Chronic PD and HD: what are the relevant KPI for physicians and patients?

Justine Bacchetta, MD, PhD

Hopital Femme Mère Enfant
Bron, France

ERKNet/ESPN

Workshop on fundamentals in pediatric dialysis

21 - 22 October 2021

Poll: which of the above KPI would you consider as meaningful in pediatric dialysis?

KPI = key performance indicators

A- growth

B- bicarbonate levels

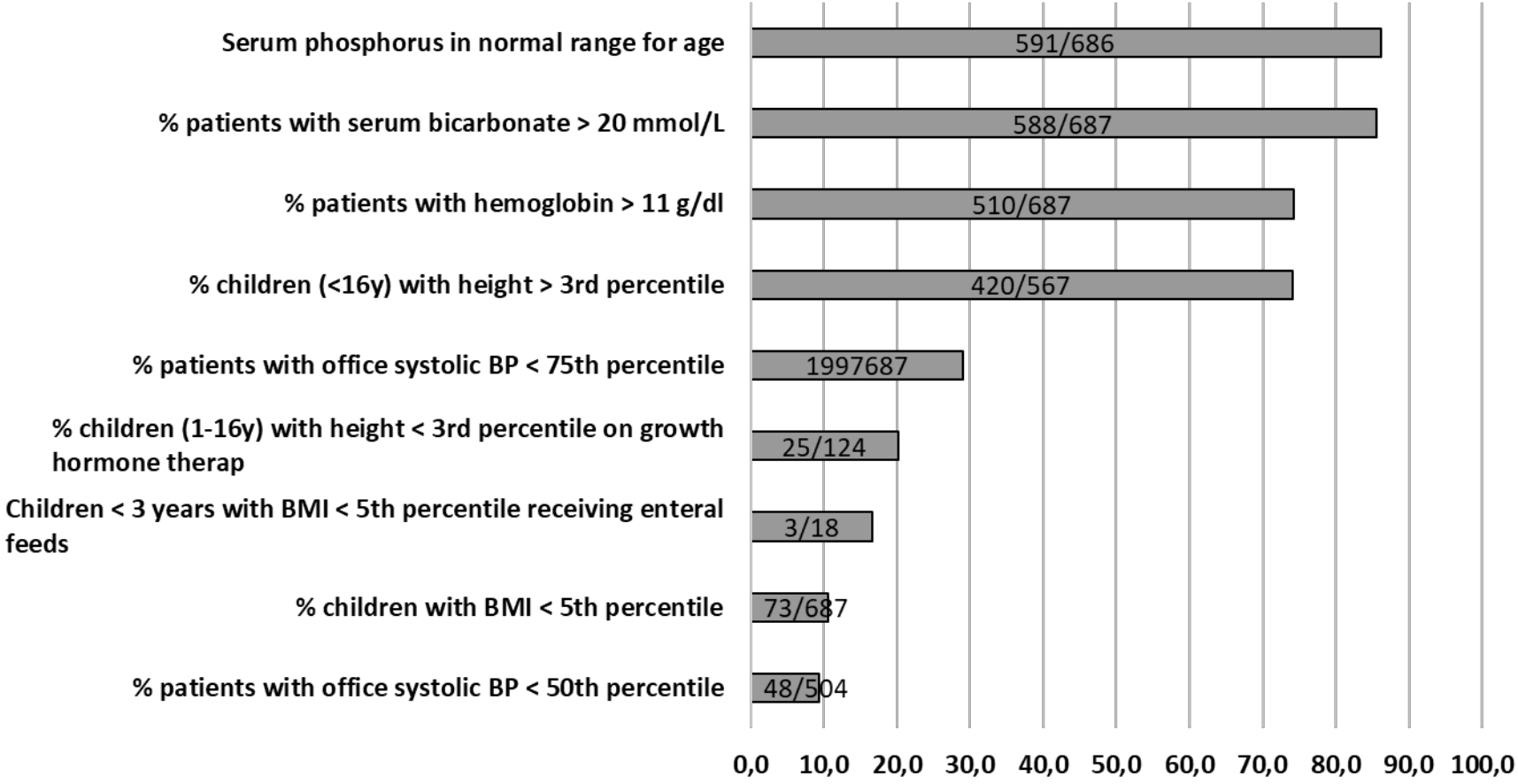
C- phosphate levels

D- hemoglobin levels

E- PTH levels

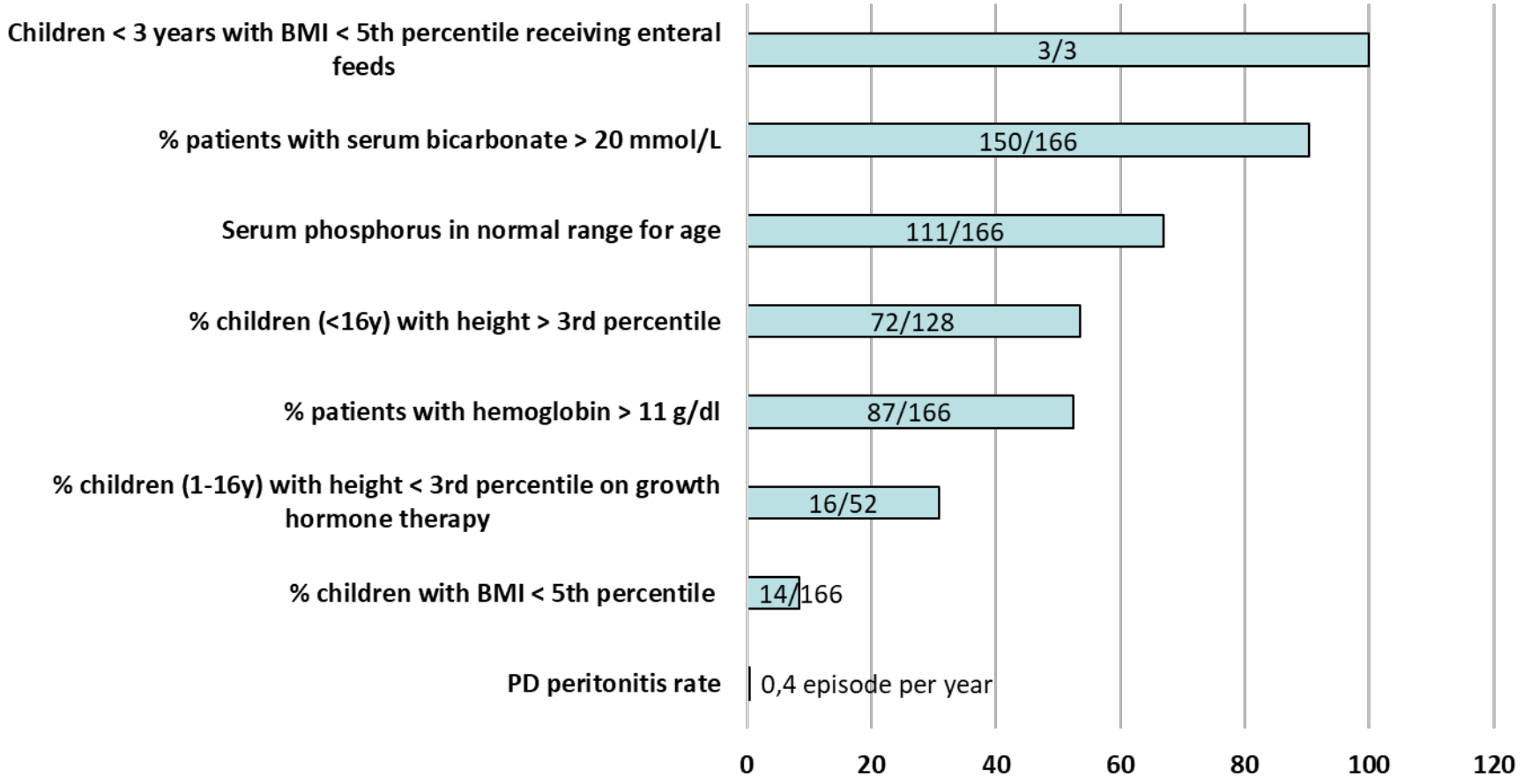
KPI Monitoring in ERKReg: CKD3-5

Updated 14/04/21

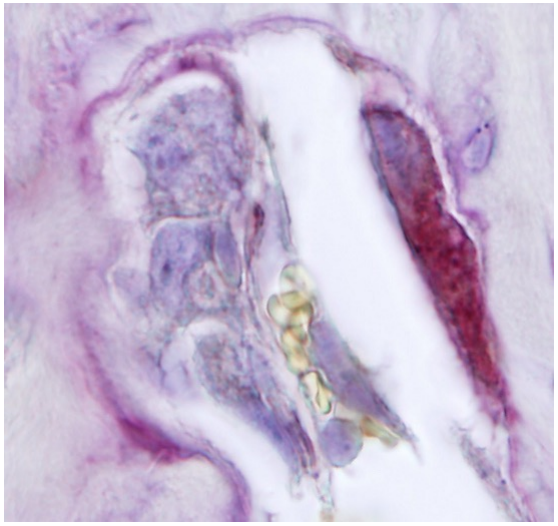


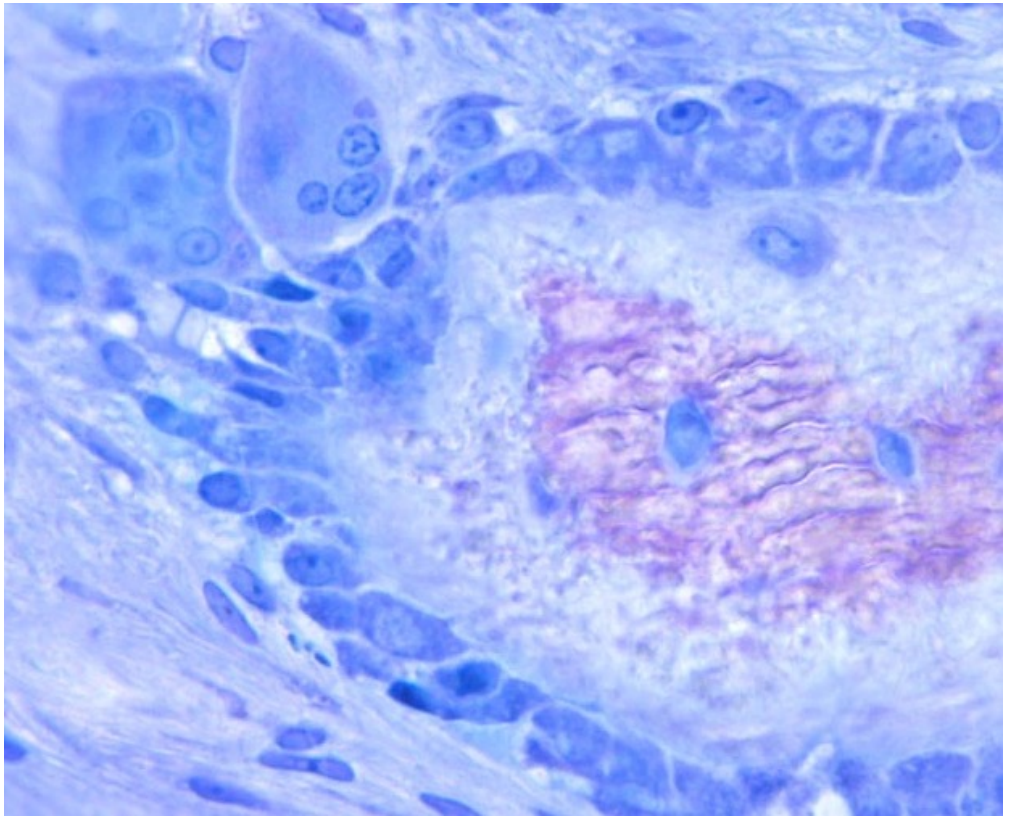
KPI Monitoring in ERKReg: dialysis

Updated 14/04/21



Keep it simple: is growth adequate?





Growth in pediatric CKD

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

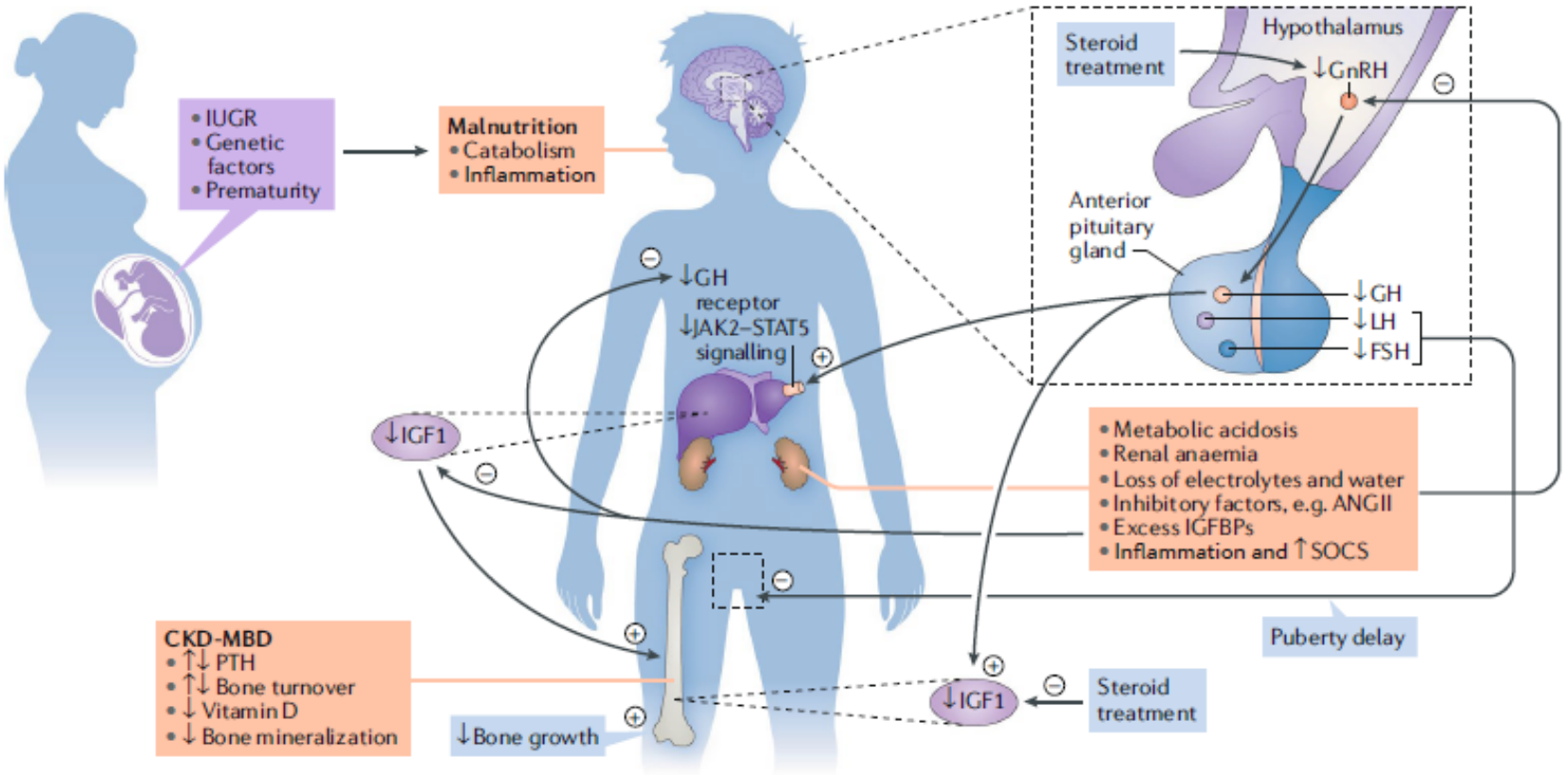
- **Causes of growth retardation in CKD**
- Inadequate intake of calories and proteins
- Water, electrolyte and acid-base imbalance
- Malnutrition
- Bone disease and CKD-MBD
- Impaired GH-IGF1 axis
- Hypogonadism
- Long-term use of corticosteroids
- Anemia
- Inflammation

Box 2 | Factors that contribute to growth failure in children with CKD

- Genetic factors
  - Parental heights
  - Gender
  - Syndromic kidney diseases
- Birth-related factors
  - Prematurity
  - Small for gestational age
  - Intensive care requirement
- Comorbidities (for example, central nervous system, liver or heart involvement)
- Age at onset of chronic kidney disease (CKD)
- Severity of CKD and residual renal function in patients on dialysis
- Metabolic disturbances
  - Salt and water metabolism
  - Metabolic acidosis
  - CKD–mineral and bone disorder (MBD)
- Anaemia
- Malnutrition
  - Altered taste sensation
  - Anorexia
  - Vomiting
  - Dietary restrictions
  - Nutrient losses in dialysate
  - Infections and inflammation
- Protein–energy wasting
  - Infections and inflammation
  - Uraemic toxins
  - Oxidative stress
  - Inflammatory cytokines
- Hormonal disturbances affecting
  - Somatotropic hormone axis
  - Gonadotropic hormone axis
  - Parathyroid hormone and vitamin D metabolism or action
  - Gastrointestinal hormones

Drube, Nature Reviews in Nephrology, 2019

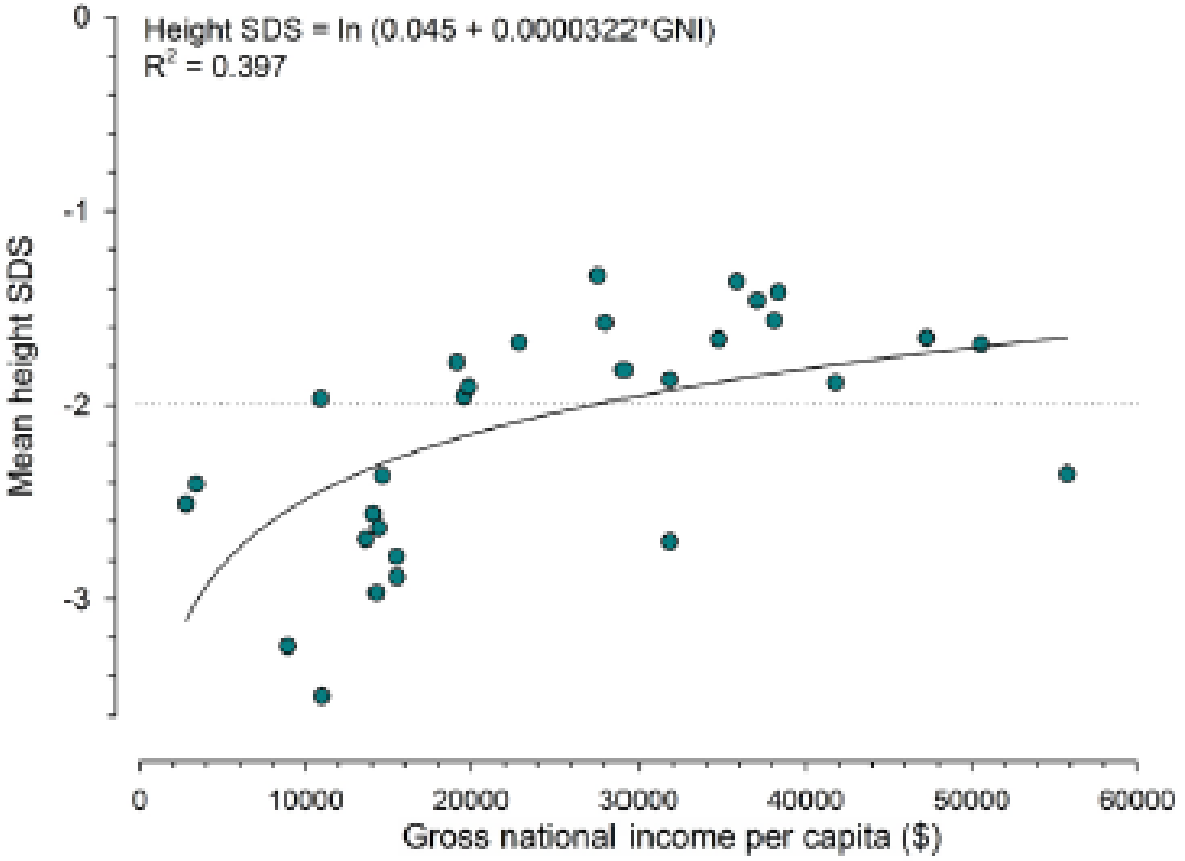
Growth in pediatric CKD



Drube, Nature Reviews in Nephrology, 2019

Growth and standardized height as markers of global child morbidity in CKD

- **IPPN registry**
  - 1773 patients
  - Age 0-19 years



Shaefer, Periton Dialysis Int 2012

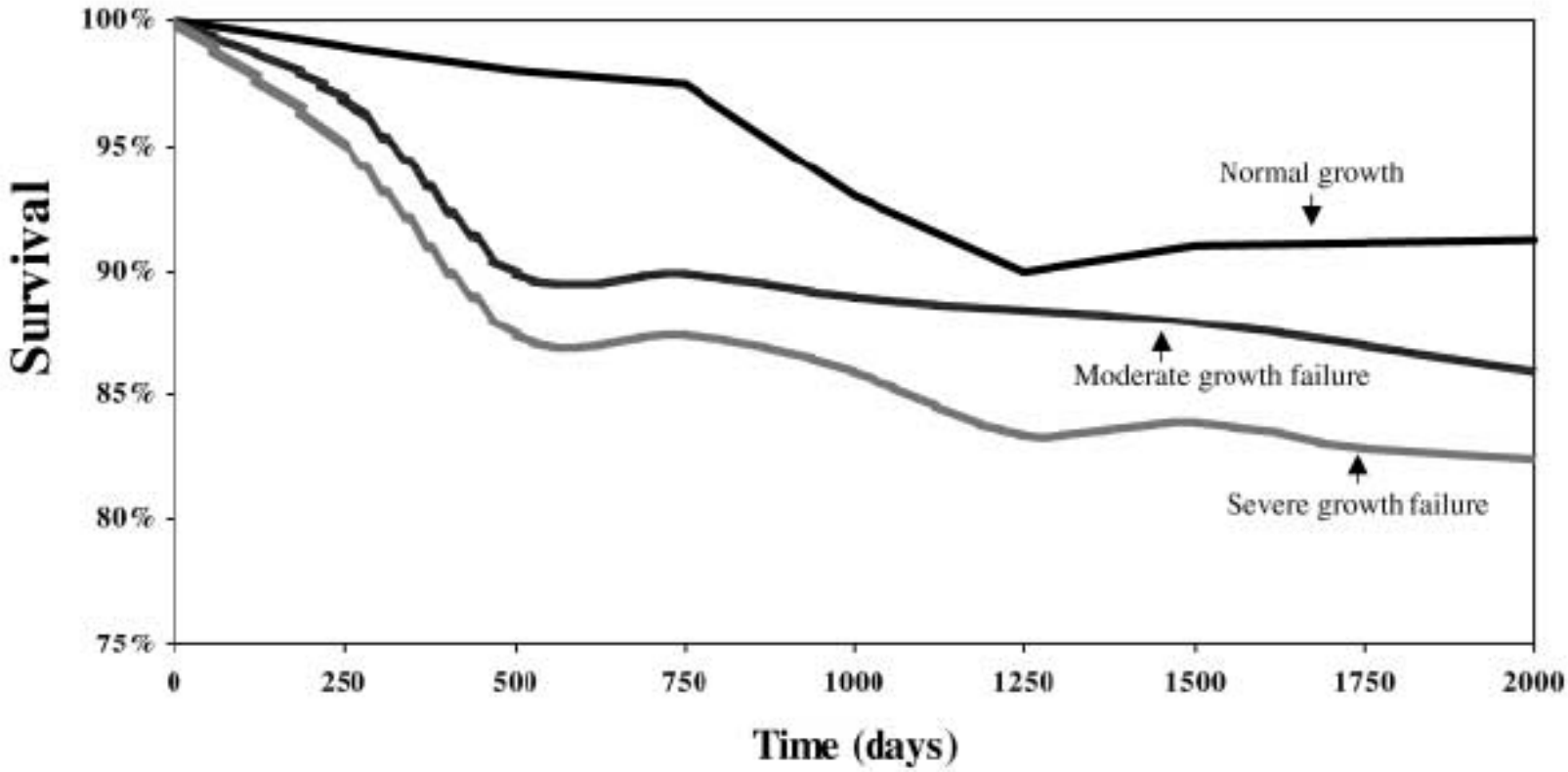
Growth failure as a risk factor for hospitalization

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

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)

Furth, Pediatric Nephrology 2002

Growth as a marker of survival

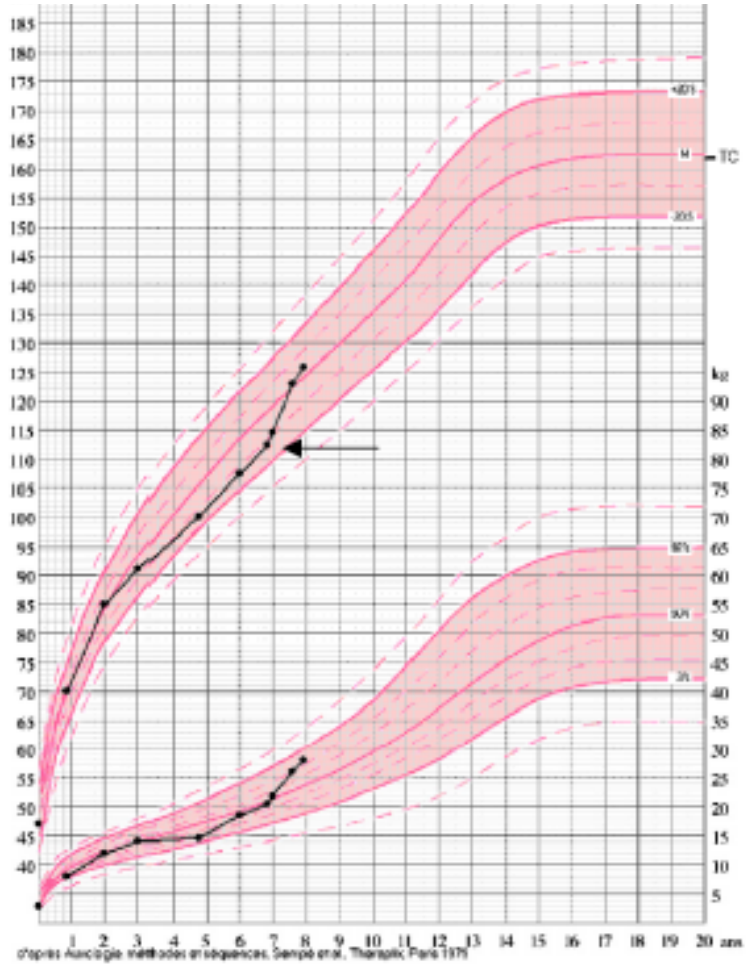


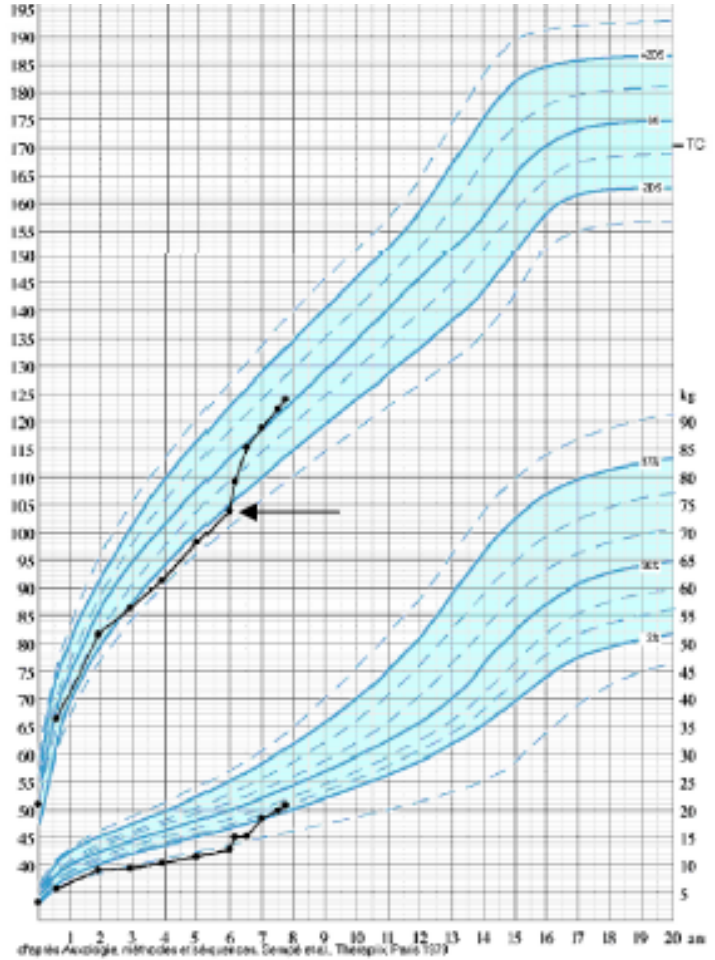
Furth, Pediatric Nephrology 2002

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[4,10], Rukshana Shroff[3], Burkhard Tönshoff[5] and Dieter Haffner[1,2], 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**

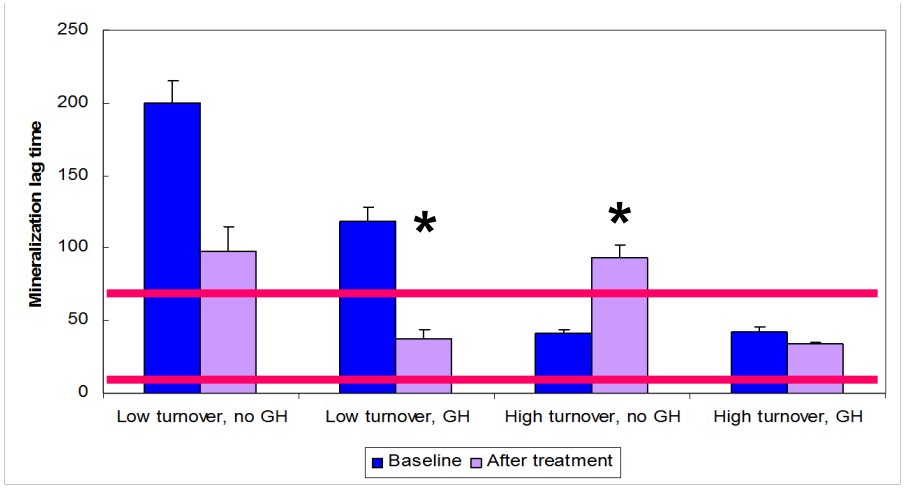
Assessment type	Age (years)	Recommended intervals of assessment (months)			
		CKD stage 3	CKD stage 4	CKD stage 4–5	CKD stage 5D
Length[a] or height	0–1	0.5–2	0.5–2	0.5–2	0.5–2
	1–3	1–3	1–2	1–2	1–2
	>3	3–6	1–3	1–3	1–3
Length velocity[a] or height velocity	0–1	0.5–2	0.5–2	0.5–2	0.5–1
	1–3	1–6	1–3	1–3	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)[11,15,16]. CKD, chronic kidney disease. [a]Supine length is measured using a validated length board or mat up to a length of 80 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)

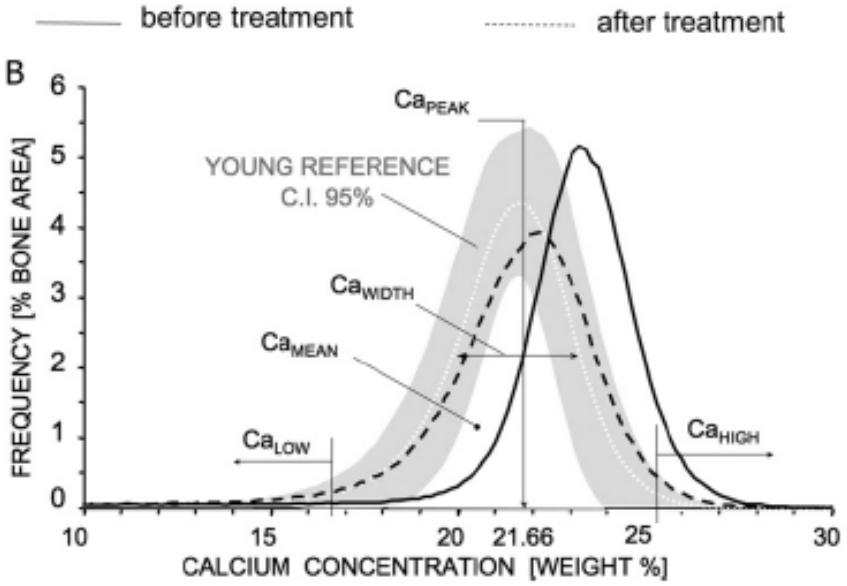
rhGH therapy improves mineralization, whatever the type of the underlying osteodystrophy

- **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



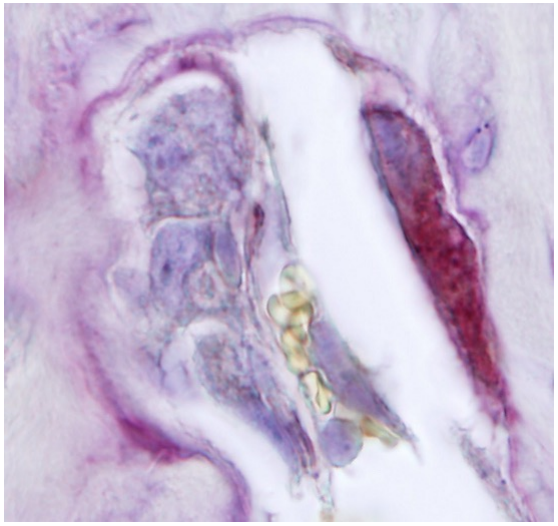
Bacchetta, cJASN, 2013

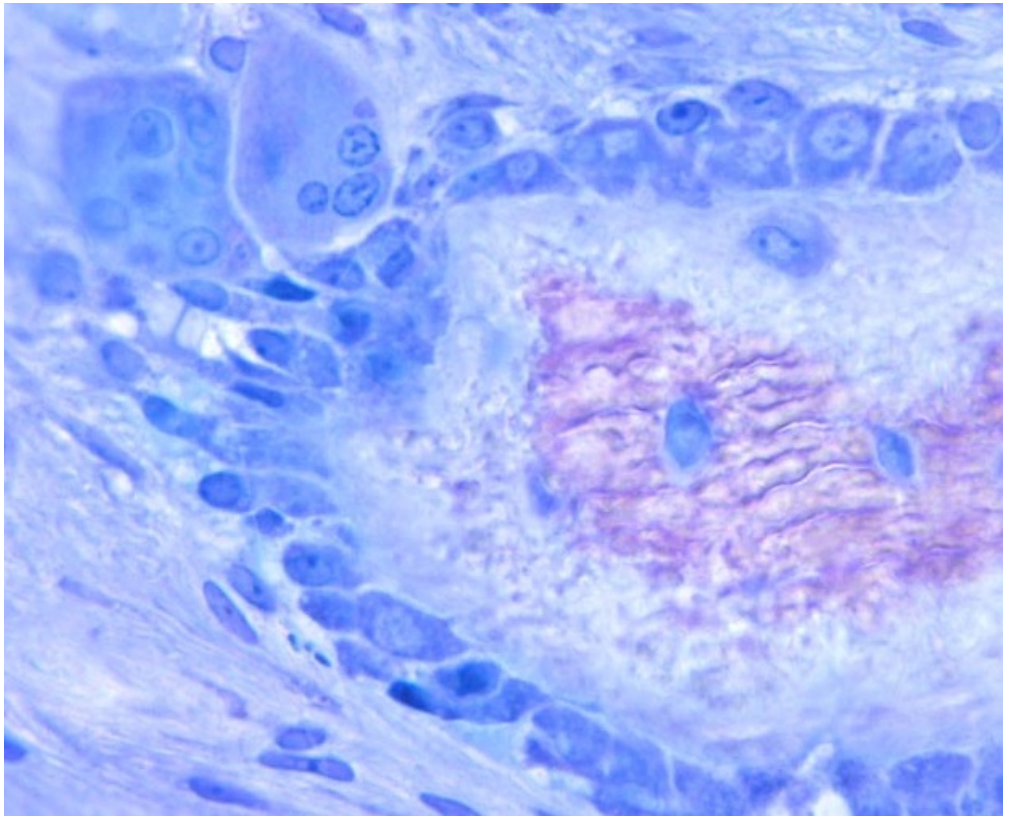
- **Study from Austria and Poland**
  - 18 children, hemodialysis
  - rhGH for one-year
  - Paired analysis before/after
  - **Baseline: high prevalence of low bone turnover**



Nawrot-Wawrzyniak, AJKD 2013

Keep it (relatively) simple: nutrition





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]

Received: 20 May 2020 / Revised: 3 October 2020 / Accepted: 6 November 2020 / Published online: 14 December 2020

Frequency of follow-up

Table 1 Parameters and frequency of nutritional assessment in children with CKD stages 3b–5D[#]. Anthropometric measurements

Measure	Age 0–1 year[∞] Minimum interval (weeks)		Age 1–3 years Minimum interval (months)		Age > 3 years Minimum interval (months)	
	CKD 3b–5	CKD 5D	CKD 3b–5	CKD 5D	CKD 3b–5	CKD 5D
Height or length for age (centile or SDS)	6	2–4	2	1	3	3
Height or length (centile or SDS)	8	4	3	2	6	6
Height velocity for age (SDS)	N/A	N/A	3	2	6	6
Estimated euvolemic weight and weight for age (centile or SDS)	6	4	2	1	3	3
BMI for height age (centile or SDS)	N/A	N/A	2*	1*	3	3
Weight for length* (centile or SDS)	6	6	2*	1*	N/A	N/A
Head circumference for age (centile or SDS)	6	4	2	2	N/A	N/A

[#] Earlier stages of CKD and other kidney diseases are not addressed in this table, as clinical conditions can vary and physician discretion is required. Further details are addressed in [2]

*Weight for length should be used for children < 2 years of age or up to 3 years if accurate standing height measurement is not possible

[∞] Infants and toddlers cannot be categorized with the stage of CKD as there may be spontaneous improvement in kidney function up to 2 years of age. A suggested method to characterize the stage of CKD in this age group is to use the KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, substituting a GFR > 1 but ≤ 2 SDS below the mean for moderate reduced GFR (stages 3–4) and severely reduced GFR > 2 SDS below the mean for stage 5 [3]

Nelms Pediatr Nephrol 2021

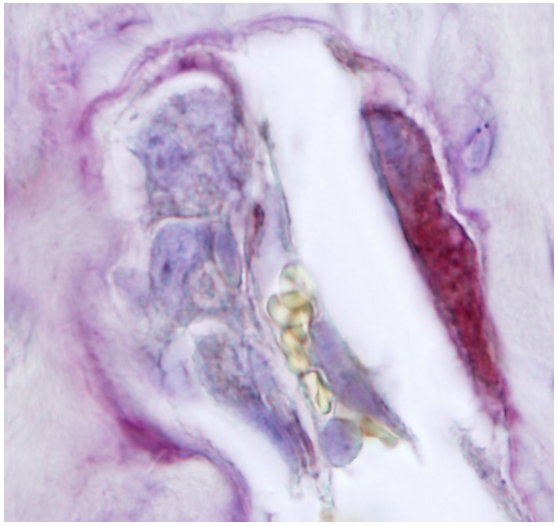
Frequency of follow-up

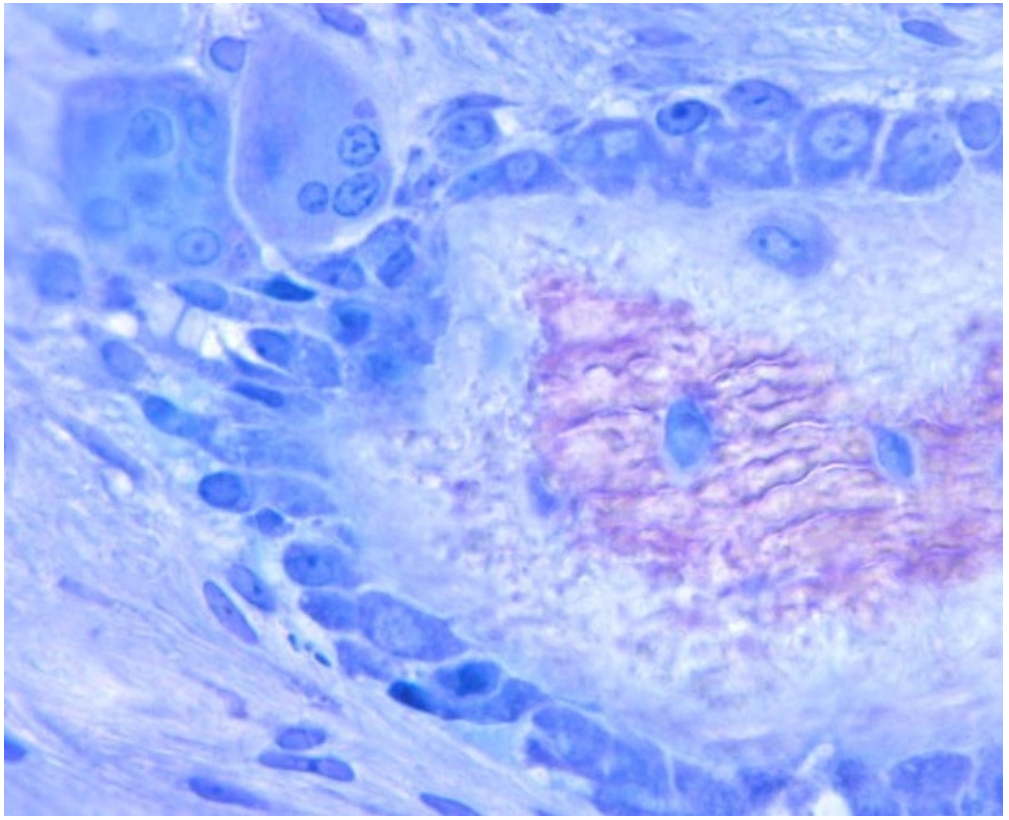
Table 3 Parameters and frequency of nutritional assessment in children with CKD stages 3b–5D[#]. Dietetic contacts[†]

	CKD 2–3a	CKD 3b–5	CKD 5D
0–6 months of age	3 months	1 month	1 month
6–12 months of age	3 months	1 month	1 month
Age 1 year and older	1 year	3 months	1 month

Nelms Pediatr Nephrol 2021

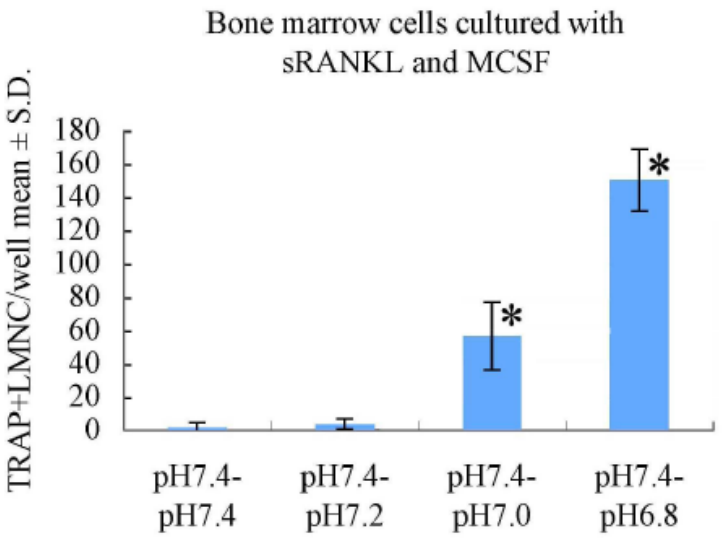
Keep it (relatively) simple: biological parameters

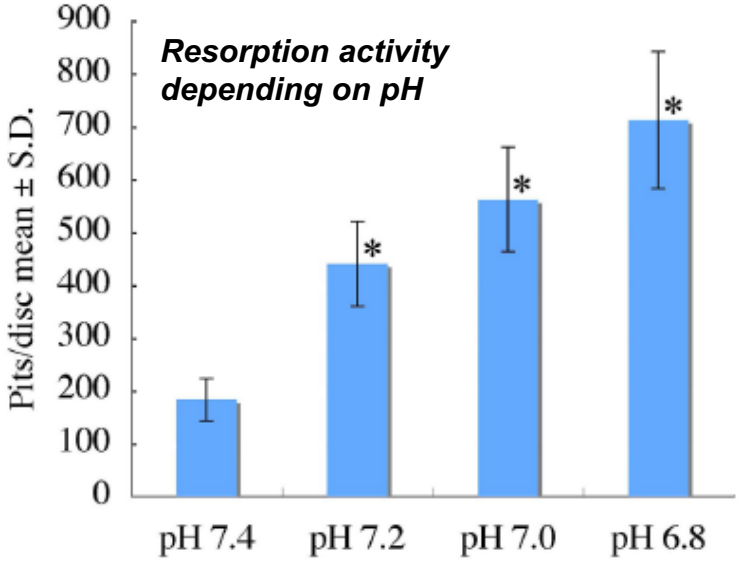




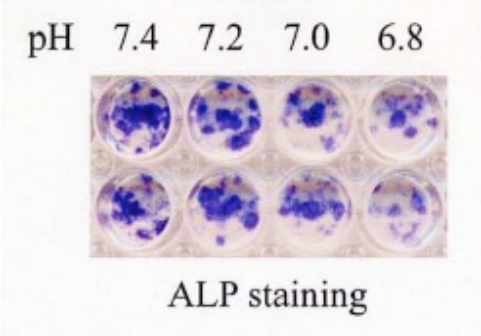
KPI Bicarbonate levels > 20 mmol/L: acidosis and bone metabolism

- Stimulation of osteoclastic differentiation
- Stimulation of osteoclastic resorption





- Inhibition of osteoblastic differentiation



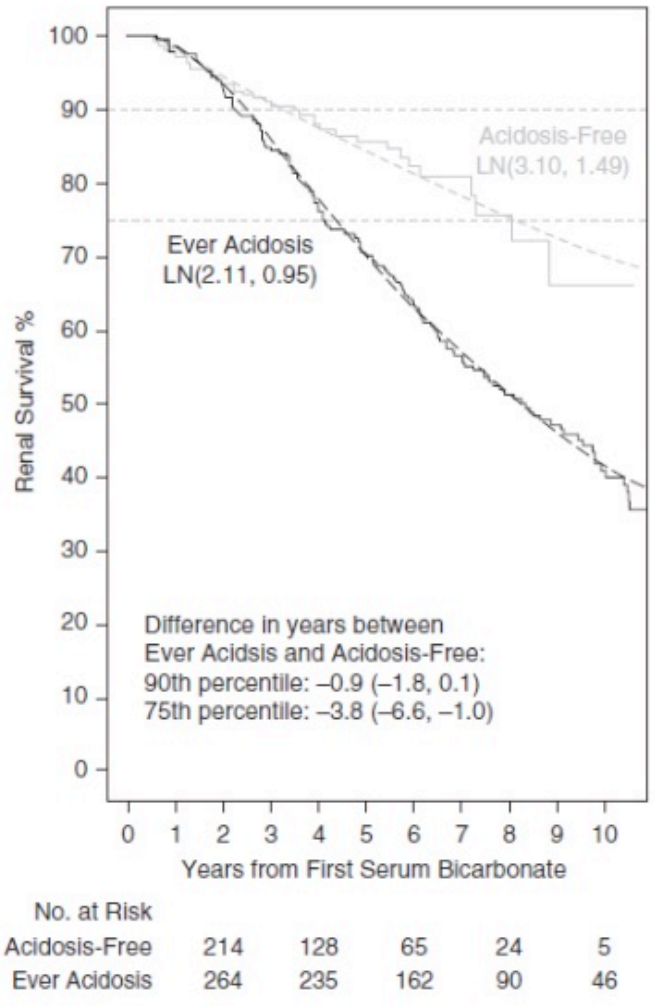
Harambat Kidney Int 2017

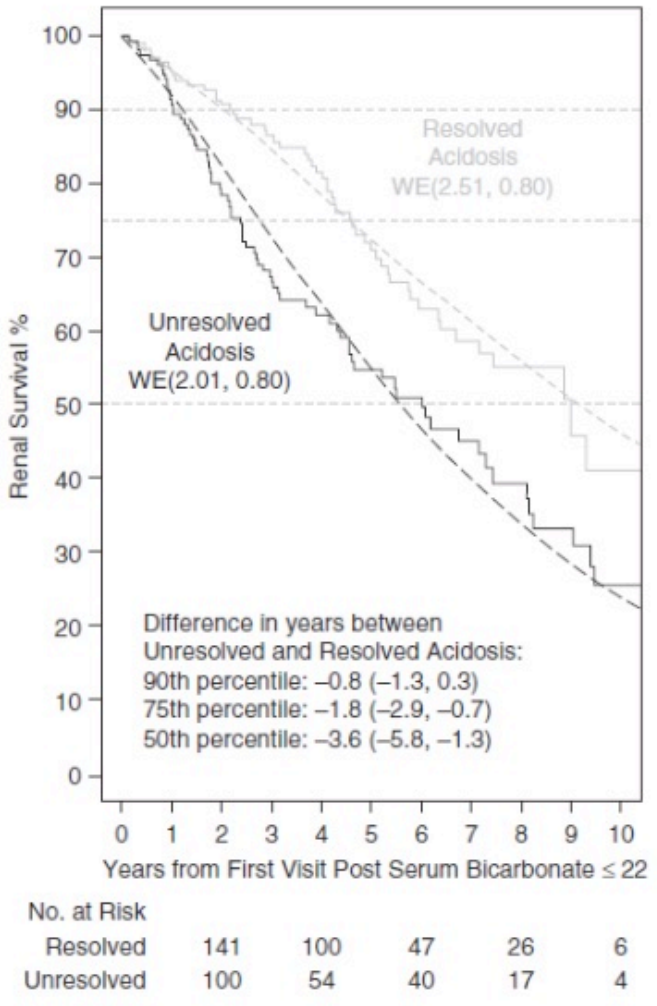
Bicar<22 as a risk factor for CKD progression in the 4C cohort

Kraut, Kidney International 1986

Kato, BioScience Trends 2013c

Acidosis and the risk of CKD progression in children



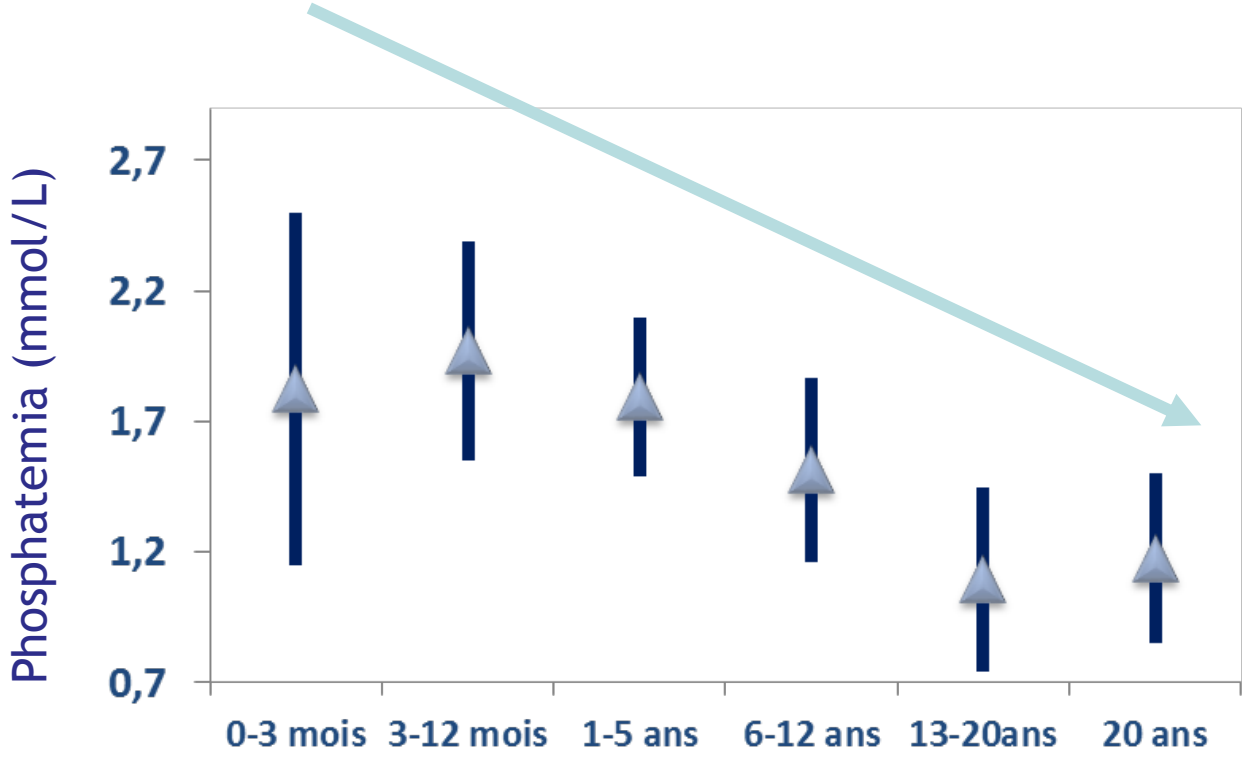


Threshold here 22 mmol/L

Only 36% of patients with acidosis were supplemented in this CKID study

Brown cJASN 2020

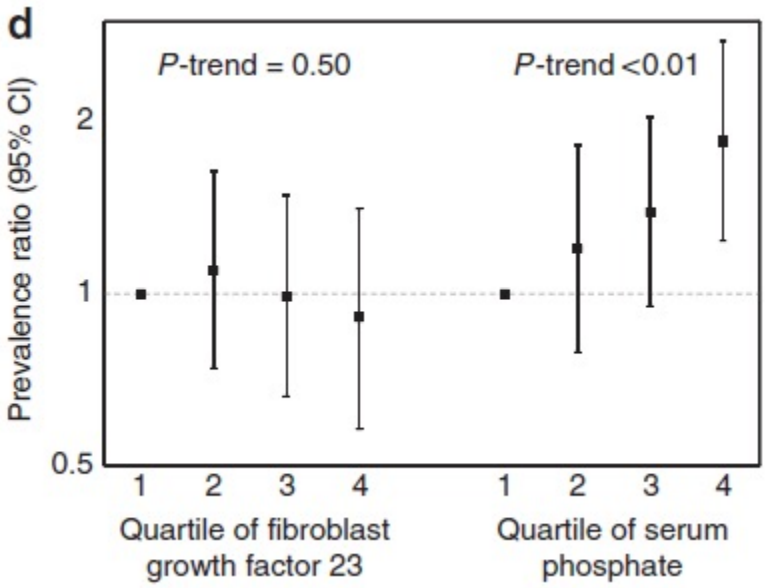
KPI phosphate within the normal range: reference values for phosphate must be adapted to age +++

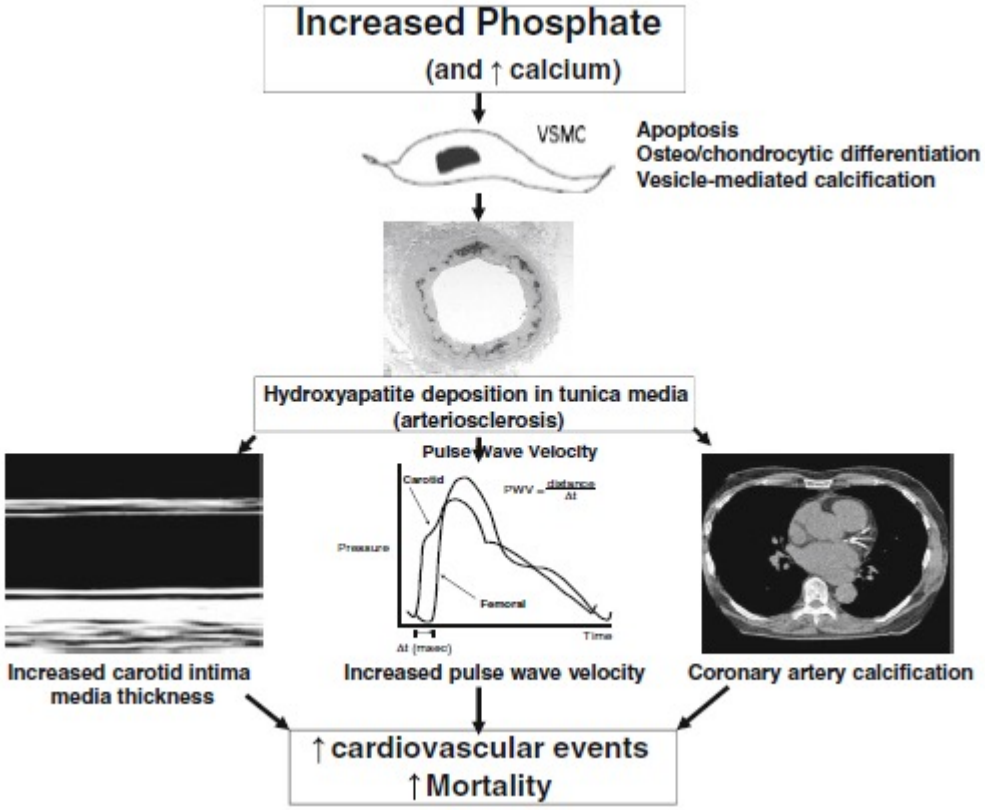


=> Z-score of phosphate depending on age ++++

Ardeshirpour Pediatr Endocrinol Rev 2007

Phosphate is a/the vascular toxin/silent killer





Vascular calcifications

=> In adults do not forget that hypophosphatemia in dialysis is also a risk factor for mortality (denutrition) and that daily HD may induce hypophosphatemia in infants with further mineralization defects!

Scialla, Kidney International 2013

Shroff, Pediatric Nephrology 2013

KPI Hb> 11 g/dL: impact of anemia on QOL

- **CKID study**
  - 773 patients

Anemia (hemoglobin < 5th percentile for age, sex, and race)	231 (30%)
Use of iron supplement	216 (28%)
Use of ESA	50 (6%)

Pediatric Nephrology (2020) 35:1659–1667
https://doi.org/10.1007/s00467-020-04569-5

ORIGINAL ARTICLE

Check for updates

A longitudinal analysis of the effect of anemia on health-related quality of life in children with mild-to-moderate chronic kidney disease

Joann Carlson[1] · Arlene C. Gerson[2] · Matthew B. Matheson[3] · Sharon Manne[4] · Bradley A. Warady[5] · Stephen R. Hooper[6] · Marc Lande[7] · Lyndsay A. Harshman[8] · Rebecca J. Johnson[9] · Shlomo Shinnar[10] · Amy J. Kogon[11] · Susan Furth[11]

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 Stabouli[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)**

STATEMENTS

1. Clinical Evaluation of Bone Disease

1.1. In children with CKD, take a clinical history and perform a physical examination to look for CKD-MBD-related bone disease.

1.2. The frequency of assessment is based on the underlying cause and stage of CKD, the patients' age, symptoms, presence of comorbidities and extent of abnormalities in previous CKD-MBD measures. More frequent assessment during periods of rapid growth in infancy and adolescence is required.

Table 1. Suggested intervals of clinical assessment (in months) by CKD stage and age (adapted from [13, 31)

	CKD stage			
	2	3	4	5/5D
History[a], length[b] or height, clinical evaluation[c] (in months)				
Age 0–1 years	1–3	0.5–2	0.5–2	0.5–1
Age 1–3 years	3–6	1–3	1–2	1–2
Age >3 years	3–6	3–6	1–3	1–3
During puberty	3–6	1–3	1–3	1–3

2. Serological Evaluation of Bone Disease

2.1. Measure serum levels of Ca, P, ALP, PTH and 25(OH)D in children with CKD Stages 2–5D as markers of CKD-MBD. Where available, use ionized Ca levels in timely and appropriately processed samples.

2.2. The frequency of monitoring is based on the presence and severity of abnormalities including age, stage and progression of CKD, signs and symptoms and concomitant medications.

2.3. Consider age-related normal ranges of serum Ca, P and ALP and CKD stage-dependent PTH target ranges in the diagnosis and management of bone disease in children with CKD.

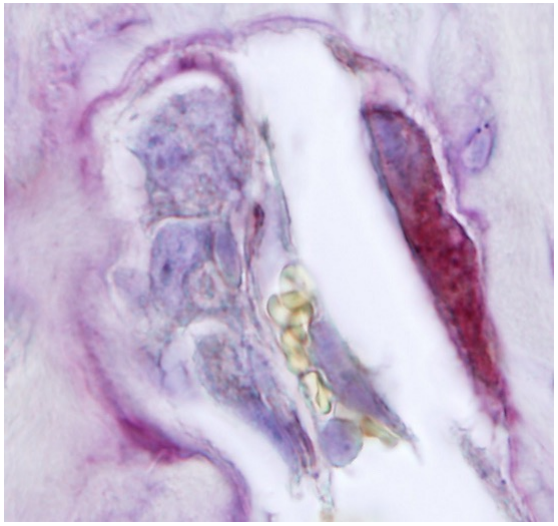
2.4. Use trends in serum biomarkers considered together, rather than single laboratory values, to guide therapeutic decisions.

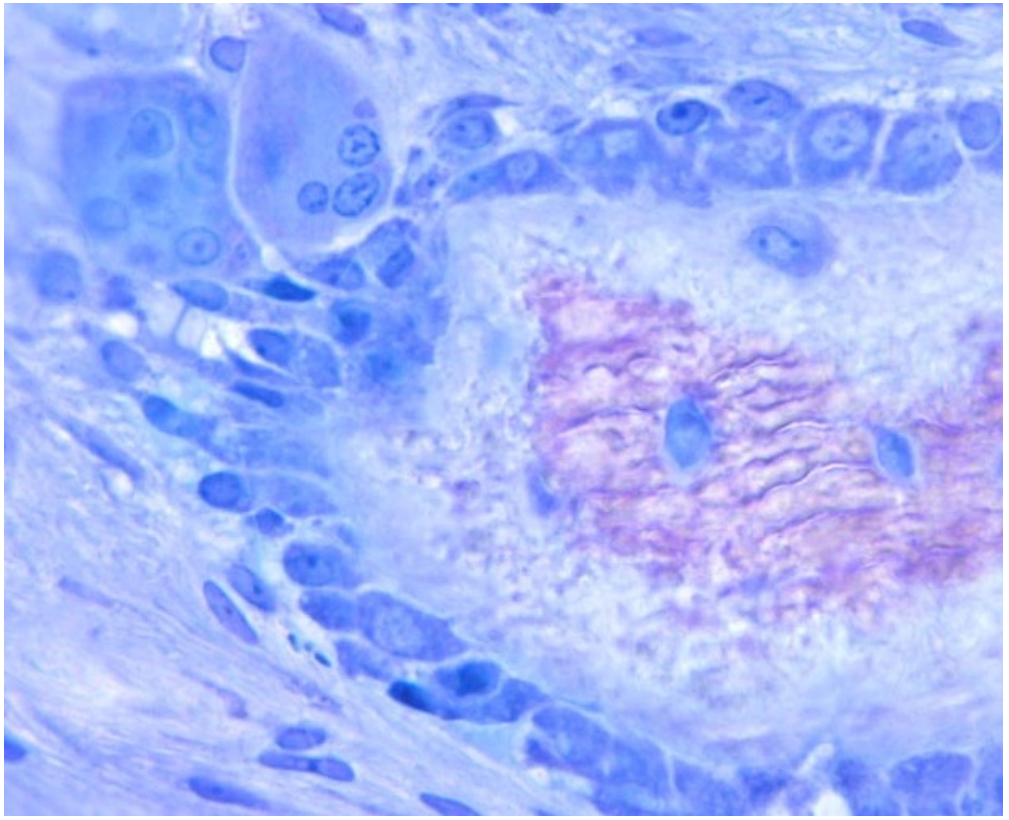
2.5. Monitor serum bicarbonate levels regularly and maintain within the normal range.

Table 2. Suggested intervals of assessment (in months) of serum markers of bone health and acid–base balance in children by CKD stage (adapted from [11, 12, 21, 46)

	CKD stage			
	2	3	4	5/5D
Ca, P	6	6	3	1
Total ALP	12	6	3	1–3
PTH	12	6	3	1–3
25(OH)D[a]	12	6	3–12	3–12
Bicarbonate	6	6	3	1

The future: other KPI?





PTH is not an official KPI in ERKReg…
PTH is not the perfect biomarker 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

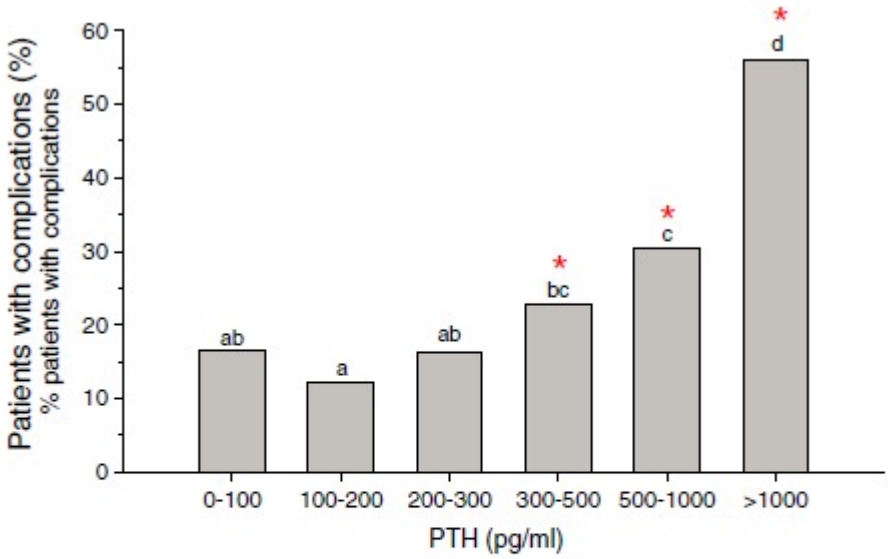


Fig. 3 Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extraosseous calcifications, radiological osteomalacia and/or osteopenia) stratified by time-averaged mean parathyroid hormone (PTH) levels. Groups sharing same letters do not differ significantly;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

Haffner Pediatr Nephrol 2013

PTH levels: different guidelines… different targets…

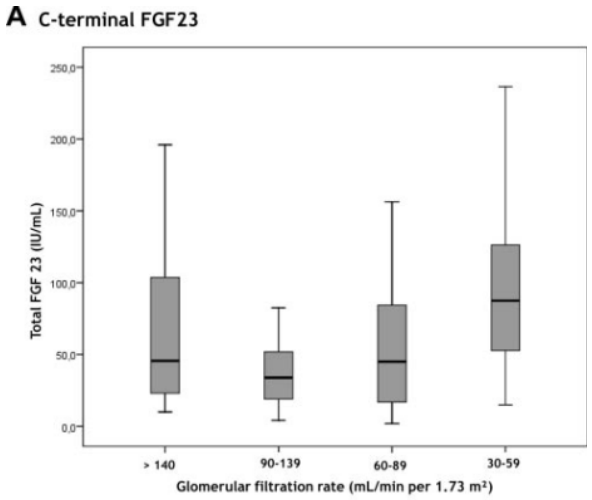
- **K-DOQI 2005**
  - PTH 3-5 times above the upper normal limit : **200-300** pg/mL
- **European guidelines 2006**
  - European Pediatric Dialysis Working Group
  - Keep PTH levels within 2-3 times the upper normal limit: **120-180** pg/mL
- **K-DIGO 2017**
  - PTH 2-9 times above the upper normal limit : **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

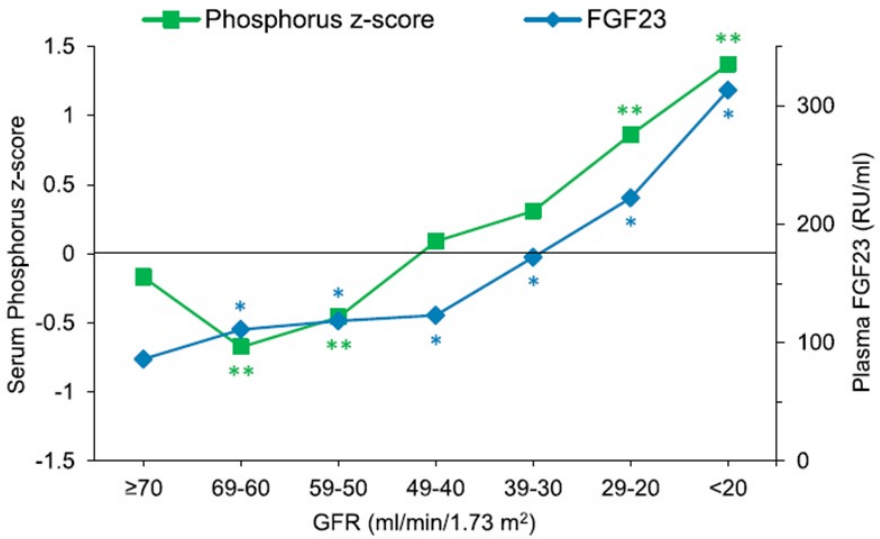
It is not a problem of numbers, rather a problem of trends and global philosophy!

In registries, we may think as xx-UNL for the local assay…

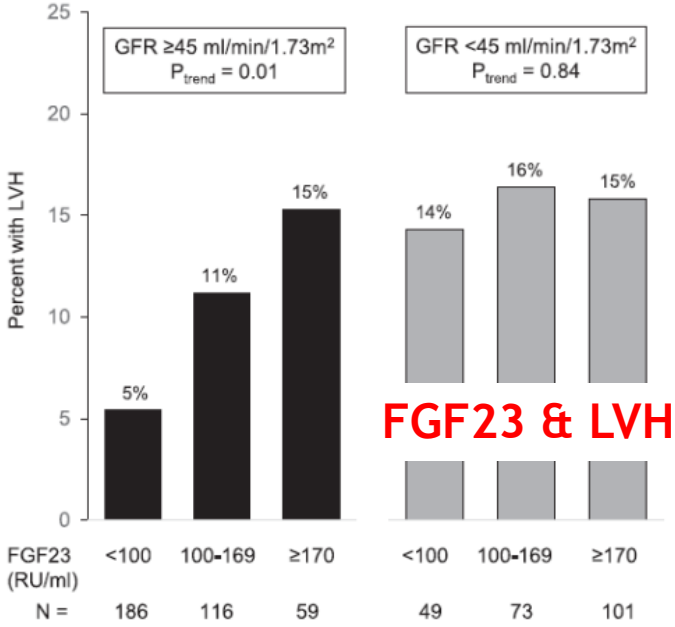
Haffner Pediatr Nephrol 2013

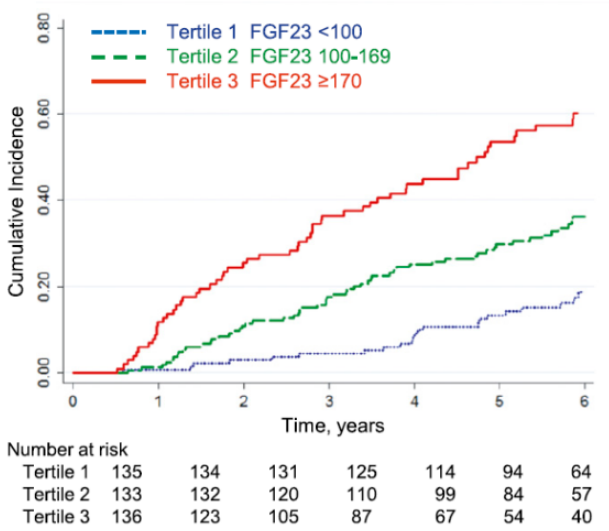
A good KPI should be associated with outcomes…





Increase of FGF23 with eGFR decline





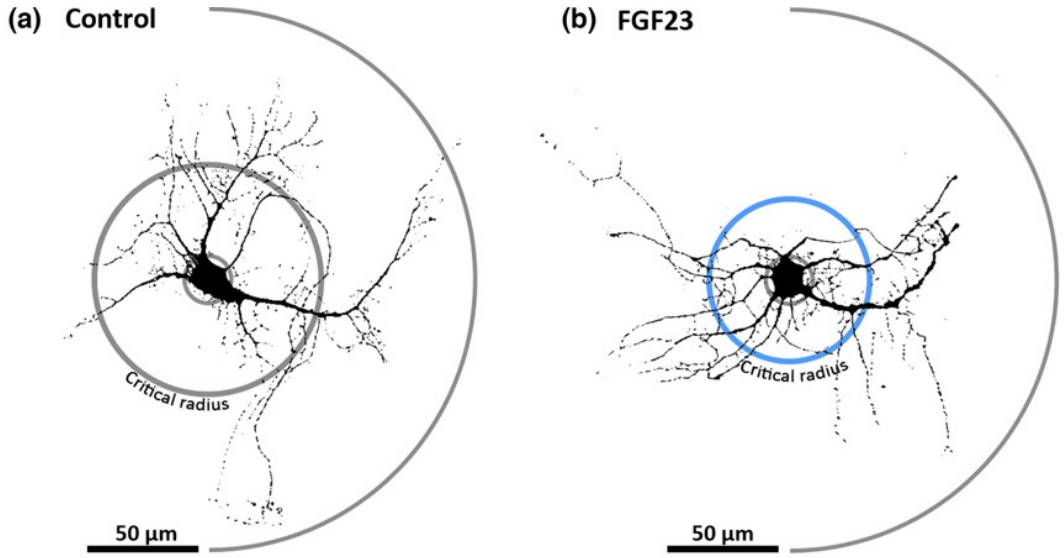
Bacchetta JCEM 2010; Portale cJASN 2012; Mistnefes cJASN 2018; Portale cJASN 2016

FGF23 & CKD progression

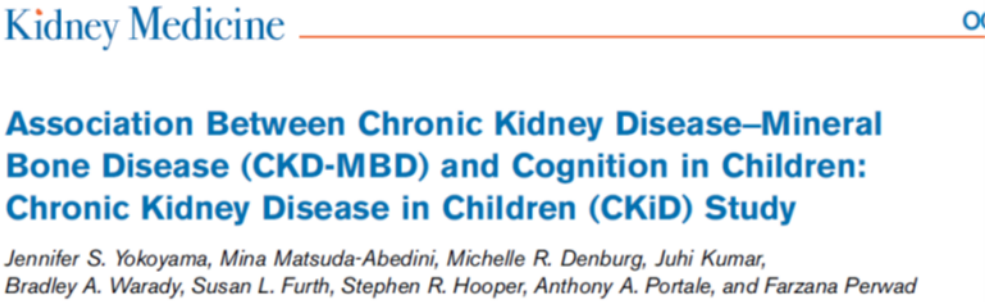
FGF23 as a potential KPI?

- **In vitro model of primary murine hippocampal cultures**
- **Incubation with FGF23 ± α-Klotho**
- Enhanced number of primary neurites
- And reduced arborization

⇒ **Resulting in a less complex neuronal morphology**



- **Clinical study in CKID**
- Increased levels of FGF23 associated with lower performance in targeted tests of executive function, specifically attention regulation
- independent of glomerular filtration rate


Kidney Medicine

Association Between Chronic Kidney Disease–Mineral Bone Disease (CKD-MBD) and Cognition in Children: Chronic Kidney Disease in Children (CKiD) Study

Jennifer S. Yokoyama, Mina Matsuda-Abedini, Michelle R. Denburg, Juhi Kumar, Bradley A. Warady, Susan L. Furth, Stephen R. Hooper, Anthony A. Portale, and Farzana Perwad

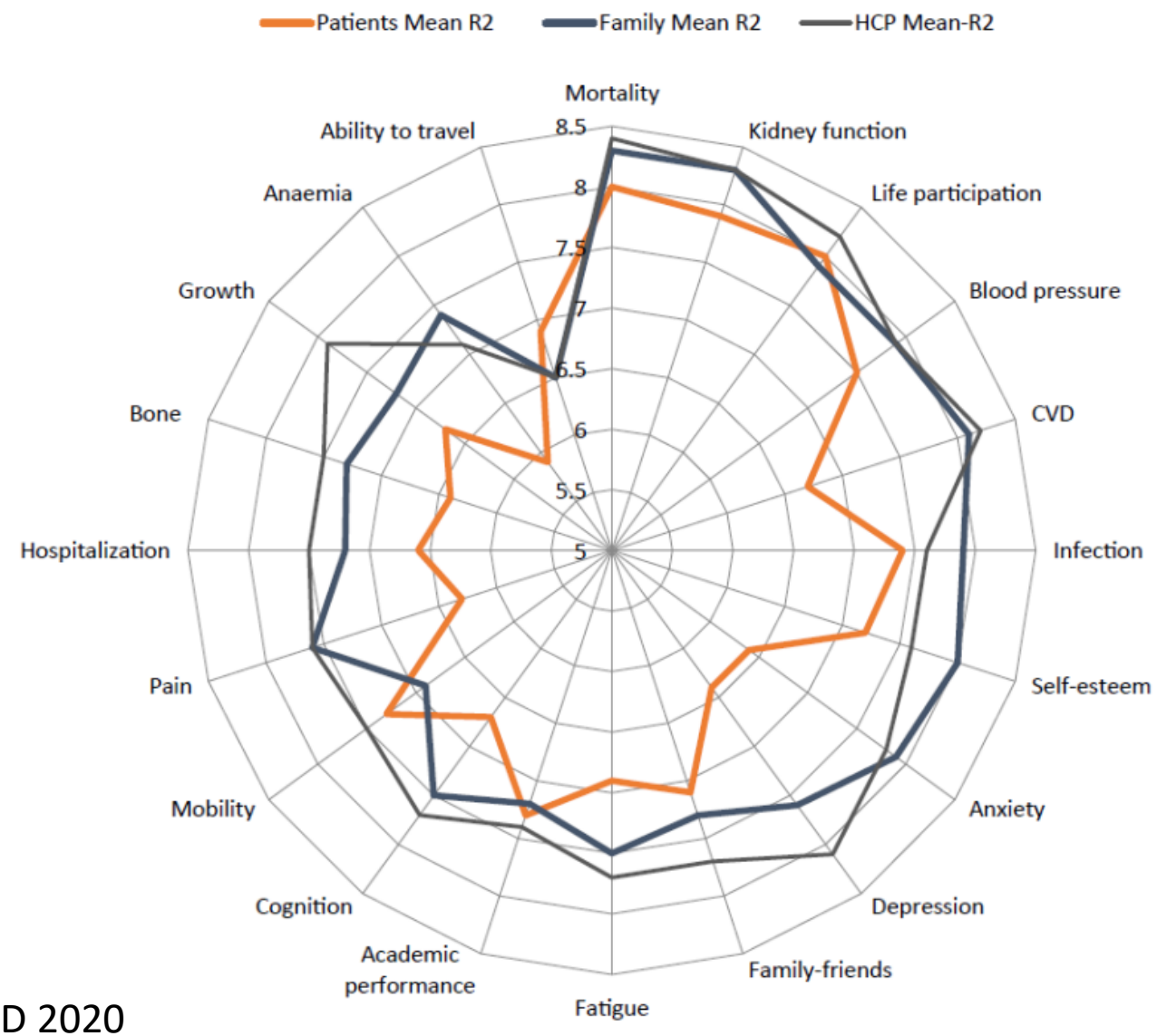
Hensel J Neurochemist 2016 / Yokoyama Kidney Med 2020

Proposed new KPI by the group

Updated 14/04/21

List of potential KPIs that could be added
• ***Low or normal trauma fractures*** *in last 12 months/bone pains/deformities.* worries that no accurate data will be collect. It was decided during the Oct 2020 meeting that a specific online survey specific for bone deformities be performed. • ***% of children with BMI >90th percentile*** This information is already being collected. An appropriate KPI could be programmed on that data. • *Treatment modality (HD vs PD vs preemptive)* • *In HD patient - Vascular access type* This is not capture in the moment but can be considered for the future • *Calcium and Phosphate control* **Proportion of patients below and above the normal range for age**; this information is already being collected and an appropriate KPI could be programmed on that data.

The SONG initiative: do physicians and patients share the same view on KPI???



Logeman, AJKD 2020