european society for paediatric nephrology

Bone Evaluation in Children with Chronic Kidney Disease and Dialysis

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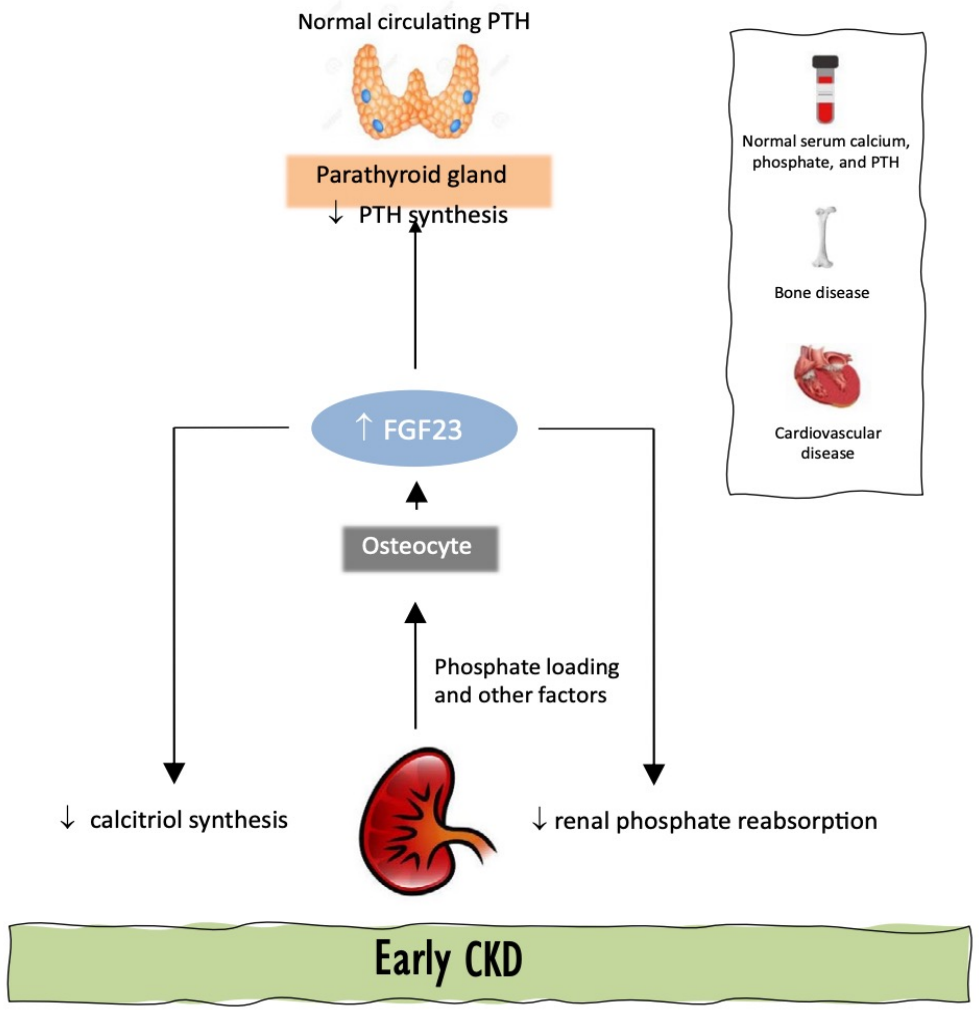
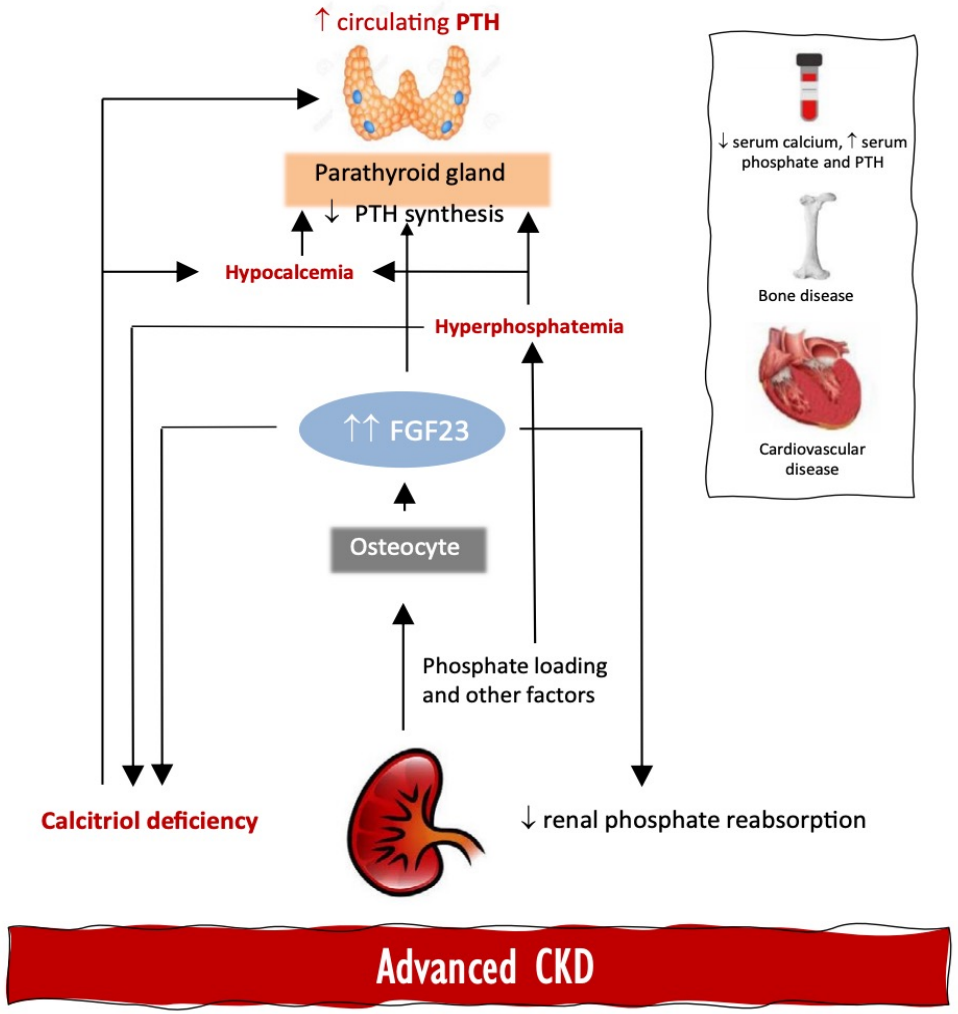
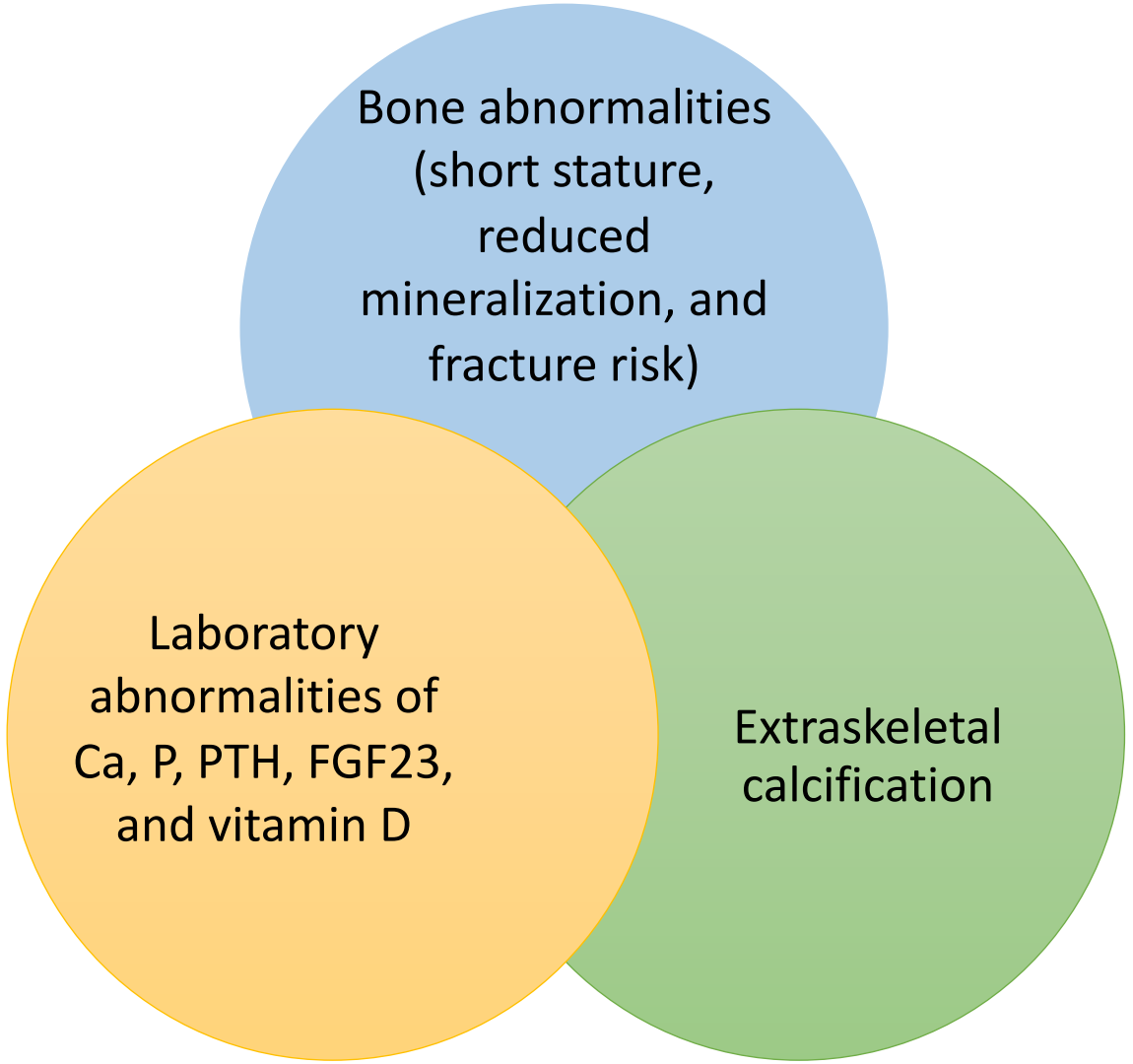
ESPN CKD-MBD Working Group Meeting, 28 April 2021





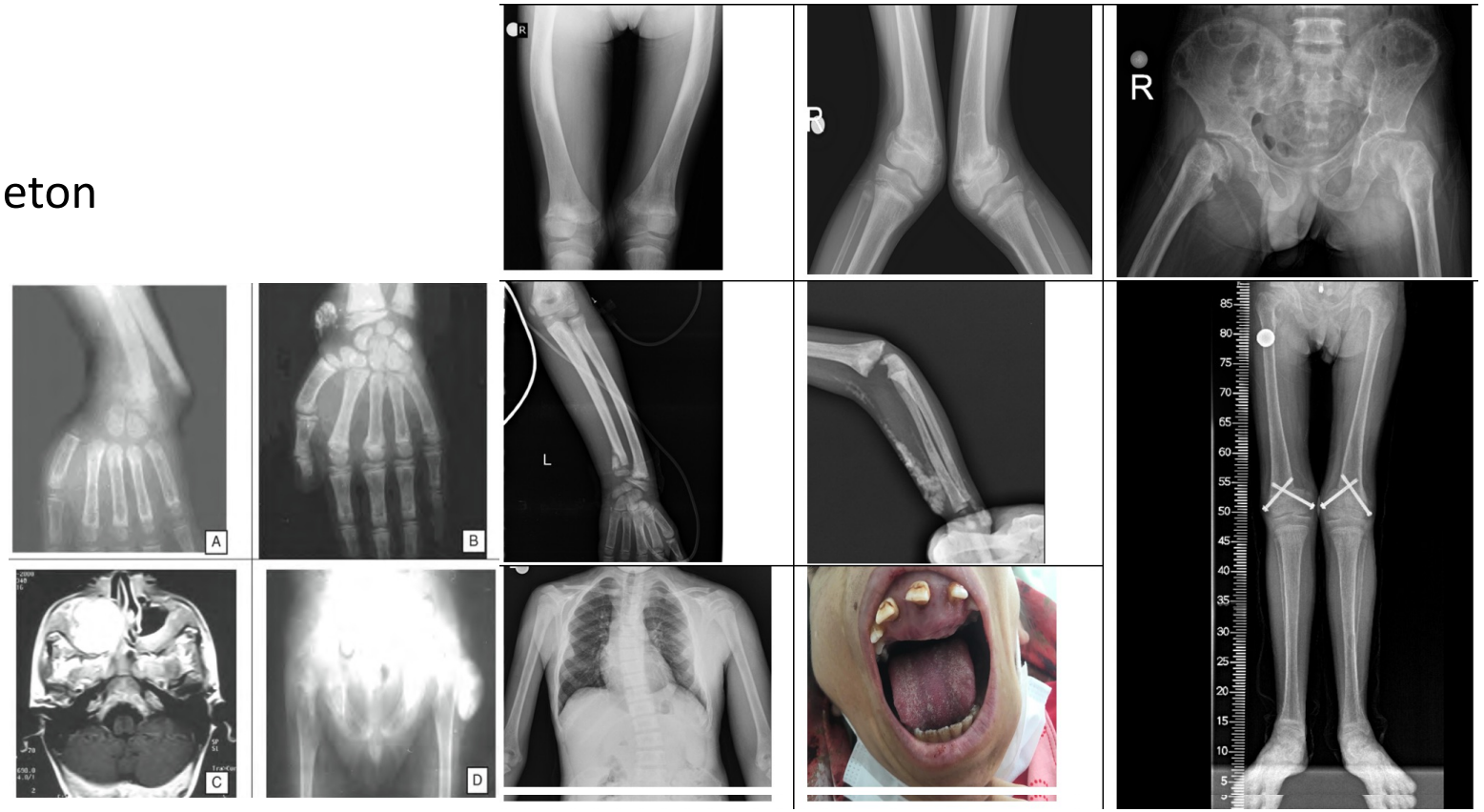
Santos F, et al. Calcific Tissue Int 2021

Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD)



CKD-MBD in children

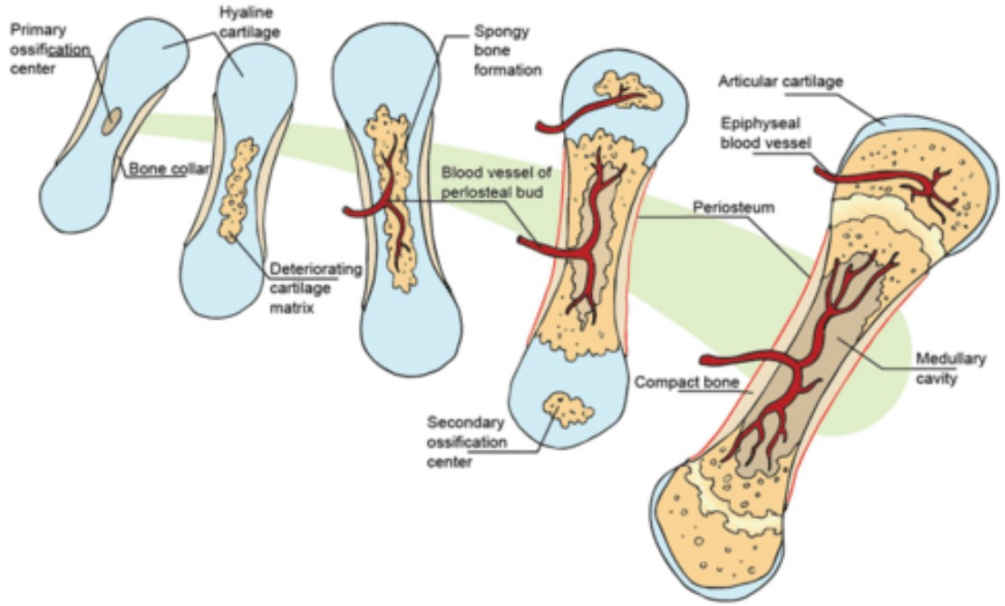
- widely prevalent
- associated with pronounced disturbances in the growing skeleton
  - short stature
  - bone pain and deformities
  - fractures
  - slipped epiphyses
  - ectopic calcifications

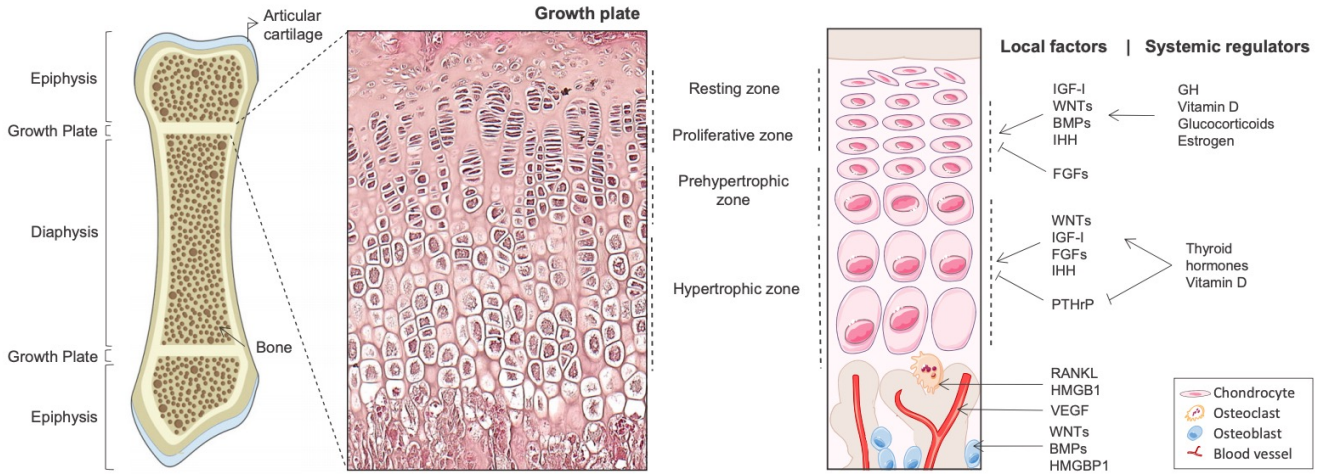


Why so different from adults?

Growing bone

- Bone modeling
  - Endochondral bone formation - lenght
    - The growth plates promote longitudinal growth until young adulthood
    - Cancelous bone develops at secondary ossification center
  - Periosteal bone formation - width
    - Compact bone develops starting at primary ossification center
- Bone remodeling

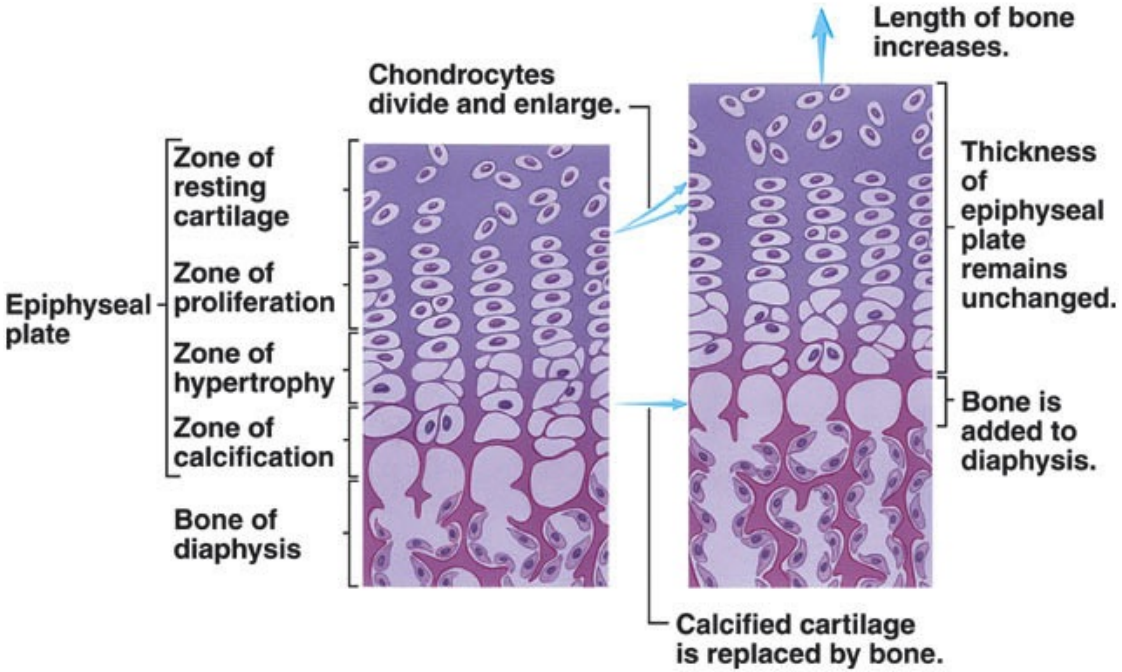




Fernandes-Iglesias A, et al. Pediatr Nephrol (2020) 35:367–374

Uremia-related disturbances in the normal physiology of the growth plate of long bones

Normal condition



Uremia

- Disorganization of the columnar arrangement
- Alteration of the maturation process
- Marked irregularity of the metaphyseal bone/cartilage interface
- Disequilibrium between bone apposition rate and cartilage production and progression
- Expansion of the hypertrophic zone
- Reduction of the proliferative activity
- Low height of terminal chondrocytes

Fernandes-Iglesias A, et al. Pediatr Nephrol (2020) 35:367–374

european society for paediatric nephrology

era edta CKD-MBD working group
Chronic Kidney Disease Mineral and Bone Disease

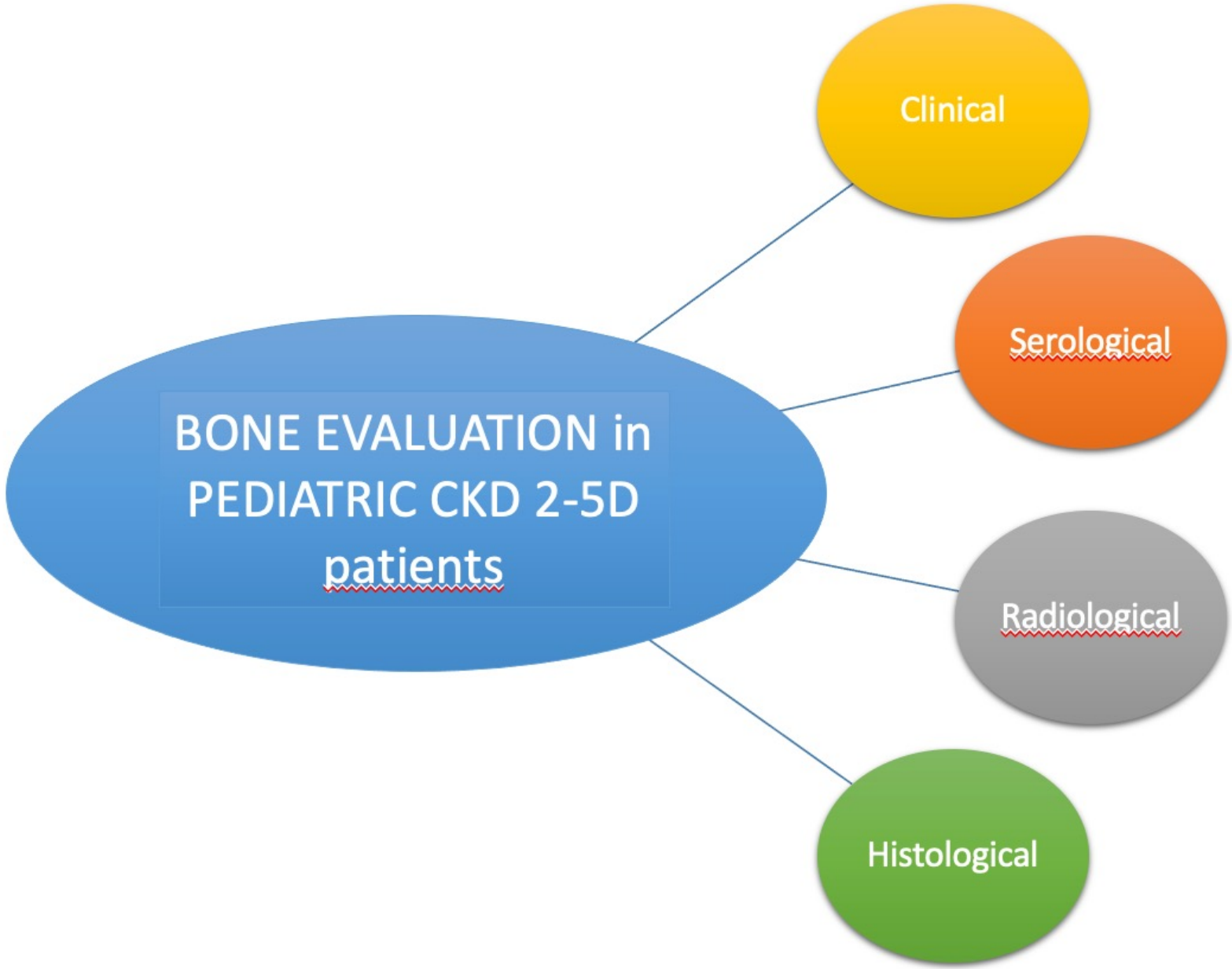
ndt Nephrology Dialysis Transplantation

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)**

SPECIAL REPORT

Bakkaloglu SA, et al. NDT 2020


BONE EVALUATION in PEDIATRIC CKD 2-5D patients
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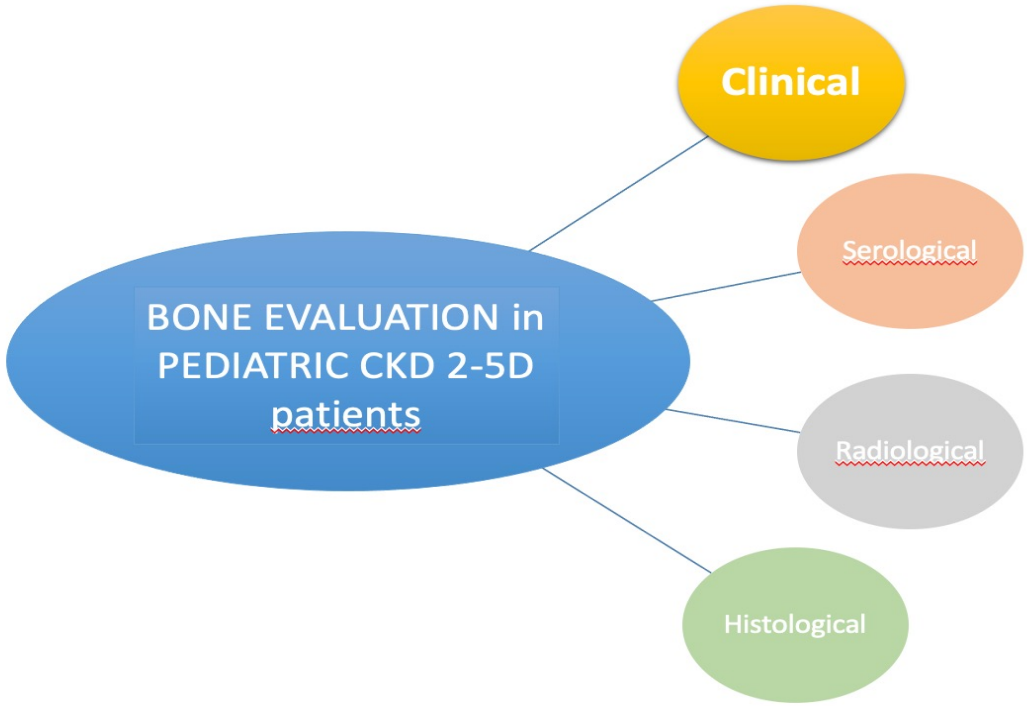


Regular clinical examination focusing on skeletal growth and bone/joint evaluation is essential

- Focused prenatal-antenatal and postnatal clinical history and detailed musculoskeletal examination
- Recumbent length before age 2
- Growth velocity every six months
- Utilize growth curves plotted on standard centile growth charts

Clinical Evaluation

Suggested intervals of clinical assessment by age and CKD stage

	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

more frequent assessment during periods of rapid growth (infancy and adolescence)

- underlying cause
  genetic diseases with specific bone involvement
- stage of CKD
- the patients' age
- symptoms
- presence of comorbidities
- extent of abnormalities in CKD-MBD measures

Bakkaloglu SA, et al. NDT 2020

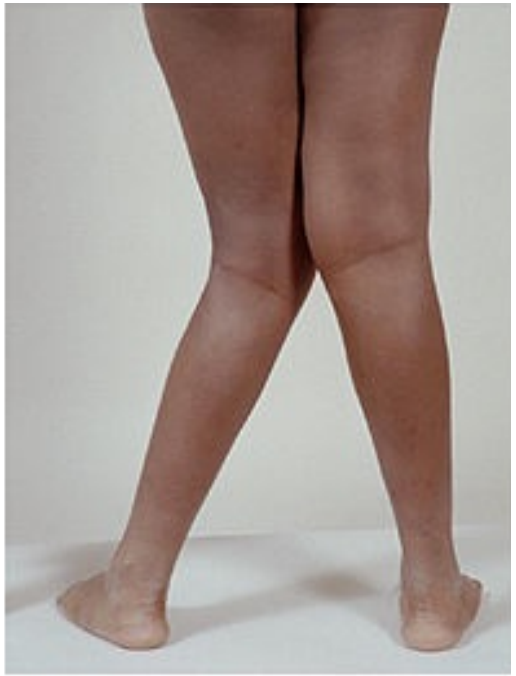
Important patient-level outcomes

- growth failure

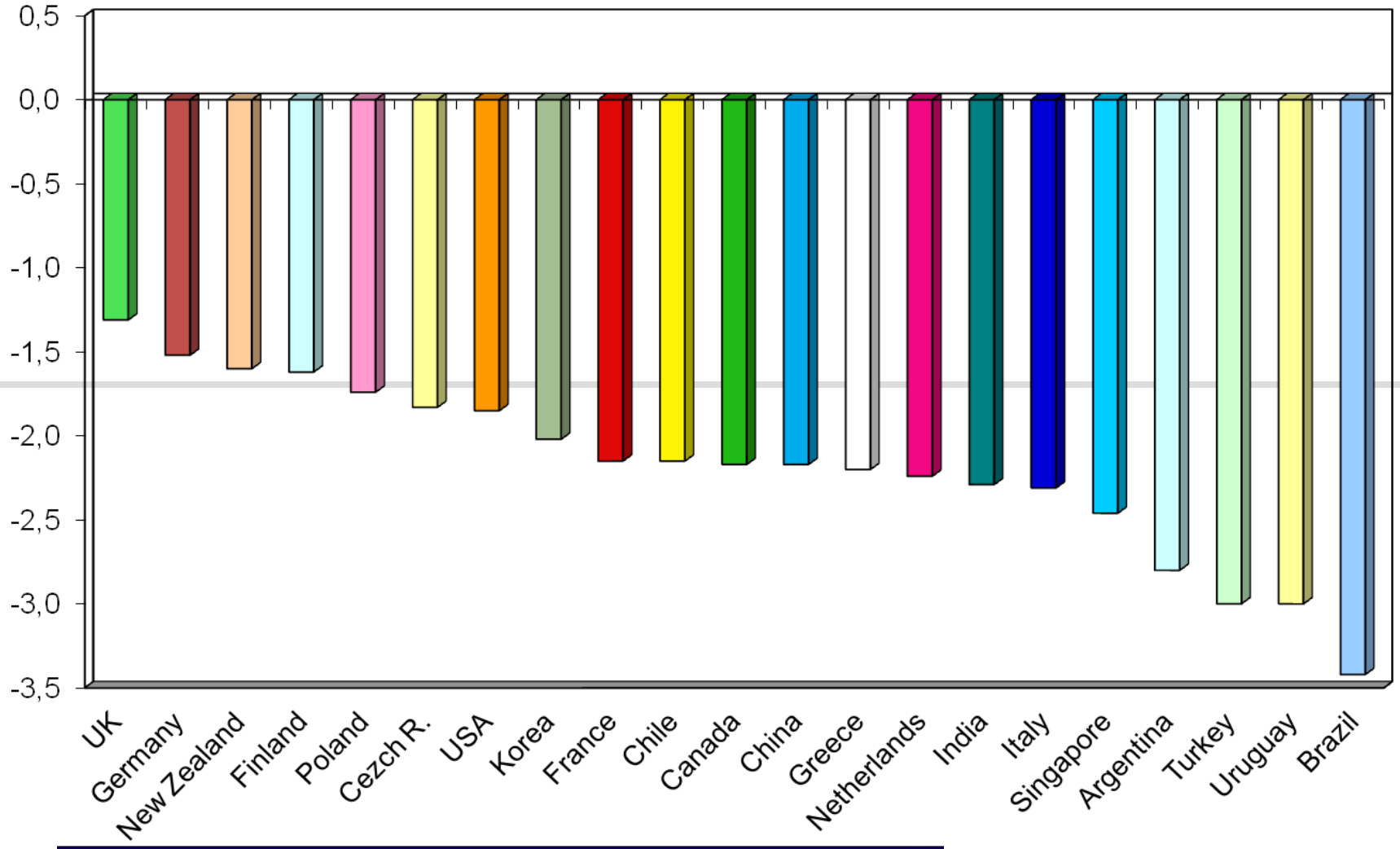
- achievement of peak bone mass in children
- skeletal deformities
- pain

- fracture

- physical function
- quality of life



Statural Growth – Height SDS - IPPN



International Pediatric Peritoneal Dialysis Network

multifactorial

role of GH?

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*

Nat Rev Nephrol 2019

Important patient-level outcomes

- growth

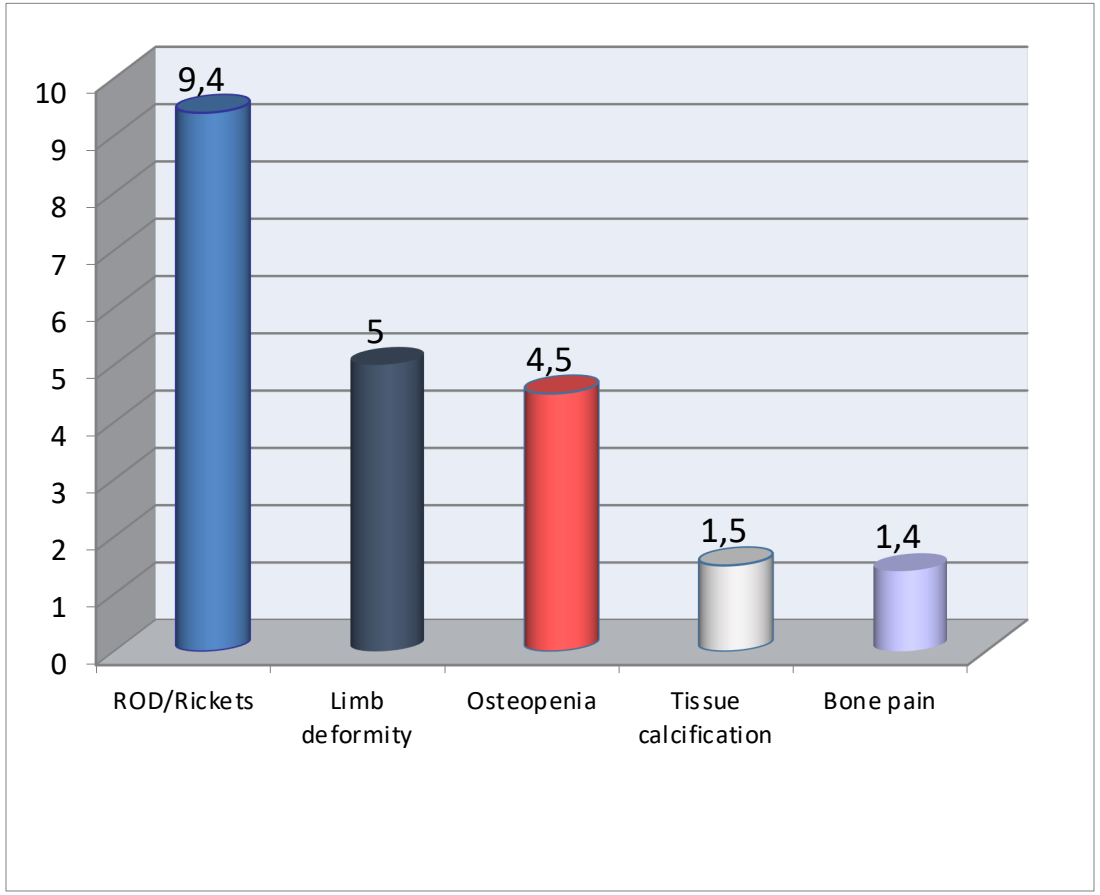
- achievement of peak bone mass in children
- skeletal deformities

- pain

- fracture

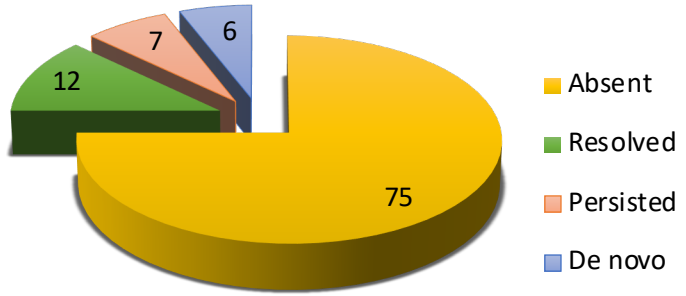
- physical function
- quality of life

Signs of Mineral and Bone Disorder in Children on Peritoneal Dialysis



139/890 (15%) patients

*more than one item per patient permitted

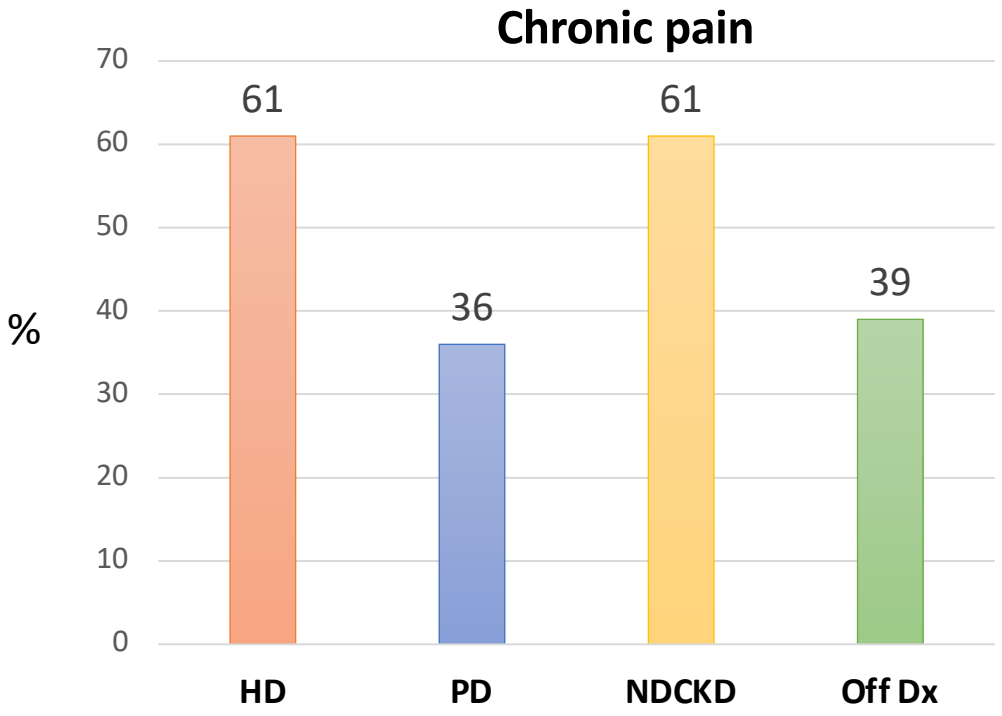


271 patients
after 12 months

Borzych D, et al. KI 2010

Prevalence and severity of chronic pain in CKD patients: a systematic review and meta-analysis

68 studies representing 16558 patients from 26 countries



moderate/severe 62%

Overall chronic pain

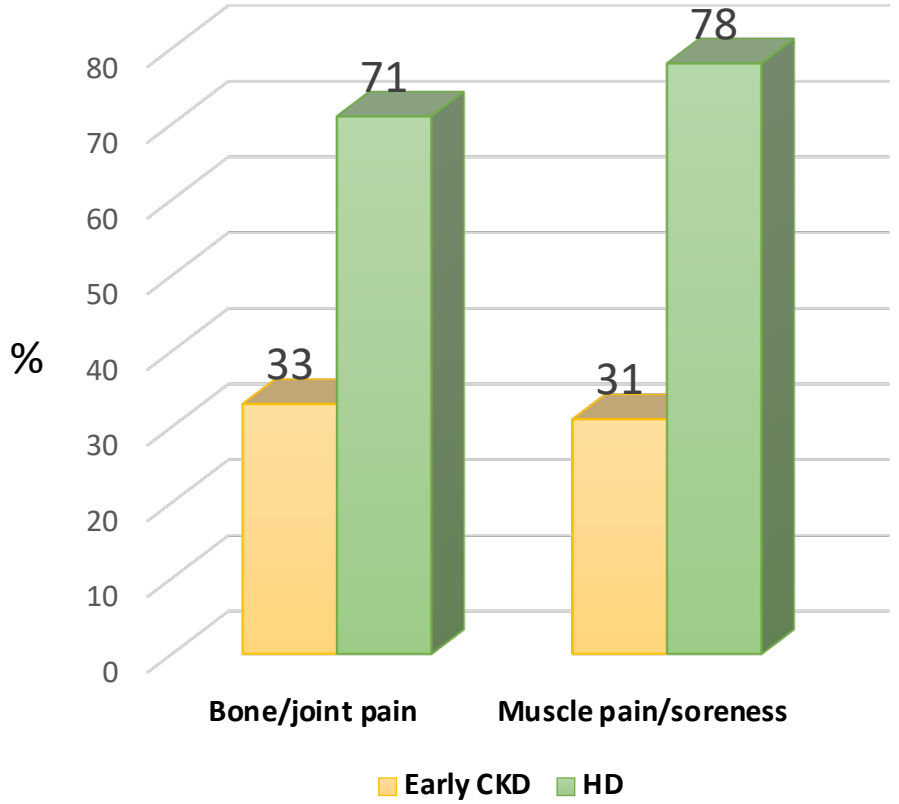
Musculoskeletal pain

Bone/joint pain

Muscle soreness

Neuropathic pain

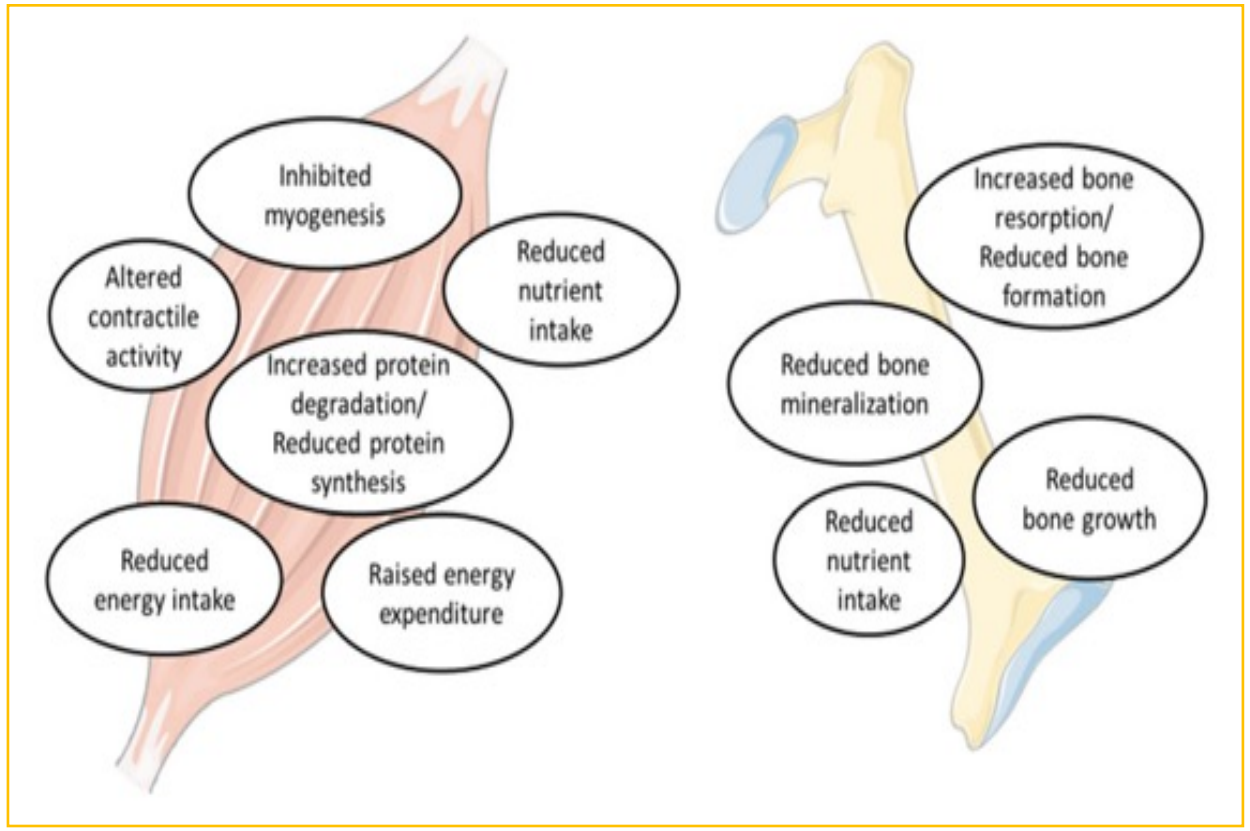
Musculoskeletal pain accross diverse CKD stages in adults



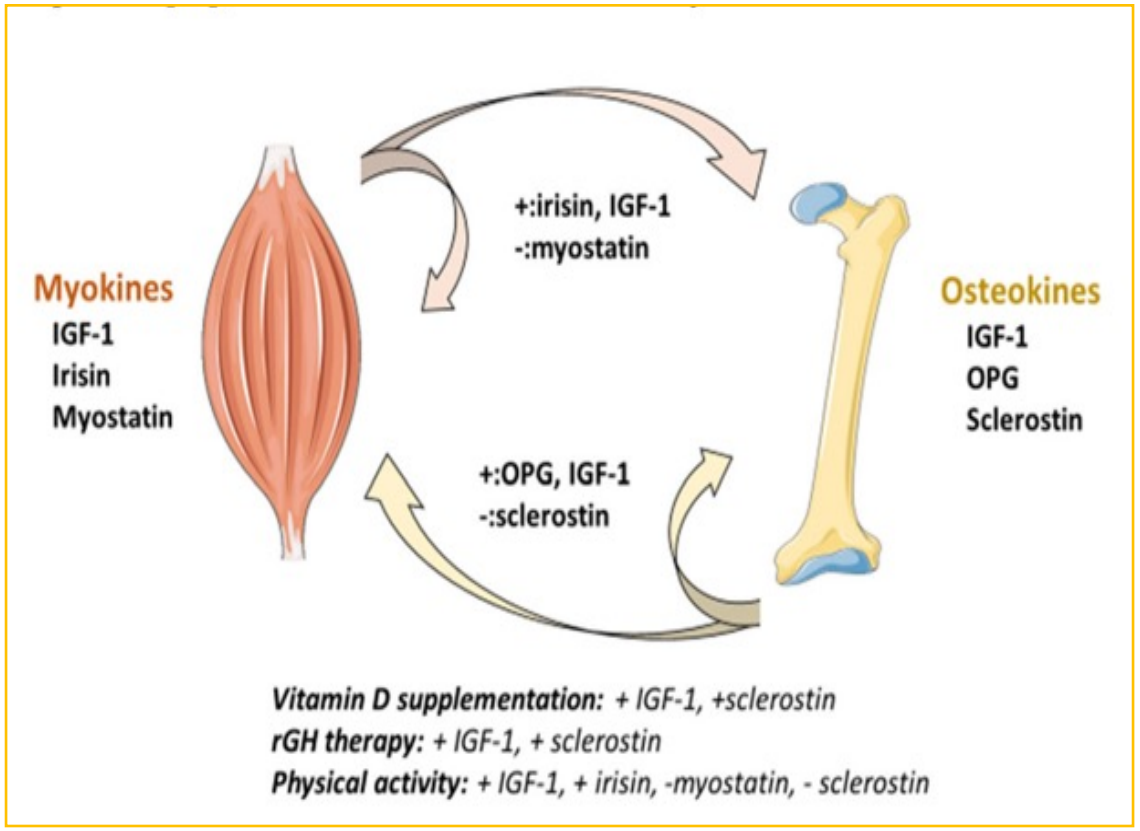
Davison SN, Canadian J Kidney Health Dis 2021

Bone-muscle unit

Cellular and metabolic effects of CKD on bone and muscle



Bone-muscle crosstalk and osteomyokines



Karava V, et al. Pediatr Nephrol 2021

Important patient-level outcomes

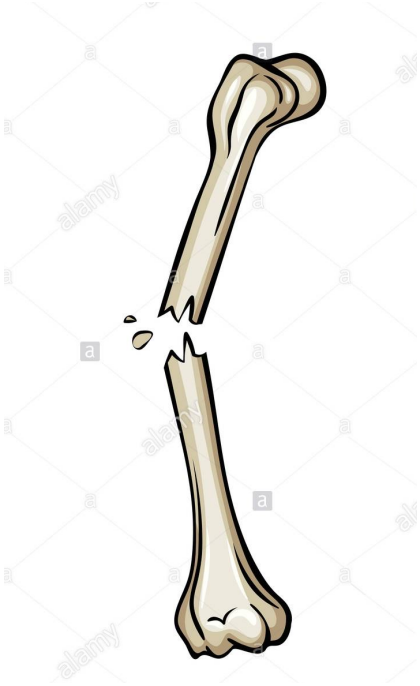
- growth

- achievement of peak bone mass in children
- skeletal deformities

- pain

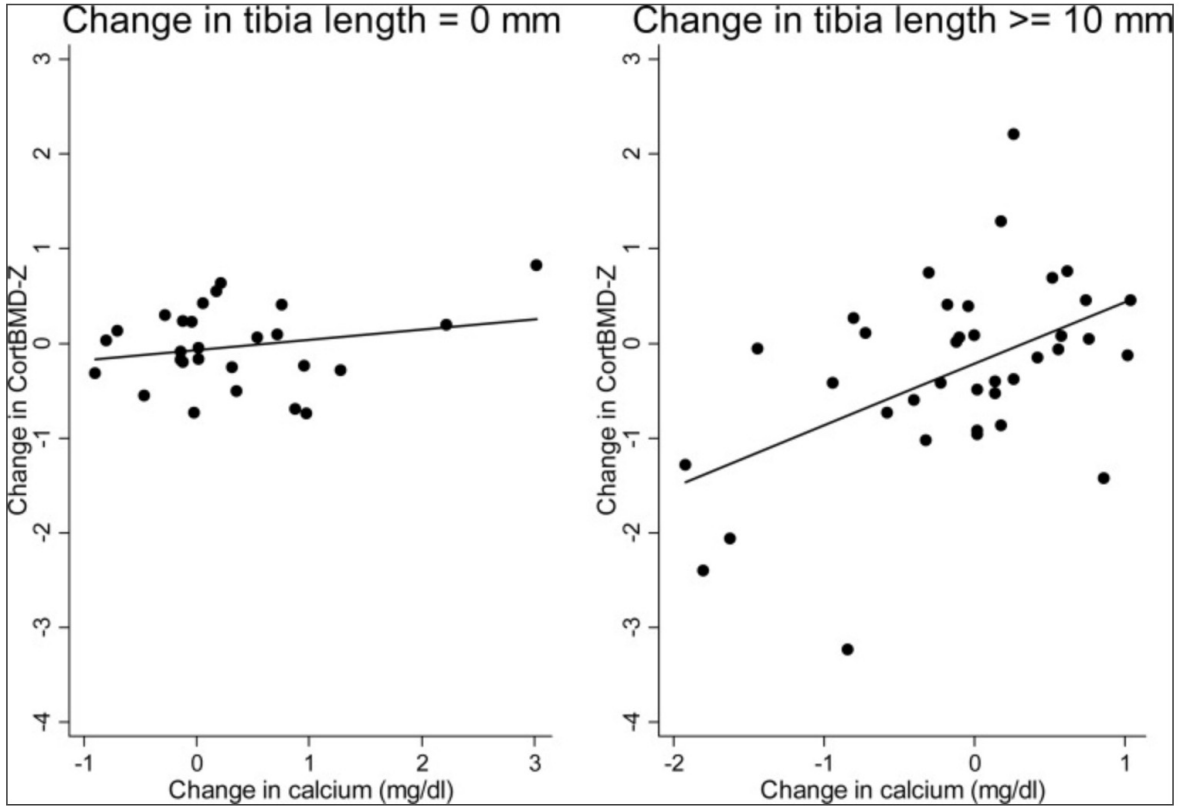
- fracture

- physical function
- quality of life



Fracture risk in children with CKD – longitudinal study

- n= 170
  - incidence of fracture (6.5%) was 4-fold higher than that reported in healthy children
  - lower CortBMD Z-score was associated with increased fracture risk
  - greater PTH and 1,25$(OH)_2$D and lower calcium concentrations were independently associated with baseline and progressive cortical deficits in childhood CKD



Denburg M, et al. J Clin Endocrinol Metab. 2013 May; 98(5): 1930–1938.

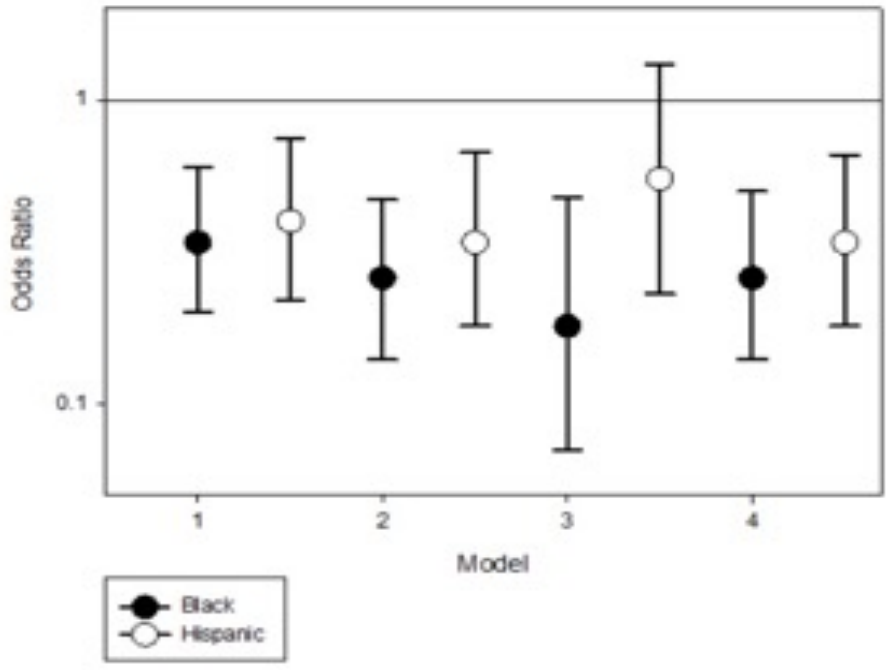
Race and ethnicity predict bone markers and fracture in children with CKD

- 762 children 1.5-18 years, with CKD 2-4 from the CKiD cohort (2005-2017)
- Black and Hispanic children had 74% and 66% **lower risk of any self reported fracture** than white children, respectively.

- Black race
  - 23% higher PTH and
  - 33% lower 25-OHD levels vs whites
- Hispanic ethnicity
  - 14% lower 25-OHD levels vs whites

Caucasian participants having the lowest albumin corrected calcium values – but not significant in regression analysis

Odds of Prevalent Fracture relative to White children

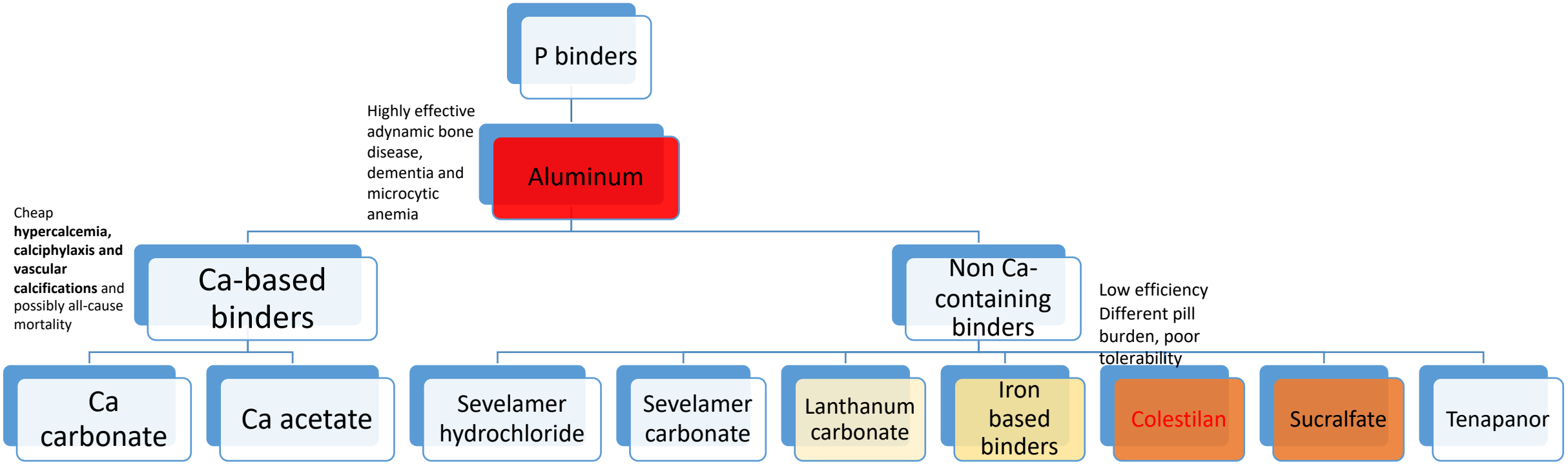


Laster M, et al. J Bone Miner Res. 2020 Sep 22. doi: 10.1002/jbmr.4182

Fracture risk in pediatric CKD

- In 537 children with CKD prior to dialysis, the reported fracture rates were 2.4-3 fold higher than healthy children
- The fracture risk factors
    - Advanced pubertal stage
    - Greater height z score
    - higher PTH levels
    - team sports participation
    - difficulty walking 2X
- The only protective factor was P binder use with a 63% lower hazard of fracture
    - 82% of patients in this study received a **Ca-based P binder**

Denburg M, et al. J Am Soc Nephrol. 2016 Feb;27(2):543-50



Pleiotrophic effect on lipid metabolism and inflammation, possibly hyperuricemia and hyperglicemia
Less hypercalcemia

Higher P binding capacity than Sevelamer,
high cost and a low gastrointestinal tolerability,
Bone toxicity due to accumulation?

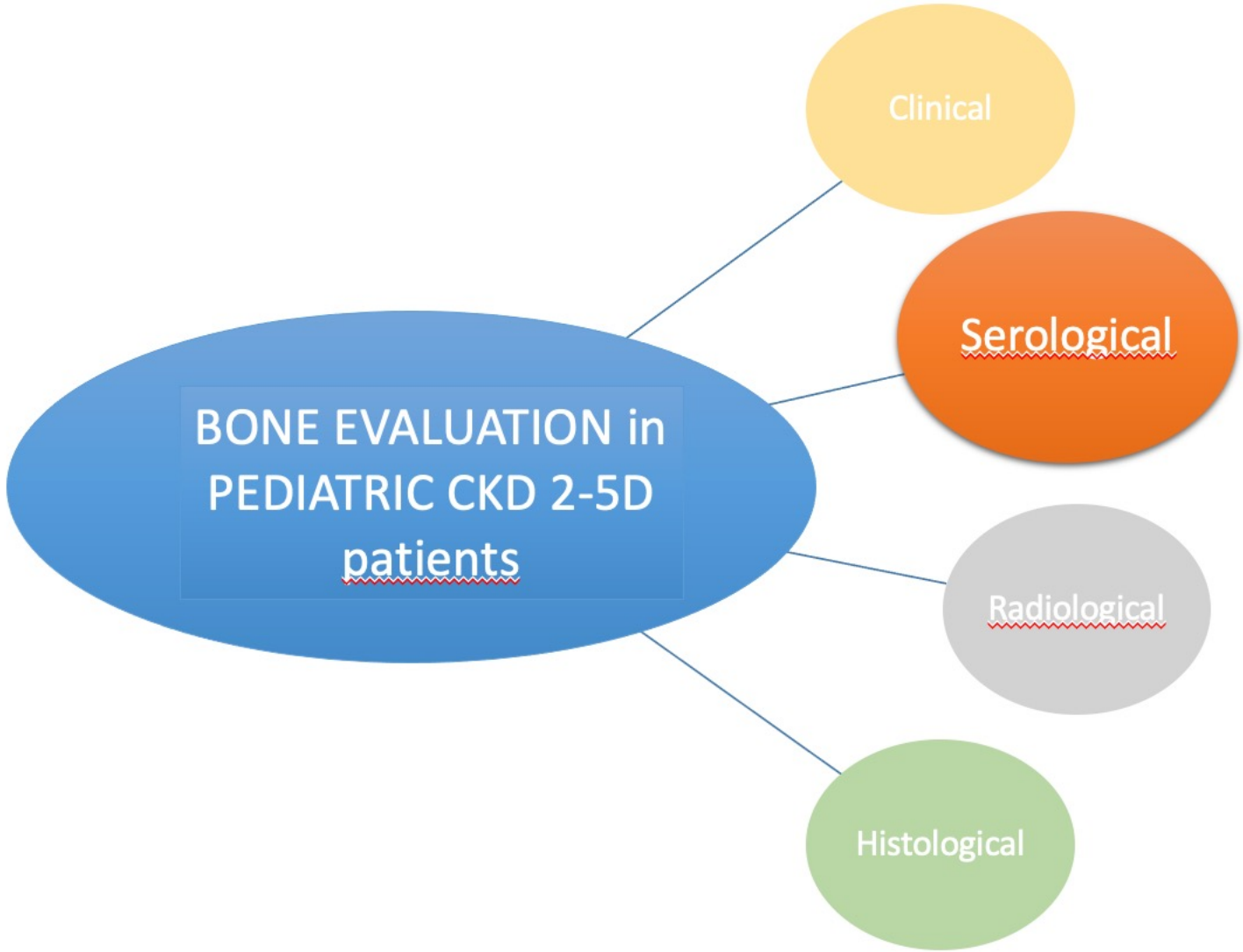
Effective P binding throughout GI tract, insoluble, min. iron absorption,
equal effectiveness but lower pill burden than sevelamer

Reduces P, LDL and total cholesterol, HbA1C and uric acid levels
Not on the market

Pharmacological Treatment of CKD-MBD in Children

	< 1 yr	1-5 yrs	6-11 yrs	> 12 yrs	All
N	67	184	291	348	890
Phosphate binders (any)	**61.2%**	**82.7%**	**89.7%**	**95.7%**	**88.3%**
Calcium carbonate/acetate	53.7%	71.7%	71.5%	67.8%	**68.8%**
Sevelamer	4.5%	2.7%	7.2%	10.6%	7.4%
CC / CA + sevelamer	3%	8.2%	11%	16.4%	11.8%
Lanthanum carbonate	0%	0%	0%	0.8%	0.3%
Active vitamin D analogue (any)	**58.2%**	**81.4%**	**71.5%**	**76.4%**	**74.5%**
Calcitriol	26.9%	48.9%	47.1%	51.9%	47.8%
1α-calcidiol	31.3%	31.9%	22.7%	22.8%	25.3%
Paricalcitol	0%	0.6%	1%	1.7%	1.1%
Doxercalciferol	0%	0%	0.7%	0%	0.2%
Cinacalcet	**0%**	**0%**	**1.4%**	**6.1%**	**2.8%**
25-OH-Vit.D_3	**29.8%**	**30.2%**	**22.3%**	**23.3%**	**24.9%**

Borzych et al, KI 2011


BONE EVALUATION in PEDIATRIC CKD 2-5D patients
Clinical
Serological
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Histological

Serological Evaluation

Suggested intervals of assessment of serum markers and HCO_3 by CKD stage

	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

Bakkaloglu SA, et al. NDT 2020

Age-specific and CKD stage–based reference ranges for commonly used biomarkers of CKD-MBD

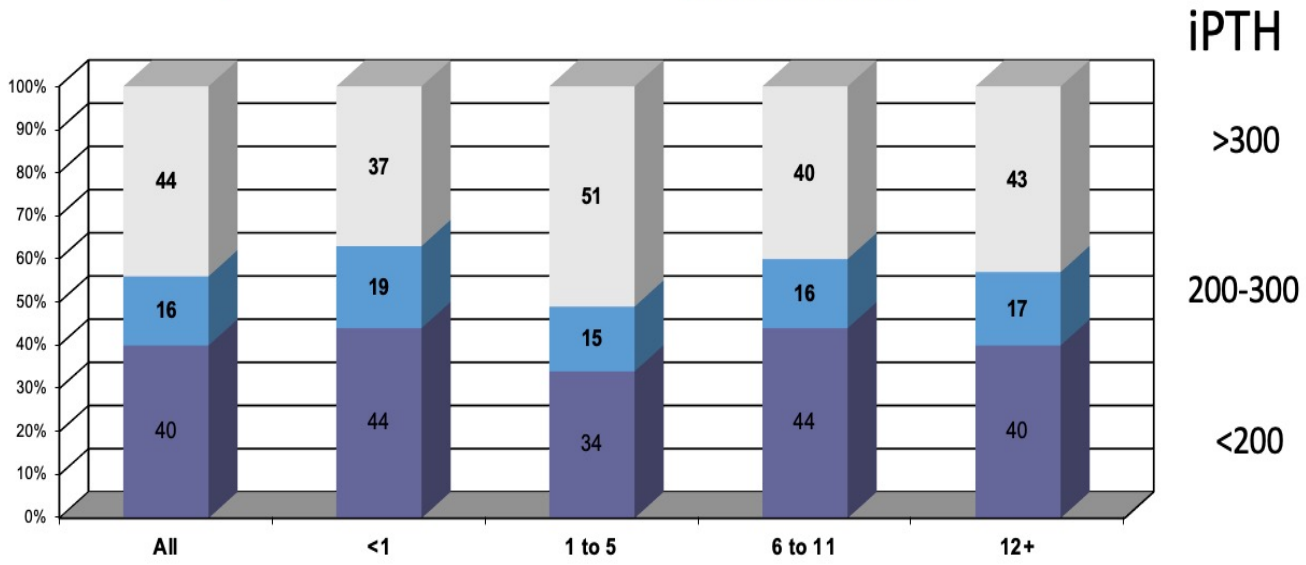
Age-specific values				Age- and sex-specific values		CKD stage-dependent values		
	iCa mmol/L	Ca mg/dL	P mg/dL		ALP[a] U/L		PTH pg/mL	25(OH)D[b] ng/mL
0–5 months	1.22–1.40	8.7–11.3	5.2–8.4	0–15 days	90–273	CKD Stage 3	35–70 [12] Normal levels [46]	>30 [12, 72]
6–12 months	1.20–1.40	8.7–11.0	5.0–7.8	15–30 days	134–518	CKD Stage 4	70–110 [12]	>30 [12,72]
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]	>30 [21]
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 M: 127–517	–	–	–
–	–	–	–	15–<17 years	F: 54–128 M: 89–365	–	–	–
–	–	–	–	17–<19 years	F: 48–95 M: 59–164	–	–	–

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

Maintaining age and/or sex specific normal values and CKD-dependent levels

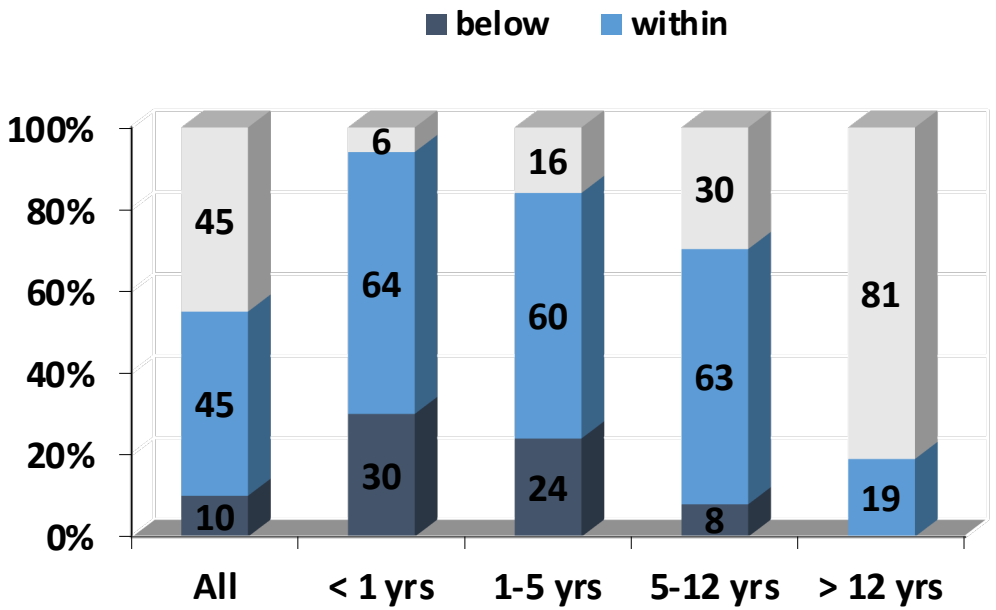
Bakkaloglu SA, et al. NDT 2020

KDOQI CKD-MBD Guideline Adherence Rates



IPPN data, n=890 patients

Phosphorus Control according to KDOQI



Maintaining calcium levels within normal limits, close to ULN

Which one of the following test gives the most accurate assessment of serum calcium levels?

- Total Ca levels
- Albumin corrected Ca levels
- Ionised Ca levels

Where available, ionized Ca

Corrected serum values underestimates the prevalence of hypocalcemia

- n=31 HD….
- Corrected calcium fail to detect hypocalcemia in 33% of the patients
- Calcium levels were much more likely to be classified as hypocalcemic according to ionized values compared to corrected serum values (87% vs. 67.7%).
- Ca homeostasis in the HD patients is most accurately assessed by ionized calcium levels

Goransson LG, et al. Nephrol Dial Transplant 2005 ; 20 : 2126-9
Gouri A, Dekaken A. Ann Biol Clin (Paris) 2012; 70: 210–212

Hidden hypocalcemia is a significant risk factor for CV events and mortality

n= 332 HD patients -- three categories:

- apparent hypocalcemia (low iCa: <1.15 mmol/L and low cCa: <8.4 mg/dL)
- hidden hypocalcemia (low iCa despite normal or high cCa)
- normocalcemia (normal iCa)
- outcome parameters: Death – CV events
- Hidden hypocalcemia was significantly associated with an increased risk compared with normocalcemia (HR: 2.56; 95% CI: 1.11-5.94), while apparent hypocalcemia was not
- Hidden hypercalcemia is a risk factor, too.

Yamaguchi S et al. Sci Reports 2020
Obi Y, et al. J Clin Endocrinol Metab 2016; 101: 2440–2449

Trends of serum biomarkers

Serial measurements

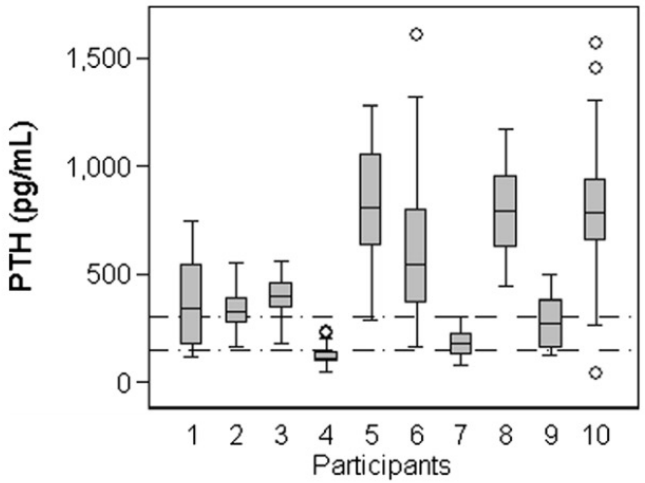
n= 10 HD patients

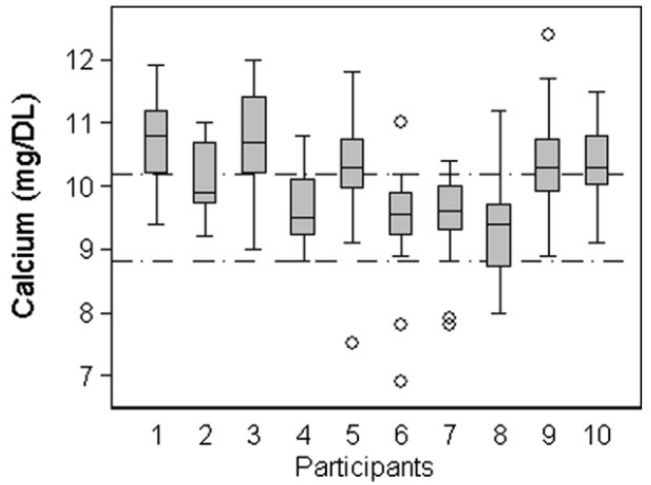
12 week follow-up

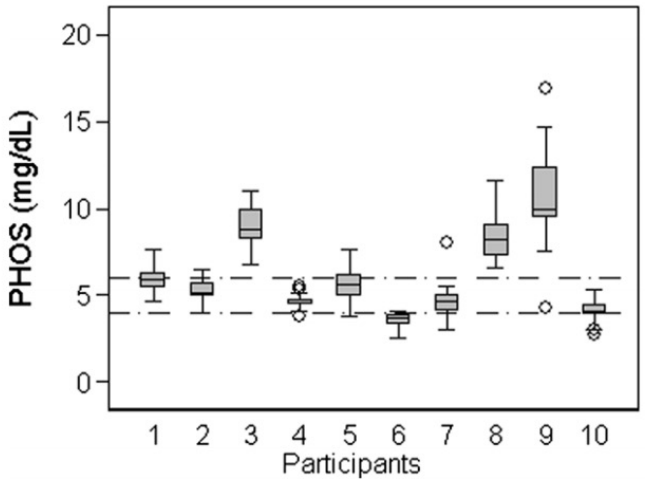
variability of calcium, phosphate, and PTH (twice weekly measurement) were 7%, 14% and 38%, respectively

44% for FGF23 and

12-19% for vitamin D metabolites



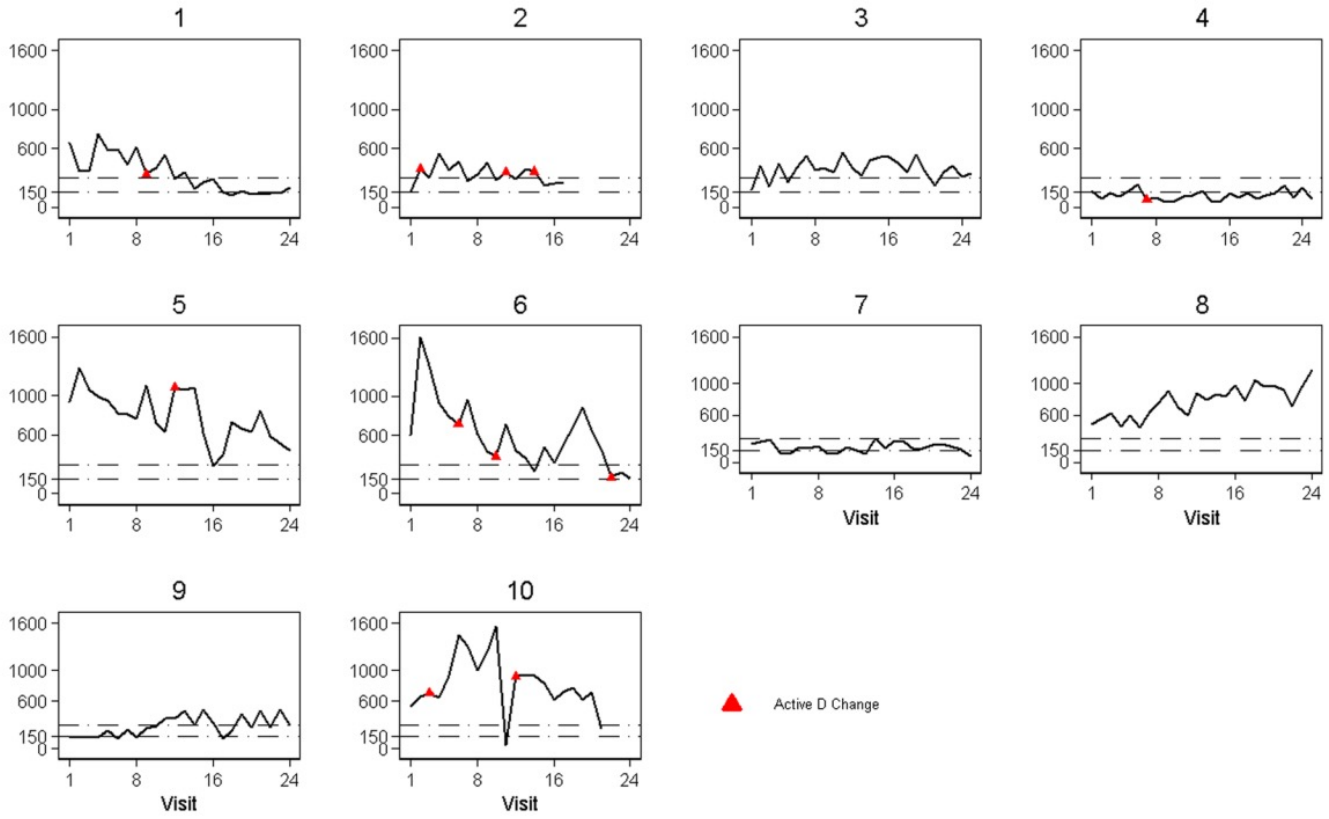


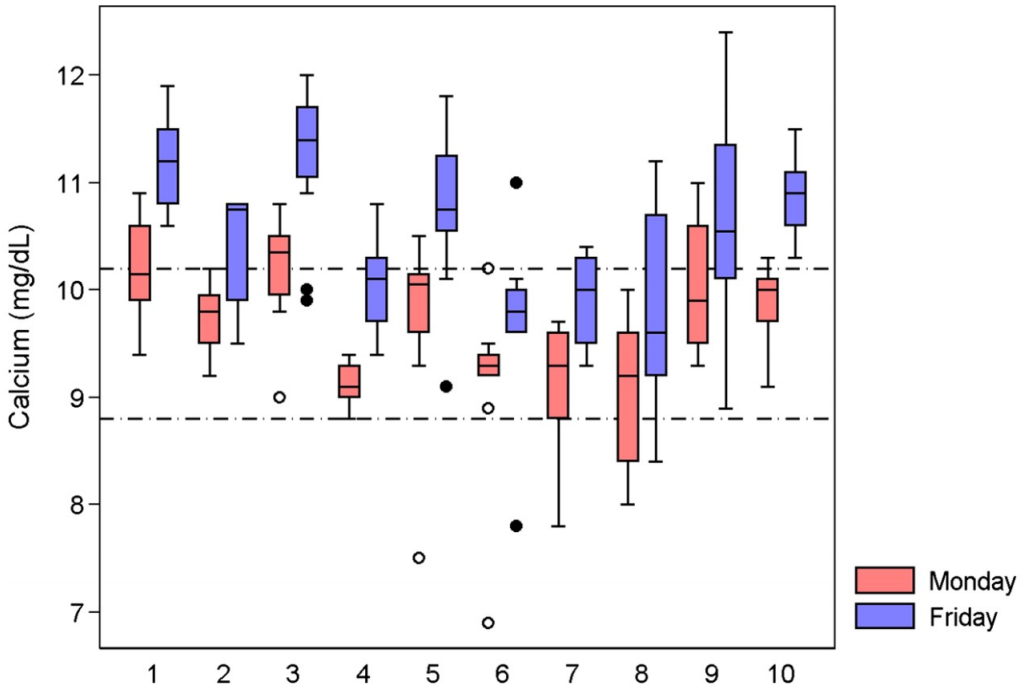


	Overall %CV Median (IQR)
Calcium	7.1 (5.9, 8.8)
Corrected calcium	6.7 (5.7, 8.3)
Phosphate	14.0 (11.7, 16.6)
PTH	38.0 (29.7, 44.2)
FGF23	44.4 (32.1, 54.4)
25(OH)D	15.2 (9.9, 18.5)
$1,25(OH)_2D$	18.5 (16.6, 32.3)
$24,25(OH)_2D$	13.1 (11.9, 16.6)

Kakajiwala A, et al. Pediatr Nephrol (2017) 32:2311–2318

Trends rather than periodic snapshots

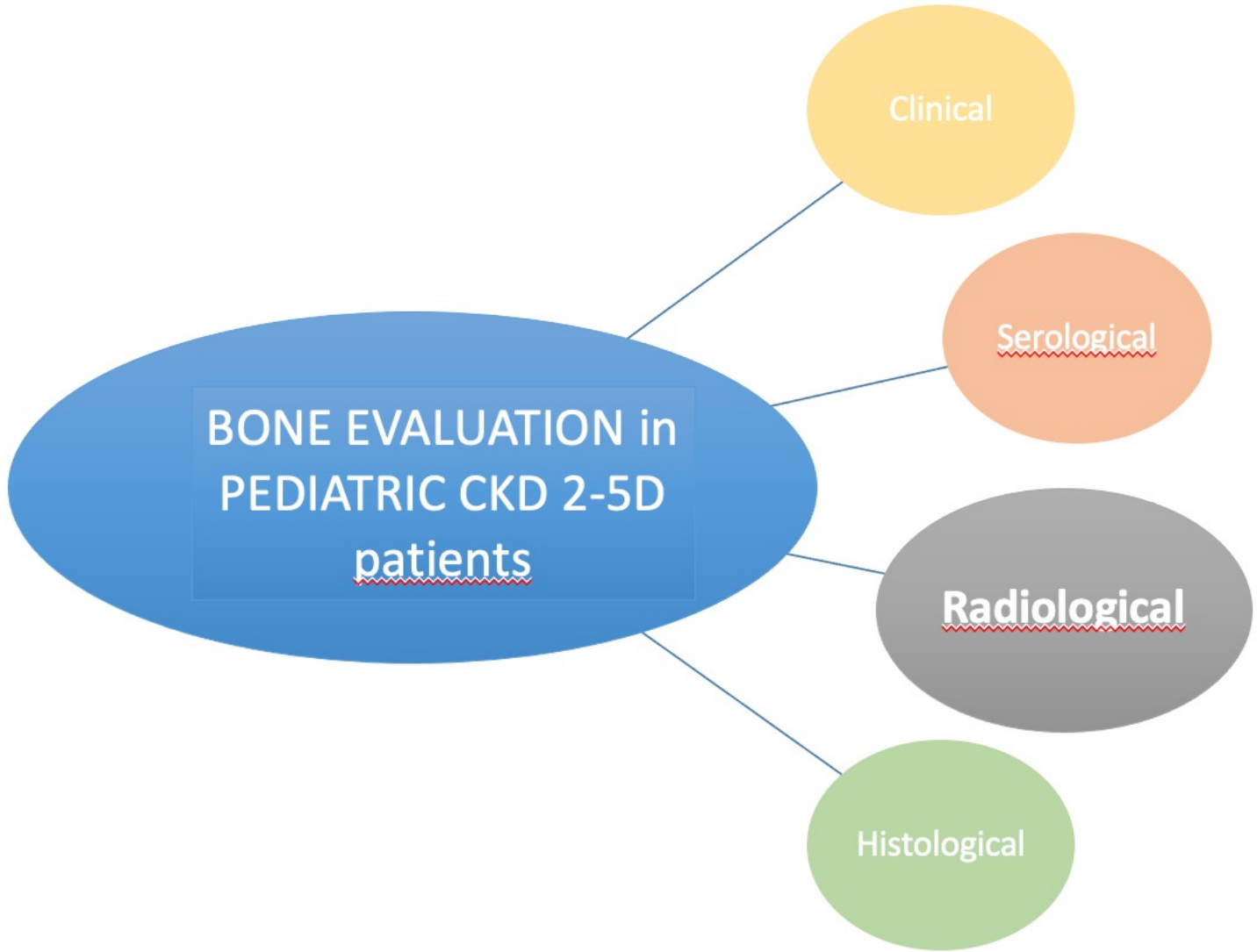




Within a 4-week period, at least 20–30% of measures would lead to a discrepant decision from the referent measure of that month

Short-term biologic variability in measures of mineral metabolism make these periodic snapshots inadequate for accurate assessment of mineral homeostasis and clinical decision-making.

Kakajiwala A, et al. Pediatr Nephrol (2017) 32:2311–2318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Serological
Radiological
Histological

Radiological Evaluation

- Dual energy X-ray absorptiometry (DXA),
- Peripheral quantitative computed tomography (pQCT),
- High resolution pQCT (HR-pQCT),
- Magnetic resonance imaging (MRI) or
- Ultrasound are not routine tools in children with CKD.

Strengths and weaknesses of bone imaging techniques in children with CKD

	Strengths	Weaknesses
Plain X-rays	Not expensive and widely available	Radiation exposure Low sensitivity Interpretation may vary
DXA	Widely used for assessing bone mineral density Minor irradiation: 2.7–3.6 μSv Not expensive and easily available Evaluation of body composition Observer independent	Two-dimensional images: major technical concern in paediatrics Systematic underestimation of BMD in children with poor growth No distinction between cortical and trabecular bone No evaluation of geometry and microarchitecture Longitudinal follow-up can be difficult with growing bones (especially for hip)
QCT, pQCT and HR-pQCT	Bone mineral volumetric compartmental densities Bone microarchitecture Bone biomechanics A non-invasive approach to mineralization (currently under evaluation) Minor irradiation Data available in paediatric CKD Ability to predict the fracture risk	Expensive, not available everywhere Lack of reference data Lack of consensus for the region of interest (ultra-distal tibia and radius) No evaluation of body composition/muscle-bone unit Highly observer dependent, particularly in relation to drawing the reference line Standardization between different scanners can be difficult
MRI	Bone mineral volumetric compartmental densities Bone microarchitecture No irradiation Evaluation of the muscle-bone unit	Expensive, not available everywhere Lack of reference data Lack of consensus for the region of interest (ultra-distal tibia and radius) Lack of reference data in paediatric CKD
Ultrasound	Not expensive, available everywhere No irradiation	Lack of reference data Lack of consensus Lack of data in paediatric CKD

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ndt
Nephrology Dialysis Transplantation

Routine serum biomarkers, but not dual-energy X-ray absorptiometry, correlate with cortical bone mineral density in children and young adults with chronic kidney disease

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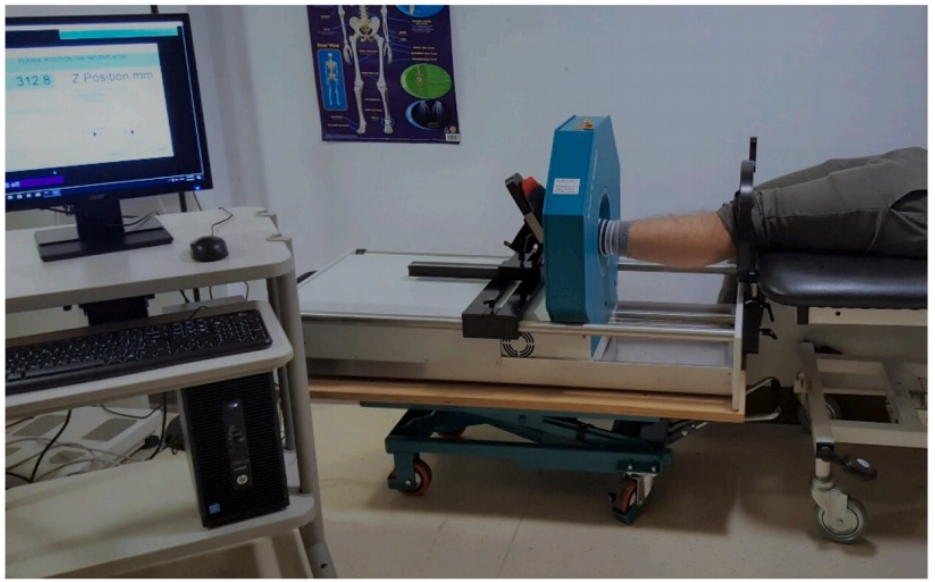
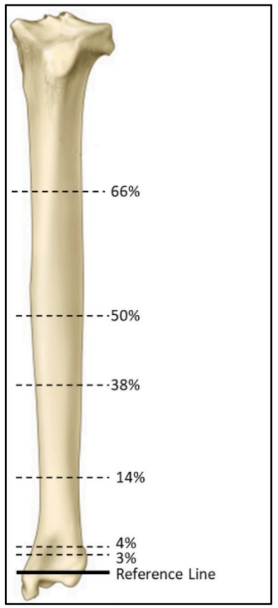
ORIGINAL ARTICLE





Fifty-five children and young adults aged 7 to 30 years

Non-dominant tibia scanned
- 3% & 4% sites for trabecular bone mineral density and
- 38% site for cortical bone mineral density and bone mineral content

pQCT is a useful tool for studying trabecular and cortical compartments separately

There are variations in pQCT scanning protocols, analysis methodology, and a paucity of reference data

Reference datasets may not be generalizable to local study populations, even when analysed using identical analysis protocols.

Lalayiannis AD, et all. NDT 2020
Lalayiannis AD, et all. Bone 2021

How often do you perform a bone X-Ray (hand/wrist or other skeletal parts) in your dialysis patients to evaluate ROD and/or bone age?

- Every six months
- Annually
- Every other year
- Only if clinically indicated

Radiological Evaluation

Plain X-Ray

osteopenia

erosions

radiolucent zones in metaphyses

signs of rickets including increased thickness of the growth plates of the long bones, with irregular, hazy appearance at the diaphyseal line, and rachitic rosaries

vascular calcifications

- clinically suspected rickets
- bone pain
- deformities
- suspected fractures
- slipped epiphyses
- delay or difficulty in walking, limping
- genetic diseases with specific bone involvement (i.e. cystinosis, oxalosis, etc).

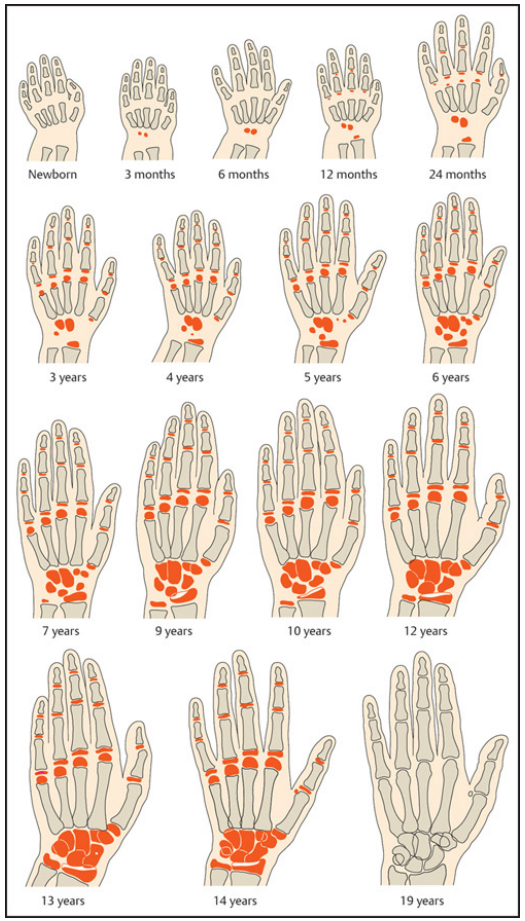
- bone age ?

Bone age determination ? ??

- Atlas methods
- Computerized methods
- Utrasound

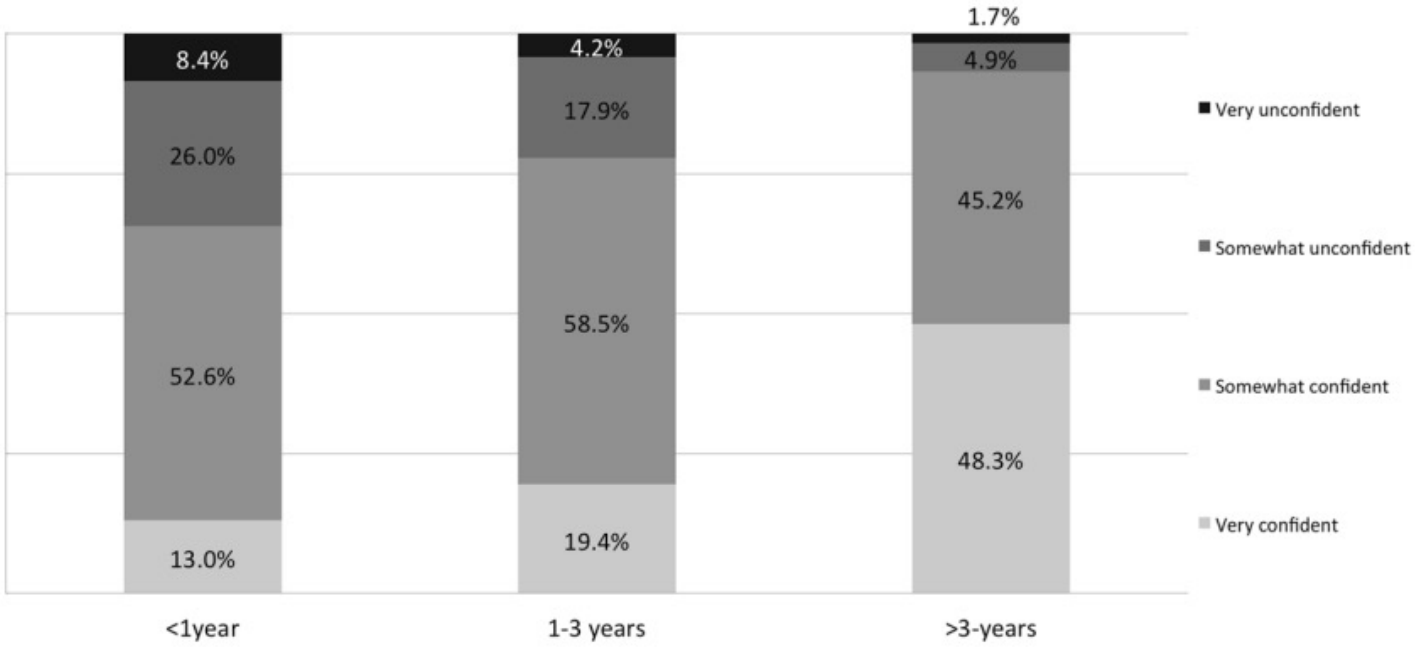
- Usage of X-Rays are suboptimal in bone age determination in children with CKD, especially in infants due to delayed skeletal maturation

- Greulich and Pyle hand/wrist – 1.4’– reliability ??
- Tanner Whitehouse 3 – 7’
- Fels – very accurate in healthy infants – too complex method
- Hemiskeleton (Sontag or Elgenmark)
- Pyle and Hoerr’s knee - foot
- Fibula length

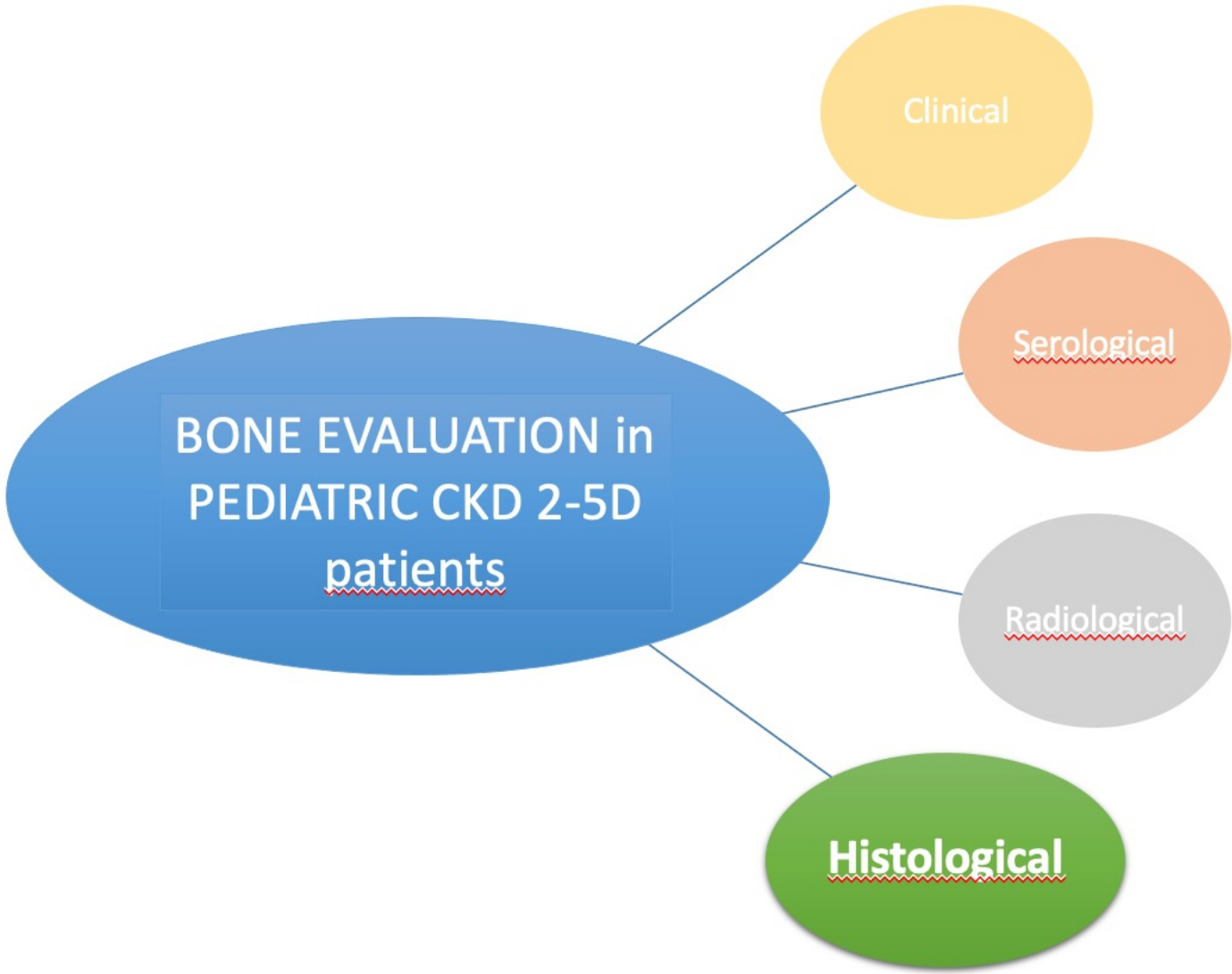


Pediatr 2021 Cavallo F, et al. Evaluation of bone age in Children: mini review

Radiologist confidence level in bone age assessment by age groups



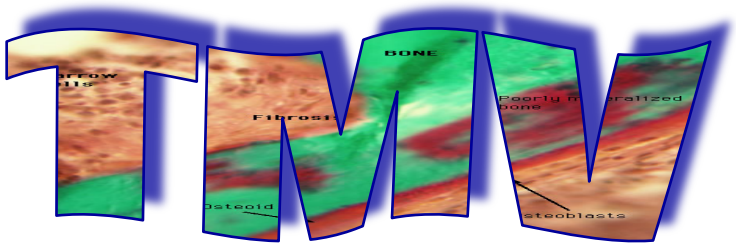
Radiologists reported greater confidence level in older children


BONE EVALUATION in PEDIATRIC CKD 2-5D patients
Clinical
Serological
Radiological
Histological

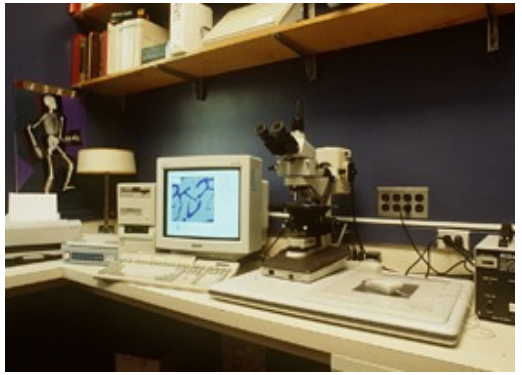
Double tetracycline labeled bone biopsy with histomorphometry

- gold standard
- quantitative
- Turnover
- Mineralization
- Volume

- expensive
- invasive and
- requires specific equipment
- requires expertise
- requires normative data



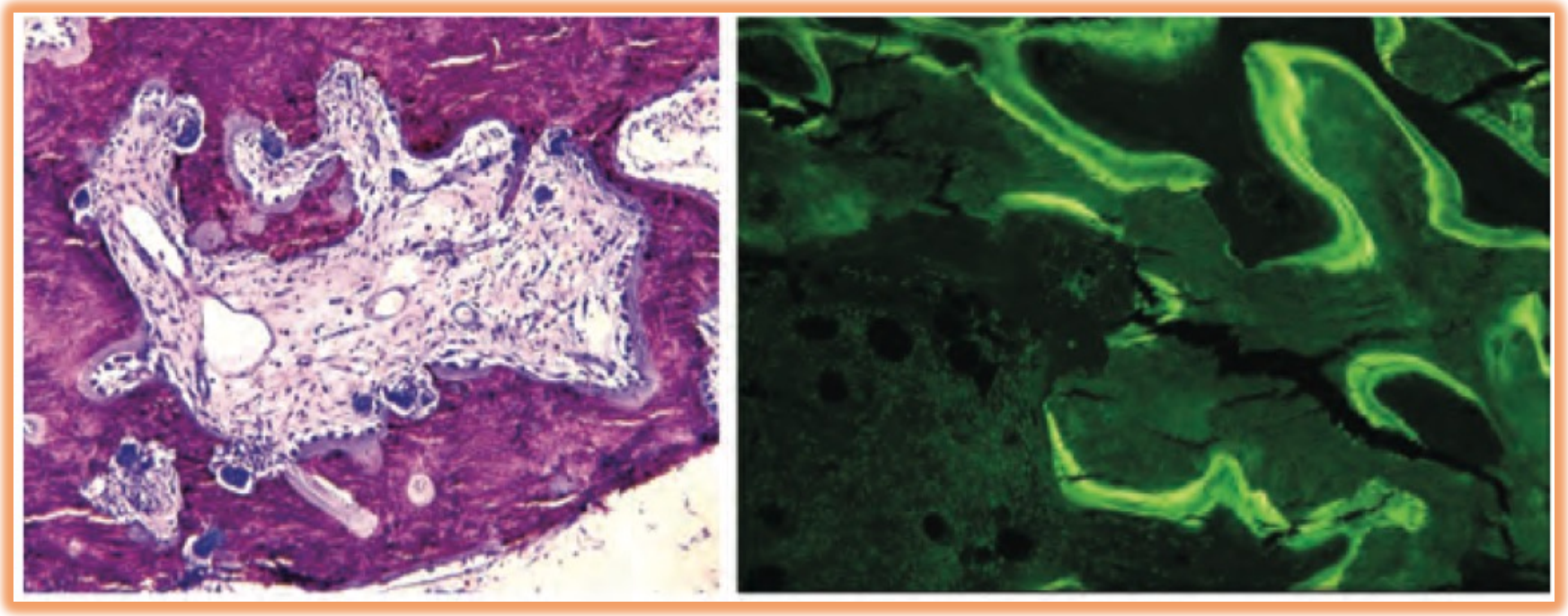
Slide Courtesy of Susan Ott

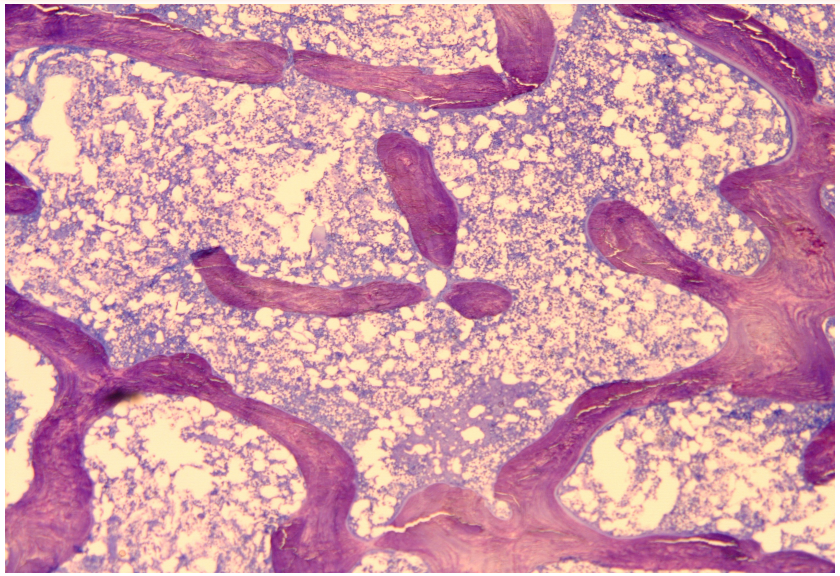


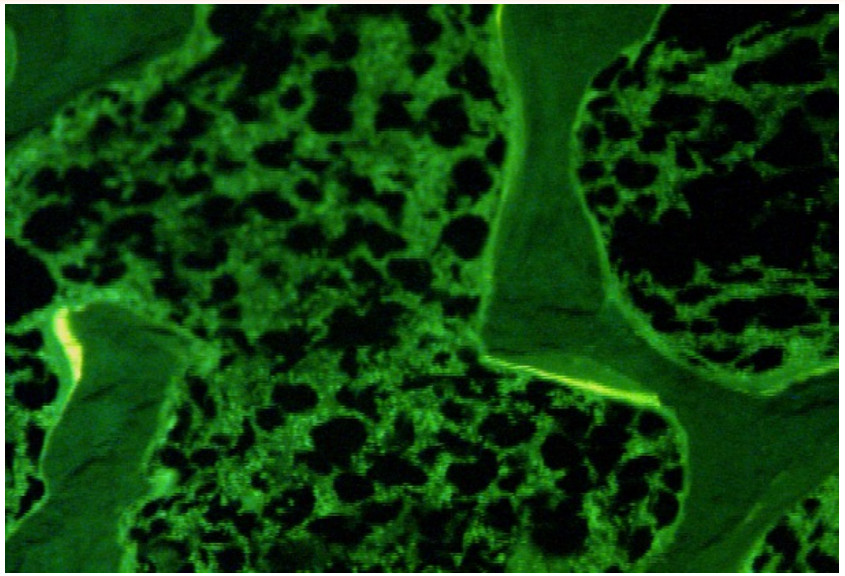
Histological Evaluation

- Bone biopsy is not routinely performed but can be considered if the clinical and biochemical findings do not explain underlying bone disease, e.g.
  - severe bone deformity or pain,
  - low energy fracture,
  - persistent hypercalcemia or hypophosphatemia despite optimizing treatment
  - suspected aluminum accumulation

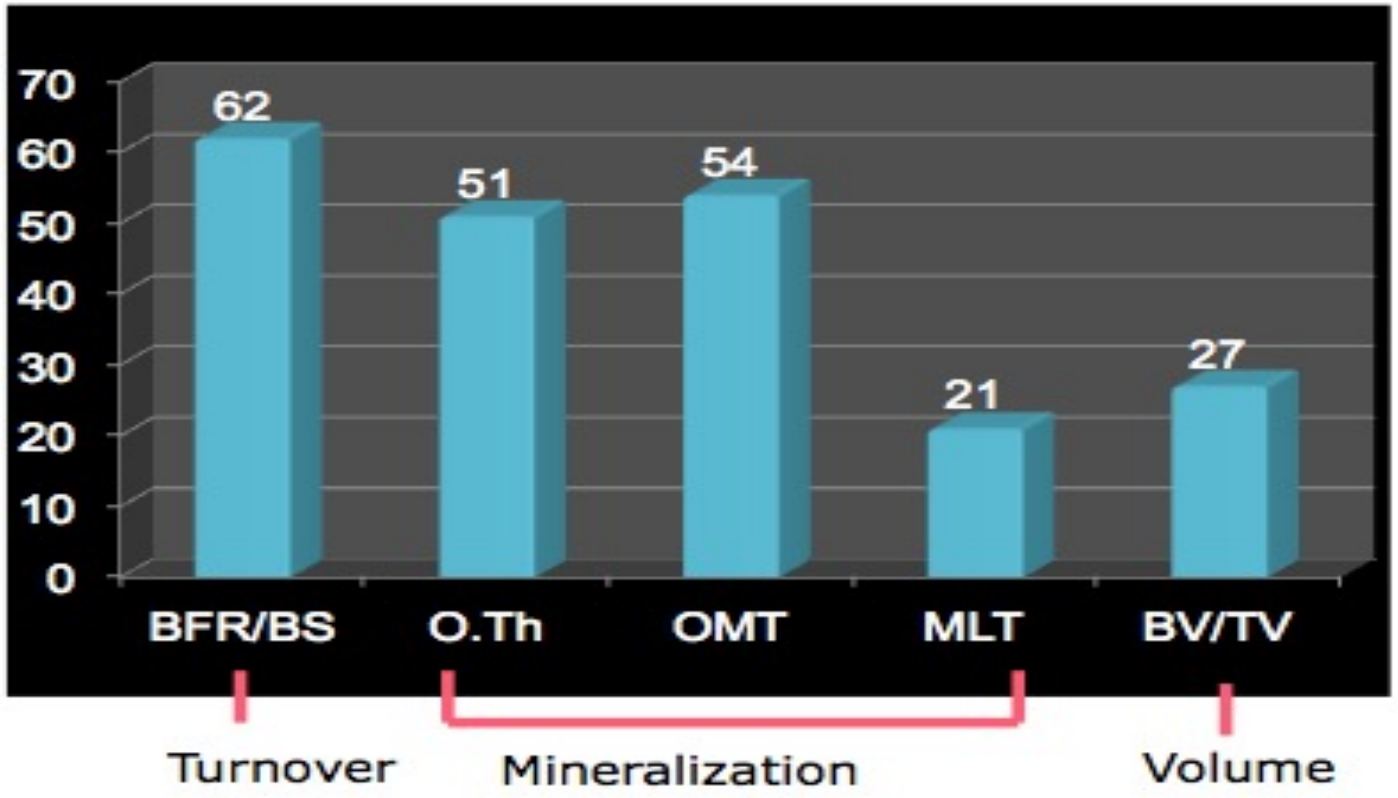
Performing histomorphometric analysis in centres with experience in interpreting paediatric bone biopsies is essential.





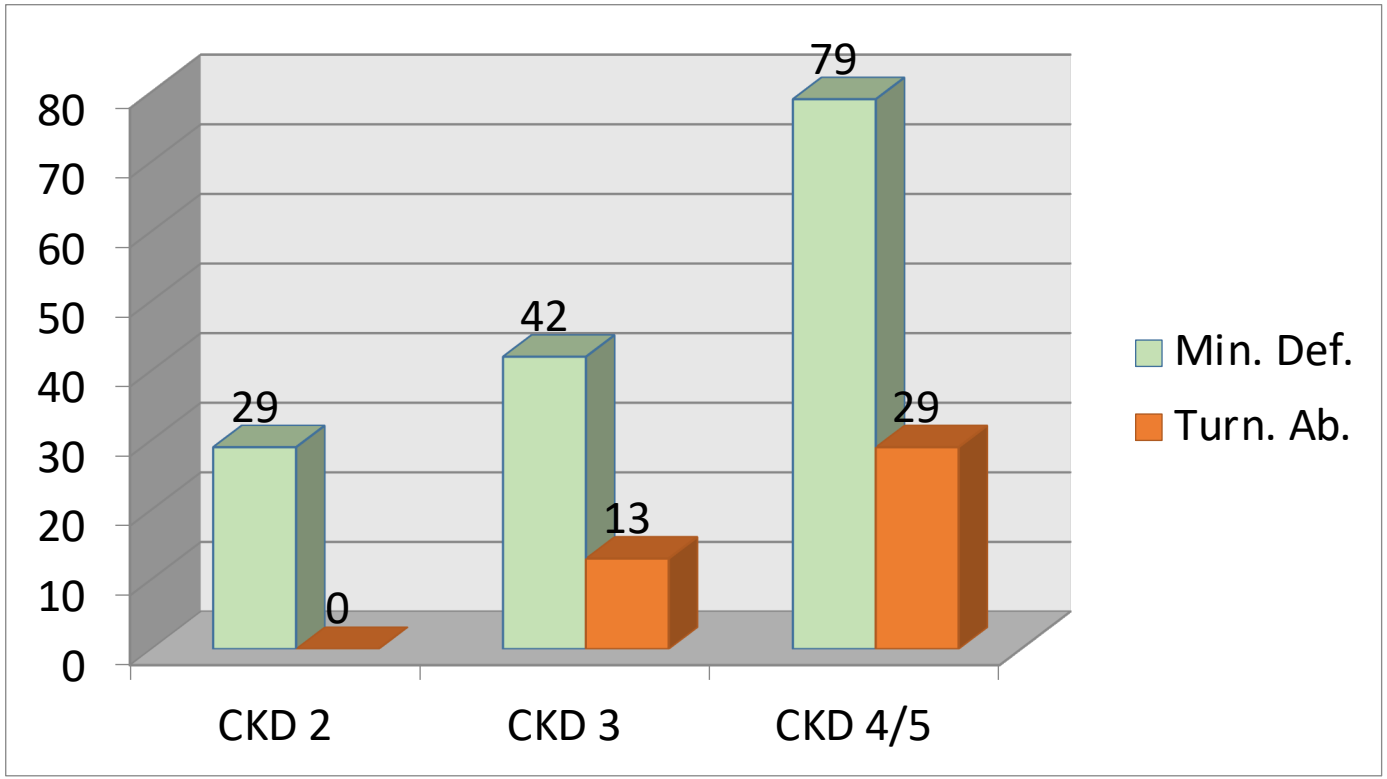


Abnormal bone histology parameters (% cases)



Turnover (BFR/BS)	Mineralization (OV/BV + OMT)	Serum Calcium (mg/dl)	Serum Phosphorus (mg/dl)
Low ($n = 7$)	Normal ($n = 5$)	9.6 ± 0.4	8.2 ± 0.6
	Abnormal ($n = 2$)	8.1 ± 2.0	8.2 ± 2.2
Normal ($n = 62$)	Normal ($n = 39$)	9.6 ± 0.1	6.0 ± 0.2
	Abnormal ($n = 23$)	8.9 ± 0.2^{a}	5.9 ± 0.3
High ($n = 92$)	Normal ($n = 39$)	9.2 ± 0.2	6.2 ± 0.2
	Abnormal ($n = 53$)	8.8 ± 0.1	6.5 ± 0.2

Bakkaloglu SA, et al. Clinical JASN 2010



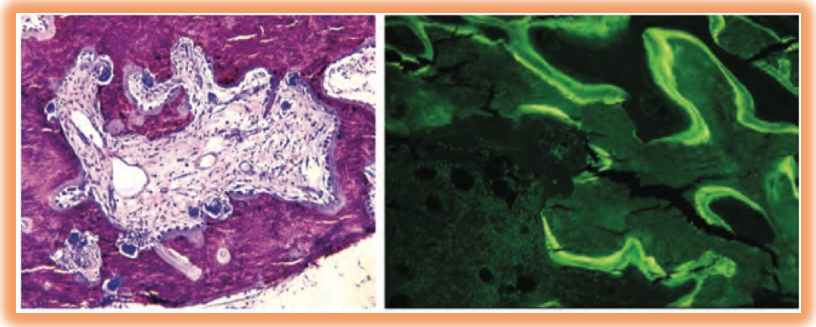
What mediates defective skeletal mineralization in early CKD, if not circulating calcium, phosphorus, and vitamin D?

Altered osteocyte-specific protein expression?

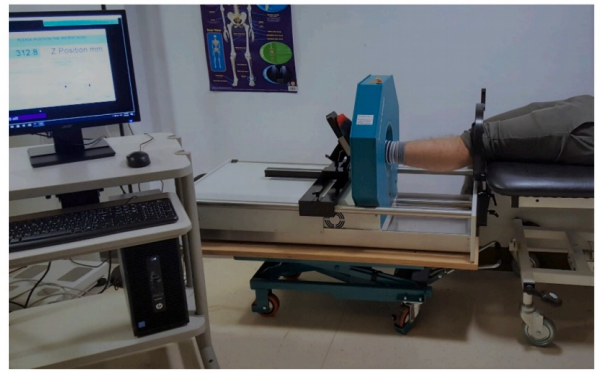
Wesseling-Perry K, CJASN 2012

Bone biopsy is the only direct and reliable method to evaluate cellular and molecular events in bone

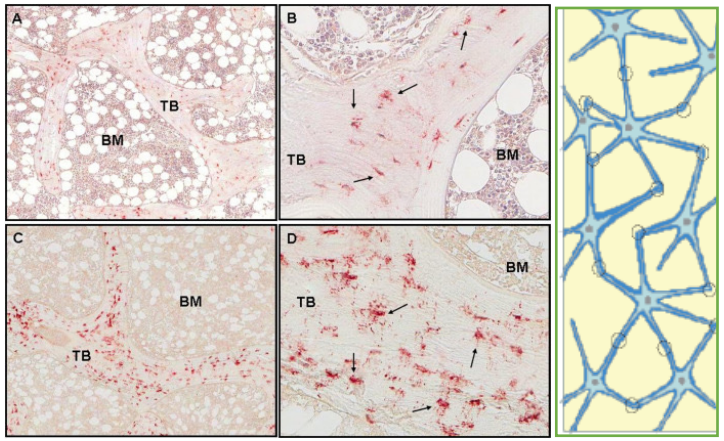
bone histomorphometry



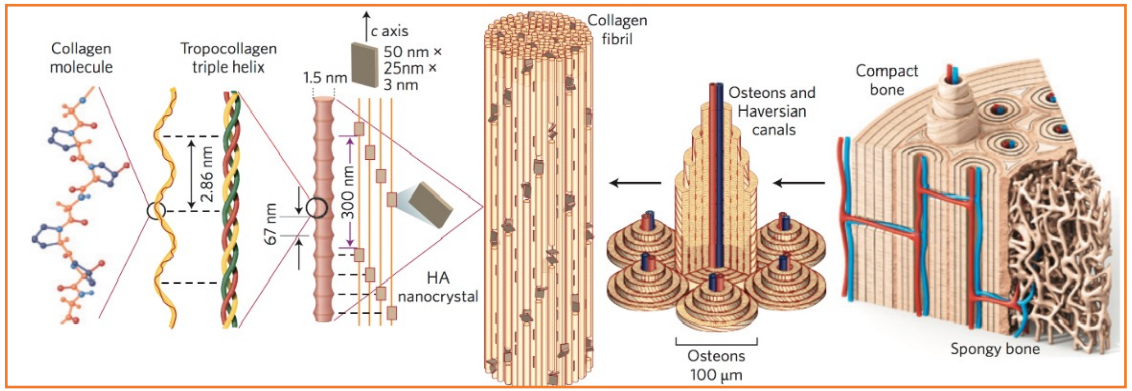
comparative new radiodiagnostic imaging



bone biology/protein expression studies - invention and validation of new serum biomarkers



bone quality studies



Lalayiannis A, et all. Bone 2021
Bakkaloglu, CJASN 2010,
Pereira, Bone 2009,
Malluche Nat Rew Nephrol 2012

Conclusion

- Bone evaluation in children with CKD is not straightforward and should focus on detailed musculoskeletal examination and pediatric patient-centered outcomes
- Overall, noninvasive diagnostic tools are not sufficiently sensitive and specific that can be relied upon for accurate assessment of bone
- Disease course during regular follow-up and trends in MBD measures are important to guide treatment

Promoting optimal growth, a measure of quality of care, with strong muscles, physical activity and positive calcium balance is critical





The world needs "**childish**" **thinking**: **bold ideas**, **wild creativity and especially optimism...**

Adora Stivak