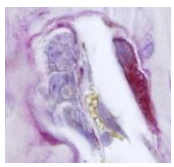


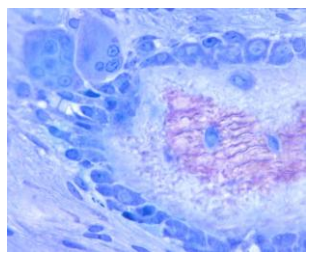
Fig 3. Distribution of serum bone marker concentrations in children with and without rhGH treatment (n = 41 per group). Data are expressed as standard deviation scores (SDS). The shaded area depicts the normal range (5th to 95th percentile of biomarker concentrations in healthy children)[8]. Asterisks indicate significant deviation from distribution in the reference population (*: p<0.05, **: p<0.01).

doi:10.1371/journal.pone.0113462.g003

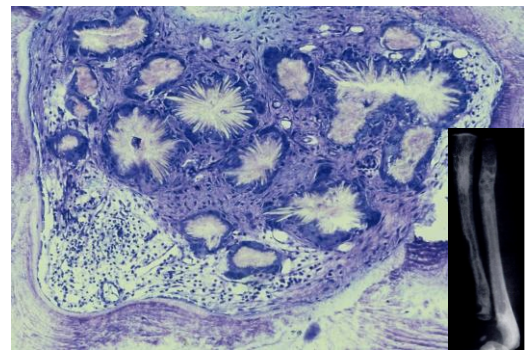
Doyon, Plos One 2015

Genetic renal diseases and specific bone impairment





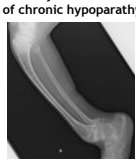
Primary hyperoxaluria 1 and bone: oxalate osteopathy

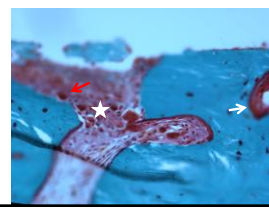


Bacchetta, Bone 2015; Bacchetta, Pediatr Nephrol 2015

Nephropathic cystinosis and bone

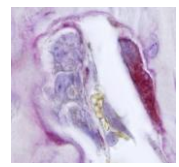
- Clinical signs
  - Pathological fractures
  - Bone pains
  - Deformities
- Unknown pathophysiology: 4 hypotheses
  - Copper deficiency
  - Bone consequences of severe hypophosphatemic rickets during infancy
  - Cysteamine toxicity
  - Abnormal thyroid metabolism
  - Role of chronic hypoparathyroidism?

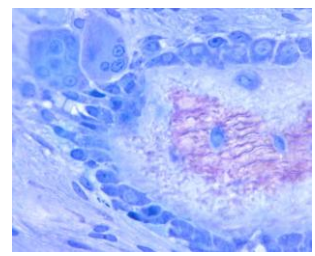




Bacchetta, Bonekey Rep. 2016

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*
- And 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