# Management of CKD-MBD in Pediatric Patients
## *The Basics*

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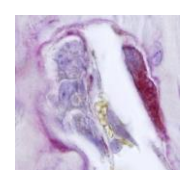
## Disclosures

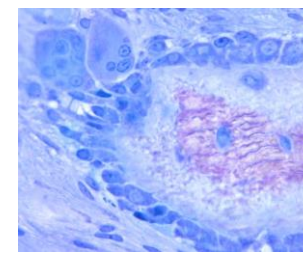
- **Consultancy and speaker**
  - Kyowa Kirin
  - Alnylam
  - Dicerna
  - Biocodex
  - Amgen
  - Pfizer
  - Alexion
  - Bayer
  - Lilly
  - Vifor
  - Mylan
  - Amolyt
- **Research grants**
  - Kyowa Kirin
  - Amgen
  - Horizon
  - Novartis
  - Crinex
- **Travel grants**
  - Kyowa Kirin
  - Alnylam

## Outline of the talk

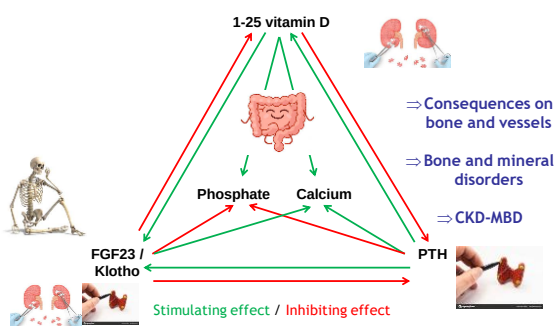
- Epidemiology of CKD-MBD in pediatric CKD
- CKD-MBD evaluation in pediatrics: what are our targets?
- Management of CKD-MBD in pediatric CKD
- CKD-MBD in infants less than 2 years: the 2023 European consensus
- Genetic renal diseases, specific bone impairment and future targeted management?

## Epidemiology of CKD-MBD in pediatrics



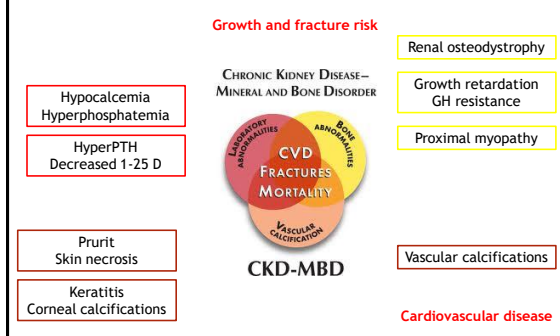


## Calcium and phosphate metabolism: everything is modified by CKD!

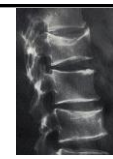



*Adapted from Bacchetta, EMC 2015*

## CKD-MBD as a multi-systemic disease, also in children…
## Leading to our two main challenges as pediatric nephrologists!



## 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)

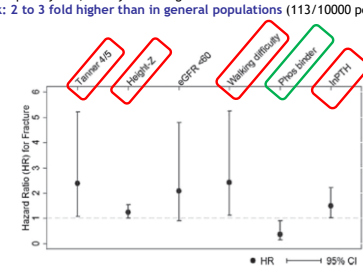


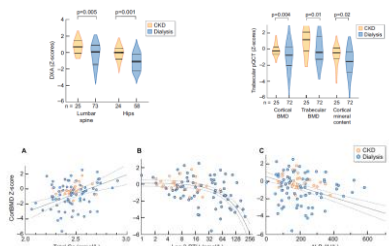

**Figure 1.** Final multivariable Cox regression model: correlates of incident fracture. [a]HR for males ≥15 years versus females ≥15 years=(3.94*0.67)=2.6. [b]PTH natural log transformed.

*Denburg, JASN 2015*

## Bone symptoms in CKD teenagers and young adults

- **UK cross-sectional multicentre study in 26 patients with CKD4-5 and 77 on dialysis**
- Between 5 and 30 years
- Clinical evaluation, DXA, pQCT and biomarkers

- **Significant bone pain that hindered activities of daily living was present in 58% of patients!**
- And 10% had at least one low-trauma fracture



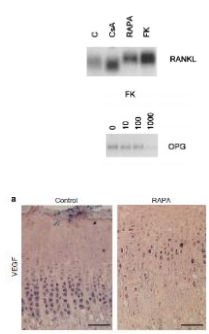

*Lalayiannis NDT 2021*

## 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

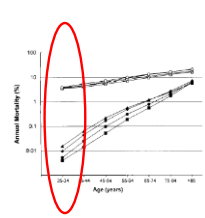
- **Calcineurin inhibitors**
  - Increased RANKL expression
  - Activation of osteoclastic activity
  - VDR inhibition
- **mTor inhibitors**
  - Animal models +++, clinical data
  - Impaired growth
  - Direct toxicity on growth plate
- **Anti-epileptic drugs**
  - Secondary rickets
- **Anti-acid drugs**
  - 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*

## Cardiovascular disease as the leading cause of mortality in CKD



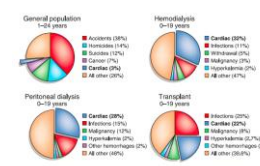




**Figure 1.** Leading causes of death in general pediatric population and in children on renal replacement therapy. Data are presented as percentages. Data for dialysis and transplant patients are from the USRDS (2011).[1] Data for general pediatric population are from Mathews et al. (2011).[1]

*Foley et al, Am J Kidney Dis 1998;32:S112-19*

*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 better the vessels**

**Cardiovascular disease**
**Vascular calcifications**
**Cardio-vascular morbi-mortality**

*Ziolkowska, Ped Nephrology 2008; Preka Pediatr Nephrol 2018; Lalayiannis KIR 2023 Epub*
*Ceika, Bone 2014 / Malluche JASN 2015*

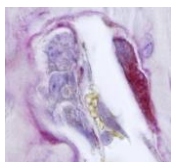
## What should be the exquisite balance of calcium in pediatric CKD?

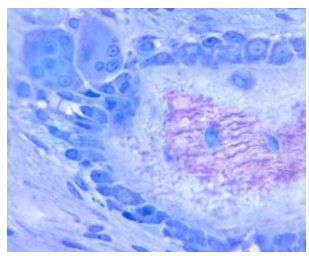
- **Not giving enough calcium supplements may be deleterious for bone in pediatric CKD**
- **Histomorphometry**: defective skeletal mineralization associated with lower calcium levels.
- **Histomorphometry**: 160 children on PD; serum calcium concentrations inversely related to mineralization (but not 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.
- European consensus ongoing…

- **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

*Wesseling-Perry cJASN 2012; Denburg JCEM 2013; Wesseling-Perry Kidney 2011; Bakkaloglu cJASN 2010; Denburg JASN2016; Jamal Lancet 2013; Preka Pediatr Nephrol 2018; Mc Alister Pediatr Nephrol 2020; Oh Circulation 2002*

## CKD-MBD evaluation in pediatrics: what are our targets?





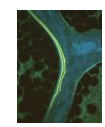
## How to evaluate CKD-MBD in pediatric CKD in daily practice?

- **Growth / nutrition / bone symptoms**
- 58% of children/teenagers with advanced CKD have bone symptoms!

- **Routine Biomarkers**
  - Calcium, phosphate
  - PTH, 25OH-D
  - ALP
  - Bicarbonates

**2020 European guidelines on Bone Evaluation**

- **Bone imaging**
  - Wrist X-ray for skeletal age
  - Targeted X-ray in case of clinical symptoms
  - No interest for 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

*Bakkaloglu, NDT 2020; Lalayiannis NDT 2021; Bacchetta Pediatric Nephrol 2023 Epub*

Nephrol Dial Transplant (2020) 1–13
doi: 10.1093/ndt/gfaa210

ndt Nephrology Dialysis Transplantation

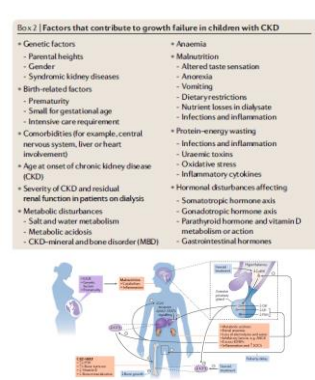
Bone evaluation in paediatric chronic kidney disease: Clinical practice points from the European Society for Paediatric Nephrology CKD-MBD and Dialysis working groups and CKD-MBD working group of the ERA-EDTA

Sevcan A. Bakkaloglu[1,*], Justine Bacchetta[2,*], Alexander D. Lalayiannis[3], Maren Leifheit-Nestler[4], Stella Staboulis[5], Mathias Haarhaus[6,7], George Reusz[8], Jaap Groothoff[9], Claus Peter Schmitt[10], Pieter Evenepoel[11,12], Rukshana Shroff[3,*] and Dieter Haffner[4,*], on behalf of the European Society for Paediatric Nephrology (ESPN) Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) and Dialysis working groups and CKD-MBD working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA)**

## First target: keep it simple… Growth

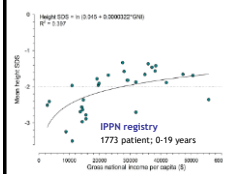
- **Parameters affecting growth**
- Age
- Primary disease
- GFR level
- Duration of CKD
- Birth parameters and parental height

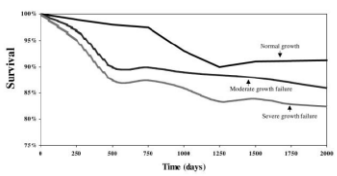
- **Causes of growth retardation in CKD**
- Inadequate intake of calories and proteins
- Water, electrolyte and acid-base imbalance
- Malnutrition
- Bone disease and CKD-MBD
- Impaired GH-IGF1 axis
- Hypogonadism
- Long-term use of corticosteroids
- Anemia
- Inflammation




*Drube, Nature Reviews in Nephrology, 2019*

## Growth as a marker of global child morbidity, as a risk factor for hospitalization and as a marker of survival in pediatric CKD




| Characteristics | Hospitalizations per patient year | Unadjusted risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|---|---|---|---|
| Standardized interval growth | | | |
| Severe growth failure (Z<−3) | 1.65 | 1.50 (1.40, 1.61) | 1.12 (1.03, 1.22) |
| Moderate growth failure | 1.59 | 1.51 (1.4, 1.61) | 1.26 (1.17, 1.36) |
| Normal growth | 1.05 | 1.0 (reference) | 1.0 (reference) |

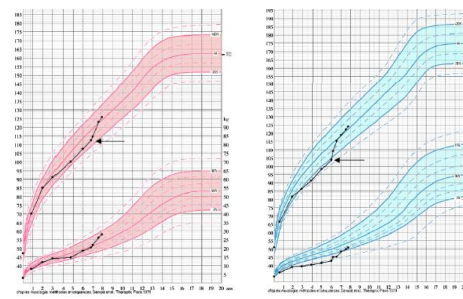
- Prevalent US pediatric patients with KF in 1990
- Followed through 1995
- Cohort of 1112 patients

*Shaefer, Periton Dialysis Int 2012*

*Furth, Pediatric Nephrology 2002*

## Daily on-line HDF promotes catch-up growth

**Mean growth velocity: 3.8±1.1 cm/year => 14.3±3.8 during the first year**
**Height SDS from -1.5±0.3 to 0.2±1.1**



*Fischbach, NDT 2009*

CONSENSUS STATEMENT

OPEN

EVIDENCE-BASED GUIDELINE

## Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease

Jens Drube[1,2], Mandy Wan[3], Marjolein Bonthuis[4], Elke Wühl[5], Justine Bacchetta[6], Fernando Santos[7], Ryszard Grenda[8], Alberto Edefonti[9], Jerome Harambat[6,10], Rukshana Shroff[3], Burkhard Tönshoff[11] and Dieter Haffner[12,13], on behalf of the European Society for Paediatric Nephrology Chronic Kidney Disease Mineral and Bone Disorders, Dialysis, and Transplantation Working Groups

Table 1 | Assessment intervals for statural growth in CKD

| Assessment type | Age (years) | Recommended intervals of assessment (months) CKD stage 3 | CKD stage 4 | CKD stage 4–5 | CKD stage 5D |
|---|---|---|---|---|---|
| Length or height | 0–1 | 0.5–2 | 0.5–2 | 0.5–2 | 0.5–2 |
| | 1–3 | 1–3 | 1–2 | 1–2 | 1–2 |
| | >3 | 3–6 | 1–3 | 1–3 | 1–3 |
| Length velocity[a] or height velocity | 0–1 | 0.5–2 | 0.5–2 | 0.5–2 | 0.5–1 |
| | 1–3 | 1–6 | 1–3 | 1–3 | 1–2 |
| | >3 | 6 | 6 | 6 | 6 |

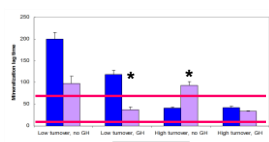
Recommendations were generated by combining those from the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines; the Caring for Australasians with Renal Impairment (CARI) guidelines; and the Clinical Guideline from the British Society for Paediatric Endocrinology and Diabetes (BSPED), the British Association for Paediatric Nephrology (BAPN) and the Paediatric Renal Interest Nutrition Group (PRING)[7,10,11]. CKD, chronic kidney disease. [a]Supine length is measured using a validated length board or stad up to a length of 50 cm (before 2 years of age) or if assessment of standing height is not feasible.

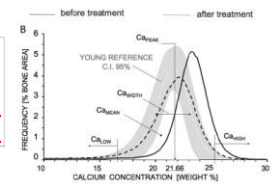
- GH therapy should not be started
  - In patients with closed epiphyses (grade X, strong recommendation)
  - In patients with known hypersensitivity to the active substance or to any of the excipients (grade X, strong recommendation)
  - In the case of unwillingness of the patient or their family (grade X, strong recommendation)
  - In patients with severe secondary hyperparathyroidism (parathyroid hormone >500 pg/ml) (grade X, moderate recommendation)
  - In patients with proliferative or severe non-proliferative diabetic retinopathy (grade X, moderate recommendation)
  - During the first year after renal transplantation (grade X, moderate recommendation)
  - In patients with acute critical illness (grade X, strong recommendation)
  - In patients with active malignancy (grade X, strong recommendation)

NATURE REVIEWS | NEPHROLOGY

## 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*

## Second target: keep it (relatively) simple… Nutrition, with a regular follow-up

Pediatric Nephrology (2021) 36:995–1010
https://doi.org/10.1007/s00467-020-04852-5

GUIDELINES

### Assessment of nutritional status in children with kidney diseases—clinical practice recommendations from the Pediatric Renal Nutrition Taskforce

Christina L. Nelms[1] · Vanessa Shaw[2,3] · Larry A. Greenbaum[4,5] · Caroline Anderson[6] · An Desloovere[7] · Dieter Haffner[8] · Michiel J. S. Oosterveld[9] · Fabio Paglialonga[10] · Nonnie Polderman[11] · Leila Qizalbash[12] · Lesley Rees[2] · José Renken-Terhaerdt[13] · Jetta Tuokkola[14] · Johan Vande Walle[7] · Rukshana Shroff[2] · Bradley A. Warady[15]

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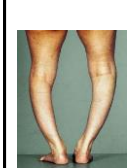
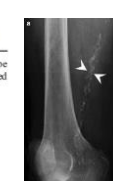
## It is crucial to assess nutritional calcium and phosphate intake in pediatric CKD-MBD: enough calcium and not too much phosphate…

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

| Age (years) | SDI calcium (mg) | SDI phosphate (mg) |
|---|---|---|
| 0–<4 months | 220 | 120 |
| 4–<12 months | 330–540 | 275–420 |
| 1–3 years | 450–700 | 250–500 |
| 4–10 years | 700–1000 | 440–800 |
| 11–17 years | 900–1300 | 640–1250 |

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





**Not enough calcium: increased risk of rickets**
**Too much phosphate: increased risk of vascular calcifications**

*Mc Allister et al Pediatr Nephrol 2020, Bacchetta et al Calcif Tissue Int 2020*

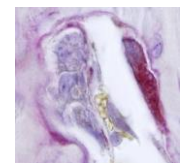
## Focus on phosphate: beware of hidden phosphates in the diet, and particularly in food additives

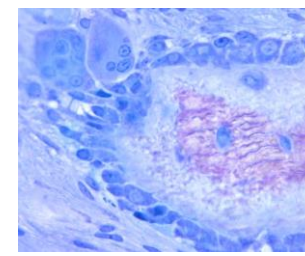
Table 3 Main food additives containing phosphate

| Name of additive | Food where the additive can be found | Function of the additive |
|---|---|---|
| Orthophosphoric acid (E338) | Cola | Acidification |
| Sodium orthophosphate (E339) | Pizza, food preparation as « preparation bags» for desserts | Anti-oxidation, acidification, texture |
| Potassium orthophosphate (E 340) | Cappuccino, soja drink, dessert cream | Acidification regulation, texture, water retention |
| Calcium orthophosphate (E 341) | Dairy products | Anti-oxidation, stabilization, firming agent |
| Magnesium orthophosphate (E 343) | Butter, ice cream, breakfast cereals, appetizers | Anti-oxidation, anti-agglomeration, thickening agent, emulsifier |
| Diphosphate (E 450) | Soft cheese | Modification of the repartition between fat and proteins in the cheese |
| Triphosphate (E 451) | Chocolate powder | |
| Polyphosphate (E 452) | Ham | Water retention |
| 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 | Cacao and chocolate desserts/chocolate-based sweets | Emulsifier, binding agent, modified starch |

*Mc Alister et al Pediatr Nephrol 2020, Bacchetta et al Calcif Tissue Int 2020*

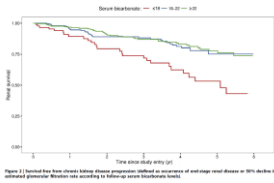
## *Third (not so simple) targets: biomarkers*

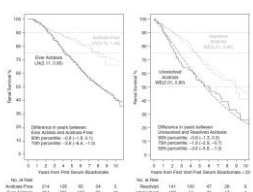




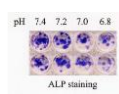
## Acidosis and the risk of CKD progression in children

**European 4C study**
Threshold here 18 mmol/L
704 patients
No association with longitudinal growth…





**North-American CKID study**
Threshold here 22 mmol/L
Only 36% of patients with acidosis were supplemented

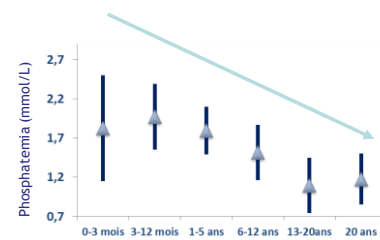



**Acidosis is also deleterious for bone!!!**

*Harambat Kidney Int 2017; Brown cJASN 2020*

*Kraut, Kidney International 1986*
*Kato, BioScience Trends 2013c*

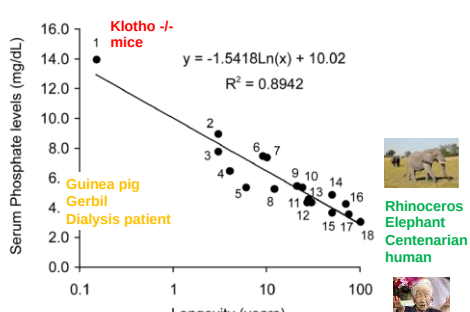
## The variation of phosphate levels with age is of utmost importance




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

Conversion factors from mg/dL to mmol/L
Calcium 4 and phosphate 3.1

## Humans are not mice… But still, there is an association between phosphate levels and longevity








**Conversion mg/dL: 0.323 mmol/L**

*Kuro-O Mech Ageing Dev 2010*

## Reference values must be adapted to age and sometimes to gender +++

Table 4. Age-specific and CKD stage–based reference ranges for commonly used biomarkers of CKD-MBD [7, 12, 13, 21, 46, 52, 72]

| Age-specific values | | | | Age- and sex-specific values | | CKD stage-dependent values | |
|---|---|---|---|---|---|---|---|
| | iCa mmol/L | Ca mg/dL | P mg/dL | ALP*U/L | | PTH pg/mL | 25(OH)D* ng/mL |
| 0–5 months | 1.22–1.40 | 8.7–11.3 | 5.2–8.4 | 0–15 days | 90–273 | CKD Stage 3 | 35–70 [12] Normal levels [46] |
| 6–12 months | 1.20–1.40 | 8.7–11.0 | 5.0–7.8 | 15–30 days | 134–518 | CKD Stage 4 | 70–110 [12] |
| 1–5 years | 1.22–1.32 | 9.4–10.8 | 4.5–6.5 | 1–<10 years | 156–369 | CKD Stage 5/5D | 200–300 [12] 2–3X ULN [46] 2–9X ULN [7] |
| 6–12 years | 1.15–1.32 | 9.4–10.3 | 3.6–5.8 | 10–<13 years | 141–460 | – | – |
| 13–20 years | 1.21–1.30 | 8.8–10.2 | 2.3–4.5 | 13–<15 years | F: 62–280<br>M: 127–517 | – | – |
| – | – | – | – | 15–<17 years | F: 54–128<br>M: 89–365 | – | – |
| – | – | – | – | 17–<19 years | F: 48–95<br>M: 59–164 | – | – |

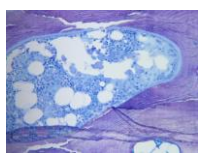
M, males; F, females, ULN: upper limit of the normal.
*Based on CALIPER study [52].
[a] The same normal reference ranges as for healthy people.
Numbers given in brackets are respective references.

*Bakkaloglu NDT 2020*

## Pediatric renal osteodystrophy and PTH levels

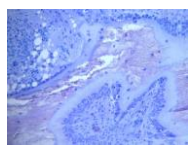
**Adynamic bone**
**« *Low PTH state* »**

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



**Osteitis fibrosa**
**« *High PTH state* »**

Growth retardation +
Calcifications +++

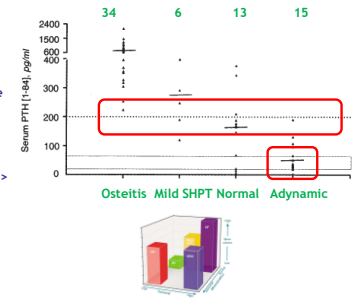


*Salusky and Kuizon, 2004*

## PTH alone is not a good predictor of the underlying renal osteodystrophy

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

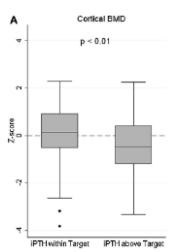
- To predict adynamic bone disease
- PTH < 200 pg/mL
  - Sensibility 100%
  - Specificity 79%
- PTH < 150 pg/mL AND Ca > 2.5 mmol/L
  - Sensibility 100%
  - Specificity 92%




*Salusky Kidney Int 1994*

*Moe et al, Kidney International 2006*

## SHPT is a predictor of cortical impairment using 3D non-invasive bone imaging techniques




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

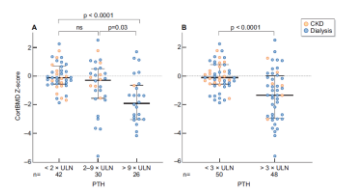
- 156 CKD II-III children
  - 69 II-III: 42 (2-521) pg/mL for PTH
  - 51 IV-V: 140 (8 to 770) pg/mL
  - 36 dialysis: 267 (10 to 1139) pg/mL
  - Aged 5-21 years
- 831 healthy controls
- Tibia pQCT

- SHPT associated with
  - **Significant reduction in cortical vBMD and area**
  - Increased cortical porosity ?

*Wetzsteon et al JBMR 2011 and then Denburg JCEM 2013*

## SHPT is a predictor of cortical impairment using 3D non-invasive bone imaging techniques

- UK cross-sectional multicentre study in 26 patients with CKD4-5 and 77 on dialysis
- Between 5 and 30 years
- Clinical evaluation, DXA, pQCT and biomarkers




*Lalayiannis NDT 2021*

## Can the combination of PTH with other biomarkers be helpful?

- 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

*Bakkaloglu SA et al Clin J Am Soc Nephrol 2010*

## PTH is not the perfect biomarker for the underlying renal osteodystrophy but…
## 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

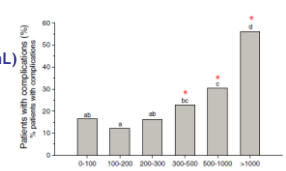



Fig. 3 Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extraosseous calcifications, radiological osteomalacia and/or osteopenia) stratified by time-averaged mean parathyroid hormone (PTH) levels. Groups sharing same letters do not differ significantly;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

*Haffner Pediatr Nephrol 2013*

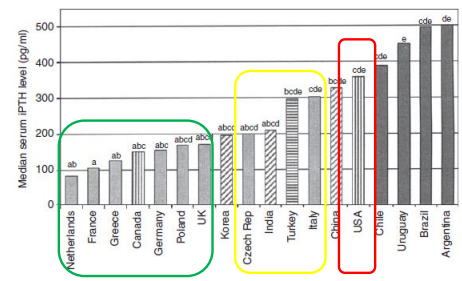
## PTH levels depend on the assays…

| Name of the assay | Manufacturer | 2nd or 3rd generation | Automated | Tracer | Epitope of coated Ab | Epitope of labelled Ab | Detection limit (ng/l) | Highest measurable value (ng/l) | Intra-assay CV (%) | Inter-assay CV (%) | Normal range (ng/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Allegro-intact PTH | Nichols Institute (San Clemente, CA, USA) | 2nd | No | 125-I | 39-84 | 1–34 | 5.0 | 1815 | <3.4 | <5.6 | 10-65 |
| N-tact PTH IRMA | DiaSorin (Stillwater, MN, USA) | 2nd | No | 125-I | 39-84 | 1–34 | 0.7 | 2000 | 2.7 | 4.3 | 13-54 |
| PTH IRMA Immunotech | Beckman-Coulter (Marseille, France) | 2nd | No | 125-I | Not specified | Not specified | 2.0 | 2600 | 7.5 | 11 | 10-65 |
| ELISA-PTH | Schering-Cis Bio (Gif sur Yvette, France) | 2nd | No | 125-I | 39-84 | 1–34 | 3.0 | 1500 | <4.3 | <3.4 | 11-62 |
| Total+Intact PTH IRMA | Scantibodies Laboratories (Santee, CA, USA) | 2nd | No | 125-I | 39-84 | 1–34 | 1.2 | 2456 | <5.0 | <7.0 | 14-66 |
| DSL PTH IRMA | DSL (Webster, TX, USA) | 2nd | No | 125-I | 39-84 | 1–34 | 6.0 | 2000 | 2.8 | 3.6 | 9-55 |
| DSL PTH ELISA | DSL (Webster, TX, USA) | 2nd | No | Alkaline phosphatase | Not specified | Not specified | 1.0 | 2000 | 5.5 | 6.2 | 16.62 |
| Elecsys PTH | Roche Diagnostics (Meylan, France) | 2nd | Yes | Ruthenium | 26-52 | 55-64 | 1.2 | 5000 | <5.4 | <7.1 | 15-65 |
| Immulite 2000-intact PTH | DPC (Los Angeles, CA, USA) | 2nd | Yes | Alkaline phosphatase | 44-84 | 1–34 | 3.0 | 2500 | <5.7 | <8.8 | 11-67 |
| PTH-ACS 180 | Bayer (Tarrytown, NY, USA) | 2nd | Yes | Acridinium ester | 39-84 | 1–34 | 1.5 | 1900 | <4.1 | <4.6 | 14-72 |
| PTH AdviaCentaur | Bayer (Tarrytown, NY, USA) | 2nd | Yes | Acridinium ester | 39-84 | 1–34 | 2.5 | 1900 | <5.2 | <5.8 | 14-72 |
| Intact PTH advantage | Nichols Institute (San Clemente, CA, USA) | 2nd | Yes | Acridinium ester | 39-84 | 1–34 | 1.0 | 1800 | <6.7 | <9.2 | 10-65 |
| LIAISON N-tact PTH | DiaSorin (Stillwater, MN, USA) | 2nd | Yes | Isoluminol | 39-84 | 1–34 | 1.0 | 2000 | <4.8 | <5.9 | 17.3–72.9 |
| CarPTH IRMA | Scantibodies Laboratories (Santee, CA, USA) | 3rd | No | 125-I | 39-84 | 1–4 | 1.0 | 2190 | <5.0 | <8.0 | 5–39 |
| BioIntact PTH advantage | Nichols Institute (San Clemente, CA, USA) | 3rd | Yes | Acridinium ester | 39-84 | 1–5 | 1.5 | 1800 | <5.5 | <8.7 | 8–50 |

DSL, diagnostic system laboratories; ELISA, enzyme-linked immunosorbent assay; IRMA, immunoradiometric assay; PTH, parathyroid hormone.
The intra- and inter-assay CVs are for concentrations > 10 ng/l. The right column identifies the member of our group (initials) who performed the assay.

*Souberbielle Kidney Int 2006*

## PTH levels depend on geography!




*Borzych, Kidney International 2010*

## 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

**It is not a problem of numbers, rather a problem of trends and global philosophy!**

*Haffner Pediatr Nephrol 2013*

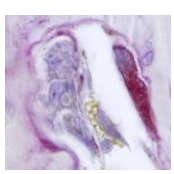
## KDIGO 2009/2017: one CRUCIAL point to keep in mind for the evaluation of CKD-MBD

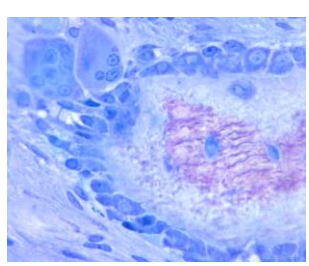
**It is recommended that therapeutic decisions are based on trends rather than on a single laboratory value, taking into account all available CKD-MBD measurements**

| 14-year old boy HD CAKUT | M1 | M2 | M3 |
|---|---|---|---|
| Calcium (mmol/L) | 2.29 | 2.26 | 2.29 |
| Phosphorus (mmol/L) | 1.56<br>*2.15* | 1.67<br>*2.03* | 1.96<br>*1.96* |
| 25 OH (nmol/L) | | | 43 |
| PTH (15-65 pg/mL) | 500 | 688 | 830 |
| *PTH (pg/mL)* | *1200* | *920* | *830* |

*Kidney International Supplements 2017: KDIGO 2017 clinical practice guideline for the diagnosis, evaluation, prevention and treatment of CKD-MBD*

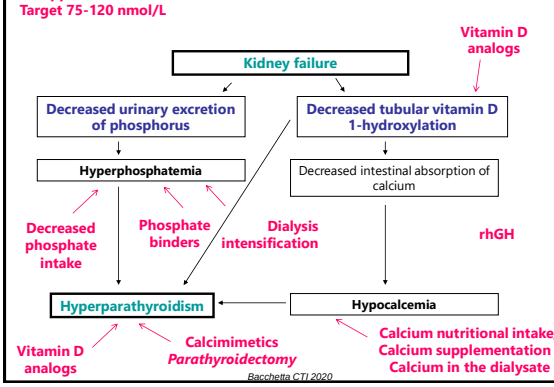
## CKD-MBD management in pediatrics



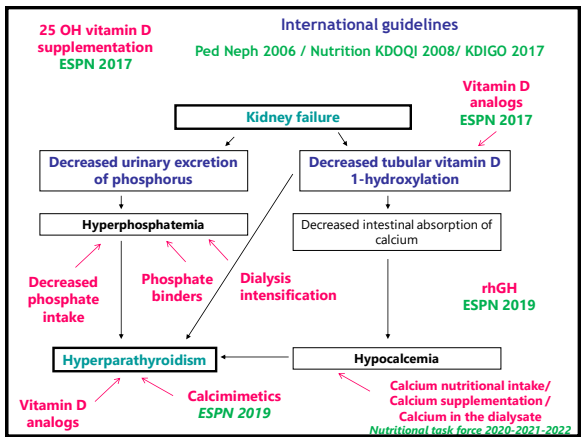


## The cornerstones of CKD-MBD management in 2023: mainly based on PTH levels

**25 OH vitamin D supplementation Target 75-120 nmol/L**




*Bacchetta CTI 2020*

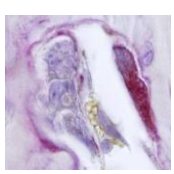


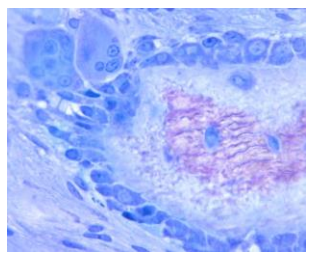

## Just a reminder from the KDIGO2017…

- **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

*Kidney International Supplements 2017: KDIGO 2017 clinical practice guideline for the diagnosis, evaluation, prevention and treatment of CKD-MBD*

## CKD-MBD in infants less than 2 years of age: the 2023 European consensus





**Diagnosis and management of mineral and bone disorders in infants with CKD: clinical practice points from the ESPN CKD-MBD and dialysis working groups and the Paediatric Renal Nutritional Taskforce**

Justine Bacchetta[1,2,3], Claus Peter Schmitt[4], Sevcan A Bakkaloglu[5], Shelley Cleghorn[6], Maren Leifheit-Nestler[7], Agnieszka Prytula[8], Bruno Ranchin[1], Anne Schön[7], Stella Stabouli[9], Johan Van de Walle[8], Enrico Vidal[10], Dieter Haffner[7], Rukshana Shroff[6]

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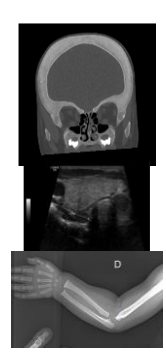
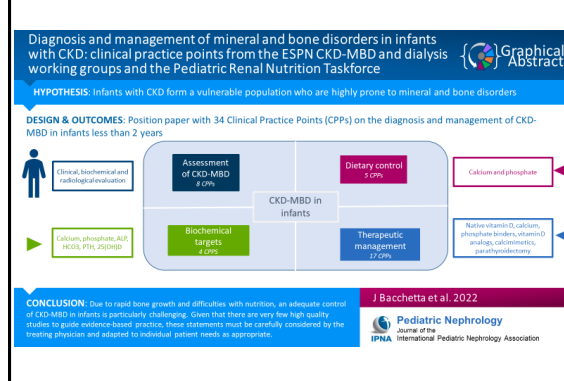
*Epub, Pediatr Nephrol 2023*

## CKD-MBD in infants: a reality with a peculiar severity

- **Infants with CKD are especially prone to MBD**
- **Period of the most rapid growth**
  - High demands of Ca and phosphate
  - To obtain a positive mineral balance and adequate endochondral ossification
  - However this balance is exquisite to avoid vascular calcifications
- Particularly vulnerable for complications such as **rickets, skeletal deformaties, bone pain, and growth retardation**
- **Secondary hyperparathyroidism**
  - May really be tricky…
  - Calcium deficiency may worsen SHPT
  - Feeding difficulties
- **Beware of CAKUT, TCF2/HNF1B and severe SHPT… « Challenge the faculty » session, ADC 2018…**

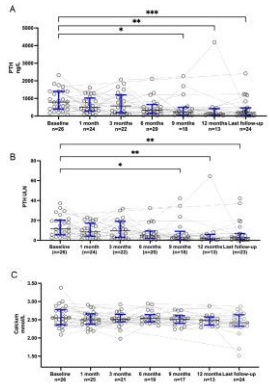


*Personal data; Ferré JCEM 2013*



## CKD-MBD in infants: the use of off-label cinacalcet

- **Survey on the use of Cinacalcet in dialysis patients less than 3 years**
- Median age of 19[12–27] months
- 26 patients
- At the start of cinacalcet
  - PTH 792[411-1397] ng/
  - 12[6-20] ULN
  - Calcium 2.56[2.43-2.75] mmol/L
  - Phosphate 1.5[1.2-1.7] mmol/L
  - ALP 660[492-905] IU/L
  - 25-D 69[50-89] nmol/L
- Initial cinacalcet dose 0.4[0.2-0.8] mg/kg/day
- Maximal dose 1.1[0.6-1.2] mg/kg/day.
- **Seven infants developed 11 hypocalcemic episodes <2.1 mmol/L**




*Bernardor, Manuscript in preparation*

Nephrol Dial Transplant (2019) 1–18
doi: 10.1093/ndt/gfz139

ndt Nephrology Dialysis Transplantation

# Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA

Justine Bacchetta[1,2,3,4], Claus Peter Schmitt[5], Gema Ariceta[6], Sevcan A. Bakkaloglu[7], Jaap Groothoff[8], Mandy Wan[9], Marc Vervloet[10], Rukshana Shroff[9,*] and Dieter Haffner[11,12,*] on behalf of the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders and Dialysis Working Group of the ERA-EDTA**

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## 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)

| In a child >3 years of age | Requirements before initiating cinacalcet therapy | Titration phase | Maintenance phase |
|---|---|---|---|
| Clinical parameters | Optimization of conventional management of CKD-MBD | Evaluation of potential side effects at every visit | Evaluation of potential side effects at every visit |
| | | Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects | Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects |
| | Evaluation of calcium intake from diet, medications and dialysate | Evaluation of calcium intake from diet, medications and dialysate | Evaluation of calcium intake from diet, medications and dialysate |
| | Calculation of QTc interval | Realization of an ECG in case of hypocalcaemia | Realization of an ECG in case of hypocalcaemia; if ECG performed for another reason and increased QTc interval, cinacalcet withdrawal |
| | Evaluation of comorbidities of interest (seizures, cardiac arrhythmia, liver disease) | | |
| | Explanation to parents | | |
| Biological parameters | Calcium level ≥2.40 mmol/L | Weekly evaluation of calcium and phosphate levels | At least monthly evaluation of calcium and phosphate levels, target range for calcium within the normal range for age and in any case >2.2 mmol/L |
| | | Cinacalcet withdrawal if calcium levels <2 mmol/L | Cinacalcet withdrawal if calcium levels <2 mmol/L and decrease/withdrawal if calcium levels between 2 and 2.2 mmol/L |
| | Persistent and secondary SHPT, no PTH threshold level clearly identified | Weekly evaluation of PTH levels, 12–24 h after cinacalcet administration | At least monthly evaluation of PTH levels, 12–24 h after cinacalcet administration, target range 100–200 pg/mL |
| | | Cinacalcet withdrawal if PTH levels <100 pg/mL | Cinacalcet withdrawal if PTH levels <100 pg/mL |
| Therapeutic parameters | Verification of concomitant therapies that can interfere with cinacalcet | 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 | |

*Bacchetta et al, NDT 2019*

## Concomitant drugs that are contra-indicated with cinacalcet

**Table 6. Concomitant drugs that are contra-indicated with cinacalcet**

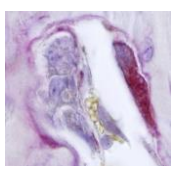
| Mechanism | Example of drug that is contra-indicated in association with cinacalcet |
|---|---|
| Potential to increase QTc | Ondansetron |
| | Albuterol |
| | Salbutamol |
| Inhibitors of CYP3A4 | Grapefruit juice |
| | Erythromycin |
| | Clarithromycin |
| | Ketoconazole |
| | Itraconazole |
| Inhibitors of CYP2D6 | Flecanide |
| | Propafenone |
| | Metoprolol |
| | Desipramine |
| | Nortroptyline |
| | Clomipramine |

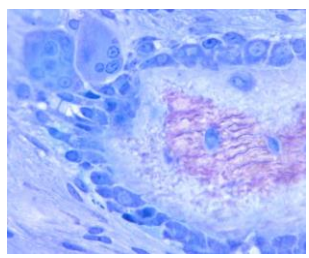
This list is not exhaustive: before prescribing cinacalcet or new therapies to patients already receiving cinacalcet, physicians in charge of the patients are responsible for checking the potential interferences and contra-indications.

Risk of increased QT interval

*Bacchetta et al, NDT 2019*

## Genetic renal diseases, specific bone impairment and future targeted management?





## The effect of primary kidney disease etiology on renal osteodystrophy: not only « genetic » diseases!

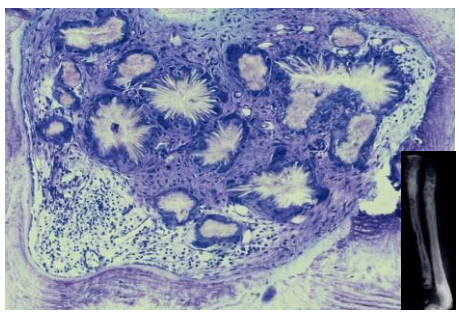
- CAKUT patients: greater mineralization defect with elevated ALP

**Table 3.** Bone Histomorphometric Variables According to Primary Kidney Disease

| | Non-glomerular | | | | |
|---|---|---|---|---|---|
| Parameter | CAKUT ($n = 82$) | Hereditary ($n = 22$) | Glomerular ($n = 85$) | Kruskal–Wallis $p$ value | Normal range |
| Bone turnover | | | | | |
| BFR/BS ($\mu m^3/\mu m^2/yr$) | 79.5 (31.7, 124.4) | 51.1 (25.5, 81.0) | 59.9 (16.0, 94.5) | 0.18 | 8.0–73.4 |
| Bone mineralization | | | | | |
| OV/BV (%) | 8.6 (5.0, 14.0) | 4.9 (3.2, 6.7)[a] | 6.9 (3.9, 11.2)[b] | 0.01 | 0.2–5.9 |
| OS/BS (%) | 47.7 ± 18.0 | 32.9 ± 11.1[a] | 43.5 ± 18.4[b] | <0.01 | 4.3–31.7 |
| O.Th (μm) | 13.4 (9.7, 20.4) | 10.2 (8.3, 12.5)[a] | 11.4 (9.2, 14.8)[c] | 0.01 | 2.0–13.2 |
| OMT (d) | 13.6 (9.3, 23.6) | 10.1 (6.4, 12.5)[a] | 11.2 (8.2, 15.1)[c] | <0.01 | 1.2–11.5 |
| MLT (d) | 39.8 (23.2, 82.7) | 27.8 (14.5, 44.3)[a] | 31.5 (20.3, 78.7) | 0.17 | 2.3–63.8 |
| Bone volume | | | | | |
| BV/TV (%) | 28.9 (25.3, 35.5) | 27.4 (20.6, 32.5) | 26.4 (22.0, 34.7) | 0.07 | 8.9–34.4 |
| Tb.Th (μm) | 150 ± 32 | 139 ± 25 | 142 ± 32 | 0.08 | 72–177 |
| Tb.n (/mm) | 2.0 (1.7, 2.2) | 1.9 (1.7, 2.1) | 1.9 (1.7, 2.2) | 0.83 | 1.3–2.7 |
| Tb.Sp (μm) | 351 (288, 429) | 366 (317, 477) | 367 (301, 455) | 0.42 | 299–587 |
| Bone fibrosis | | | | | |
| Fb/TV (%) | 1.00 (0.00, 1.00) | 0.00 (0.00, 1.00) | 0.15 (0.00, 1.00) | 0.27 | 0 |

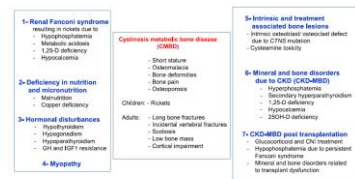
*Sirimongkolchaiyakul JBMR Plus 2022*

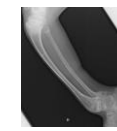
## Primary hyperoxaluria 1 and bone: oxalate osteopathy
## What will be the effects of the new RNAi therapies???



*Bacchetta, Pediatr Nephrol 2010; Bacchetta, Bone 2015; Bacchetta, Pediatr Nephrol 2015*

## The emerging concept of CMBD: cystinosis bone disease
## 2019 international guidelines



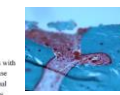


**FIGURE 4** Current understanding of the abnormalities leading to cystinosis metabolic bone disease (CMBD). Virtually all individuals with classical, nephropathic cystinosis suffer from CMBD, related to the renal Fanconi syndrome in infancy and progressive chronic kidney disease (CKD) later in life 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

*Bacchetta Bone Key 2016 / Claramunt-Taberner Nephrol Dial Transplant 2018/ Bertholet-Thomas Pediatr Nephrol 2018 / Langman J Pediatr 2017 / Florenzano JBMR 2018 / Machuca-Gayet IJMS 2020 / **Hohenfellner J Inherit Metab Dis. 2019***

## 2019 international guidelines for CMBD: evaluation

**TABLE 2** Recommended tests for CMBD

| Assessment | Methods and frequency |
|---|---|
| Growth | • Calculate genetic target height based on parental height<br>• Plot height/length and weight on growth charts in infants (monthly) and preschool children (3 monthly) and older children (6 monthly)<br>• Calculate annual height velocity<br>• 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<br>• 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 (eg, 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<br>• Obtain X-ray of the left wrist in children aged >5 years to assess bone age and prove growth potential (ie, open epiphyses) prior to initiation of GH treatment |
| Thyroid function | • Check TSH and thyroxine levels annually, more frequently if following treatment<br>• 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<br>• 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

| Treatment | Dosing |
|---|---|
| Phosphate | • Starting dose of 30–40 mg/kg/d based on elemental phosphorus in 3 to 5 doses equally spaced throughout the day<br>• 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<br>• Dosage should be adjusted to the stage of CKD |
| Citrate/bicarbonate | • Treat acidosis with alkali (citrate or bicarbonate) administered 3-4 times daily<br>• Aim to return bicarbonate levels to normal levels (22-25 mEq/L);<br>• levels >20 mEq/L may not be achieved in all patients |
| Calcium/active and native vitamin D | • Starting dose of calcitriol or alfacalcidol 0.1 to 0.75 µg depending on patient size and severity of rickets<br>• Maintain at lowest possible dose to successfully treat rickets and keep PTH in the CKD stage-dependent target range (see below)<br>• Supplementation with native vitamin D (eg, cholecalciferol) if 25 OH vitamin-D levels are reduced<br>• 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<br>• Dosage: 0.045 to 0.05 mg/kg body weight per day by subcutaneous injections in the evening<br>• Calcium, phosphorus, PTH, fasting glucose, and HbA1c levels should be monitored.<br>• 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<br>• 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 hypergonadotropic hypogonadism<br>• Testosterone patch or intramuscular |
| L-Thyroxine | • In case of hypothyroidism to normalize free $T_4$ 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.

*Hohenfellner, J Inherit Metab Dis 2019*

## ADPKD and new insights into the pathophysiology of CKD-MBD

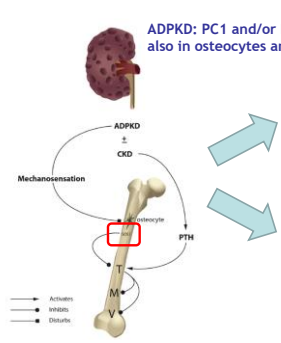
**Table 1 | Demographics and parameters of mineral metabolism in ESRD patients with and without ADPKD**

| Demographics and laboratory parameters | ADPKD ($n$ = 99) | Non-ADPKD ($n$ = 419) | $P$ value |
|---|---|---|---|
| Age, yr | 56.9 ± 8.8 | 54.2 ± 13.5 | 0.5 |
| Male sex, % | 49.5 | 63.3 | 0.02 |
| BMI, kg/m$^2$ | 24.7 ± 4.0 | 24.9 ± 4.3 | 0.8 |
| Dialysis vintage (M) | 31.8 (17.0–42.3) | 31.8 (18.6–50.9) | 0.1 |
| Renal diagnosis, % | | | <0.0001 |
| Diabetic nephropathy | 0 | 10.7 | |
| Glomerulonephritis/vasculitis | 0 | 31.5 | |
| Interstitial nephritis | 0 | 10.0 | |
| Hypertensive/large vessel disease | 0 | 4.3 | |
| Cystic/hereditary/congenital diseases | 100 | 5.5 | |
| Miscellaneous | 0 | 8.4 | |
| Etiology unknown or missing | 0 | 25.6 | |
| Diabetes mellitus, % | 5.1 | 21.2 | 0.0002 |
| CVD, % | 27.3 | 42.3 | 0.005 |
| PTX, % | 7.1 | 14.6 | 0.05 |
| Fracture, % | 6.1 | 5.7 | 0.9 |
| Calcium, mg/dl | 9.2 ± 0.6 | 9.2 ± 0.8 | 0.7 |
| Phosphate, mg/dl | 4.7 ± 1.5 | 4.4 ± 1.4 | 0.02 |
| Magnesium, mg/dl | 2.3 ± 0.3 | 2.3 ± 0.4 | 0.2 |
| biPTH, ng/l | 133.8 (69.1–228.9) | 121.7 (66.4–236.6) | 0.9 |
| 25(OH)D$_3$, µg/l | 37.7 (25.1–49.2) | 35.5 (23.6–48.5) | 0.3 |
| 1,25(OH)$_2$D$_3$, ng/l | 27.3 (20.2–34.1) | 26.7 (17.8–37.5) | 1 |
| FGF23, ng/l | 3323 (1083–9548) | 2040 (606–7573) | 0.04 |
| Sclerostin, ng/l | 2.20 (1.68–3.16) | 1.84 (1.28–2.57) | 0.001 |
| OPG, pmol/l | 9.97 (8.0–12.2) | 10.2 (7.3–14.0) | 0.7 |
| sRANKL, pmol/l | 0.075 (0.063–0.14) | 0.097 (0.063–0.17) | 0.01 |
| sRANKL/OPG | 0.009 (0.006–0.016) | 0.010 (0.005–0.021) | 0.2 |
| C-reactive protein, mg/l | 3.60 (1.50–8.30) | 3.30 (1.30–7.50) | 0.6 |
| IL-6, pg/ml | 1.71 (0.87–2.77) | 1.35 (0.63–2.37) | <0.05 |
| sE-, pg/ml | 0.21 (0.13–0.92) | 0.80 (0.63–1.89) | 0.03 |
| BsAP, ng/ml | 17.4 (13.2–27.2) | 22.6 (16.1–35.5) | <0.0001 |
| RANKL, pg/ml | 25.5 (20.8–33.1) | 30.6 (23.7–42.0) | 0.01 |
| TRAP3b, U/l | 4.65 (3.13–6.57) | 5.46 (3.84–7.59) | 0.006 |

ADPKD, autosomal-dominant polycystic kidney disease; BMI, body mass index; biPTH, biointact parathyroid hormone; BsAP, bone-specific alkaline phosphatase; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; IL-6, interleukin-6; OPG, osteoprotegerin; PTNP, procollagen type I N propeptide; PTX, parathyroidectomy; sRANKL, soluble receptor activator of nuclear factor κB ligand; TRAP3b, tartrate-resistant acid phosphatase 3b.
Data are presented as mean ±SD or median (interquartile range).

*Evenepoel Kidney Int 2020*

## 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

*Evenepoel Kidney Int 2020*

## ADPKD and new insights into the pathophysiology of CKD-MBD

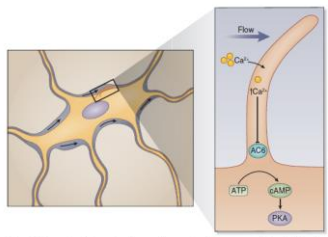



**Figure 1 | Conceptual osteocyte microenvironment and the primary cilium.** With loading, interstitial fluid flow (blue) may bend the primary cilium (brown) projecting from the osteocyte's (orange) surface. Inset: Proposed adenylyl cyclase cilia-mediated pathway. The flow-induced calcium influx inhibits adenylyl cyclase isoform 6 (AC6; blue), which in turn leads to a decrease in cyclic adenosine monophosphate (cAMP; green) and a decrease in activated protein kinase A (PKA; purple). ATP, adenosine triphosphate. Adapted from Nyguen AM, Jacobs CR. Emerging role of primary cilia as mechanosensors in osteocytes. *Bone*. 2013;54:196–204, with permission from Elsevier.

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

*Hruska Kidney Int 2020*

## Ciliopathies associated with skeletal developmental defects

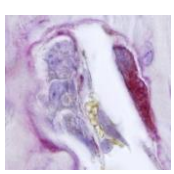
**Table 1 | Ciliopathies associated with skeletal developmental defects**

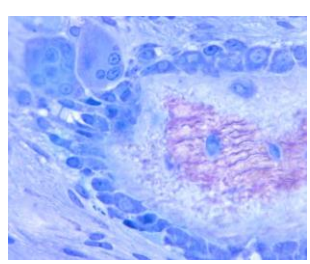
| |
|---|
| Alstrom syndrome |
| Jeune asphyxiating thoracic dystrophy |
| Bardet-Biedl syndrome |
| Ellis-van Creveld syndrome |
| Joubert syndrome |
| Mainzer-Saldino syndrome |
| Meckel-Gruber syndrome |
| Nephronophthisis |
| Oral-facial-digital syndrome |
| Polycystic kidney disease |
| Senior-Loken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

**Primary cilia were noted in rat osteocytes in 1974!**

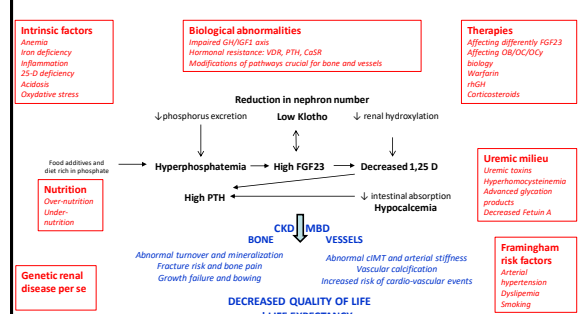
*Hruska Kidney Int 2020*

## Conclusion





## CKD-MBD: more and more complex!




*CKD-MBD chapter from Pediatric Nephrology 2021 Epub; Wesseling-Perry, Shroff and Bacchetta*

## Take-home messages of CKD-MBD in pediatrics

- **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

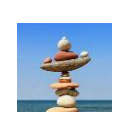
- **The assessment of CKD-MBD is of utmost importance in pediatric CKD**
- Biological markers are crucial
- Bone imaging techniques are interesting for research protocols
- We need to improve our evaluation of vessels for daily practice…

- **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

## Conclusion

- **Small changes every week are better than big changes every month…**
- **Especillay in the youngest patients…**
- **Some may say that pediatric nephrologists are obsessional…**
- **Let's see us rather as « Swiss watch-makers »…**



**2023: to avoid uncontrolled PTH levels in pediatric KF, keep phosphate under control and do not forget calcium intake!**