Bone Evaluation in Children with Chronic Kidney Disease and Dialysis

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ESPN CKD-MBD Working Group Meeting, 28 April 2021
Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD)

- Bone abnormalities (short stature, reduced mineralization, and fracture risk)
- Laboratory abnormalities of Ca, P, PTH, FGF23, and vitamin D
- Extraskeletal calcification
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 - length
    • The growth plates promote longitudinal growth until young adulthood
    • Cancellous bone develops at secondary ossification center

  • Periosteal bone formation - width
    • Compact bone develops starting at primary ossification center

• Bone remodeling

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
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

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BONE EVALUATION in PEDIATRIC CKD 2-5D patients

- Clinical
- Serological
- Radiological
- Histological
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

<table>
<thead>
<tr>
<th>History, length or height, clinical evaluation (in months)</th>
<th>CKD stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0–1 years</td>
<td>2</td>
</tr>
<tr>
<td>1–3</td>
<td>0.5–2</td>
</tr>
<tr>
<td>0.5–2</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Age 1–3 years</td>
<td>3–6</td>
</tr>
<tr>
<td>1–3</td>
<td>1–2</td>
</tr>
<tr>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Age &gt;3 years</td>
<td>3–6</td>
</tr>
<tr>
<td>3–6</td>
<td>3–6</td>
</tr>
<tr>
<td>1–3</td>
<td>1–3</td>
</tr>
<tr>
<td>During puberty</td>
<td>3–6</td>
</tr>
<tr>
<td>3–6</td>
<td>1–3</td>
</tr>
<tr>
<td>1–3</td>
<td>1–3</td>
</tr>
</tbody>
</table>

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

Jens Drube¹,², Mandy Wan³, Marjolein Bonthuis⁴, Elke Wühl⁵, Justine Bacchetta⁶, Fernando Santos⁷, Ryszard Grenda⁸, Alberto Edefonti⁹, Jerome Harambat⁴,¹⁰, Rukshana Shroff⁹, Burkhard Tönshoff⁵ and Dieter Haffner¹,²*, on behalf of the European Society for Paediatric Nephrology Chronic Kidney Disease Mineral and Bone Disorders, Dialysis, and Transplantation Working Groups
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

Borzyh 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

Musculoskeletal pain accross diverse CKD stages in adults

Overall chronic pain
Musculoskeletal pain
Bone/joint pain
Muscle soreness
Neuropathic pain

moderate/severe 62%

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

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)₂D and lower calcium concentrations were independently associated with baseline and progressive cortical deficits in childhood CKD

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

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

P binders

Aluminum

Highly effective adynamic bone disease, dementia and microcytic anemia

Ca-based binders

Ca carbonate
Ca acetate
Sevelamer hydrochloride
Sevelamer carbonate

Non Ca-containing binders

Lanthanum carbonate
Iron based binders
Colestilan
Sucralfate
Tenapanor

Cheap hypercalcemia, calciphylaxis and vascular calcifications and possibly all-cause mortality

Pleiotrophic effect on lipid metabolism and inflammation, possibly hyperuricemia and hyperglycemia

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

Low efficiency Different pill burden, poor tolerability
## Pharmacological Treatment of CKD-MBD in Children

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1 yr</th>
<th>1-5 yrs</th>
<th>6-11 yrs</th>
<th>&gt; 12 yrs</th>
<th>All</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>67</td>
<td>184</td>
<td>291</td>
<td>348</td>
<td>890</td>
</tr>
<tr>
<td><strong>Phosphate binders (any)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Calcium carbonate/acetate</td>
<td>61.2%</td>
<td>82.7%</td>
<td>89.7%</td>
<td>95.7%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>53.7%</td>
<td>71.7%</td>
<td>71.5%</td>
<td>67.8%</td>
<td>68.8%</td>
</tr>
<tr>
<td>CC / CA + sevelamer</td>
<td>4.5%</td>
<td>2.7%</td>
<td>7.2%</td>
<td>10.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Active vitamin D analogue (any)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td>58.2%</td>
<td>81.4%</td>
<td>71.5%</td>
<td>76.4%</td>
<td>74.5%</td>
</tr>
<tr>
<td>1α-calcidiol</td>
<td>26.9%</td>
<td>48.9%</td>
<td>47.1%</td>
<td>51.9%</td>
<td>47.8%</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>31.3%</td>
<td>31.9%</td>
<td>22.7%</td>
<td>22.8%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>0%</td>
<td>0.6%</td>
<td>1%</td>
<td>1.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>0%</td>
<td>0%</td>
<td>1.4%</td>
<td>6.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>25-OH-Vit.D$_3$</td>
<td>29.8%</td>
<td>30.2%</td>
<td>22.3%</td>
<td>23.3%</td>
<td>24.9%</td>
</tr>
</tbody>
</table>

Borzych et al, KI 2011
BONE EVALUATION in PEDIATRIC CKD 2-5D patients

- Clinical
- Serological
- Radiological
- Histological
Suggested intervals of assessment of serum markers and HCO$_3$ by CKD stage

<table>
<thead>
<tr>
<th></th>
<th>CKD stage</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Ca, P</td>
<td>6</td>
</tr>
<tr>
<td>Total ALP</td>
<td>12</td>
</tr>
<tr>
<td>PTH</td>
<td>12</td>
</tr>
<tr>
<td>25(OH)D$^a$</td>
<td>12</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>6</td>
</tr>
</tbody>
</table>
### Age-specific and CKD stage–based reference ranges for commonly used biomarkers of CKD-MBD

<table>
<thead>
<tr>
<th></th>
<th>Age-specific values</th>
<th></th>
<th>Age- and sex-specific values</th>
<th>CKD stage-dependent values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iCa mmol/L</td>
<td>Ca mg/dL</td>
<td>P mg/dL</td>
<td>ALP* U/L</td>
</tr>
<tr>
<td>0–5 months</td>
<td>1.22–1.40</td>
<td>8.7–11.3</td>
<td>5.2–8.4</td>
<td>0–15 days</td>
</tr>
<tr>
<td>6–12 months</td>
<td>1.20–1.40</td>
<td>8.7–11.0</td>
<td>5.0–7.8</td>
<td>15–30 days</td>
</tr>
<tr>
<td>1–5 years</td>
<td>1.22–1.32</td>
<td>9.4–10.8</td>
<td>4.5–6.5</td>
<td>1–&lt;10 years</td>
</tr>
<tr>
<td>13–20 years</td>
<td>1.21–1.30</td>
<td>8.8–10.2</td>
<td>2.3–4.5</td>
<td>13–&lt;15 years</td>
</tr>
<tr>
<td>–</td>
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</table>

**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
IPPN data, n=890 patients

Maintaining calcium levels within normal limits, close to ULN
Which one of the following tests 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

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
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
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.
BONE EVALUATION in PEDIATRIC CKD 2-5D patients

- Clinical
- 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.
<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Weaknesses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plain X-rays</strong></td>
<td>Not expensive and widely available</td>
</tr>
<tr>
<td></td>
<td>Widely used for assessing bone mineral density</td>
</tr>
<tr>
<td></td>
<td>Minor irradiation: 2.7–3.6 μSv</td>
</tr>
<tr>
<td></td>
<td>Not expensive and easily available</td>
</tr>
<tr>
<td></td>
<td>Evaluation of body composition</td>
</tr>
<tr>
<td></td>
<td>Observer independent</td>
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<tr>
<td><strong>DXA</strong></td>
<td>Bone mineral volumetric compartmental densities</td>
</tr>
<tr>
<td></td>
<td>Bone microarchitecture</td>
</tr>
<tr>
<td></td>
<td>Bone biomechanics</td>
</tr>
<tr>
<td></td>
<td>A non-invasive approach to mineralization (currently under evaluation)</td>
</tr>
<tr>
<td></td>
<td>Minor irradiation</td>
</tr>
<tr>
<td></td>
<td>Data available in paediatric CKD</td>
</tr>
<tr>
<td><strong>QCT, pQCT and HR-pQCT</strong></td>
<td>Ability to predict the fracture risk</td>
</tr>
<tr>
<td></td>
<td>Bone mineral volumetric compartmental densities</td>
</tr>
<tr>
<td></td>
<td>Bone microarchitecture</td>
</tr>
<tr>
<td></td>
<td>No irradiation</td>
</tr>
<tr>
<td></td>
<td>Evaluation of the muscle-bone unit</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Not expensive, available everywhere</td>
</tr>
<tr>
<td></td>
<td>No irradiation</td>
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<td></td>
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</tbody>
</table>
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

Alexander D. Lalayannis¹, Nicola J. Crabtree², Charles J. Ferro ³, Varvara Askiti⁴, Andromachi Mitzioni⁵, Lorenzo Biassoni⁶, Amrit Kaur⁷, Manish D. Sinha ⁸, David C. Wheeler⁹, Neill D. Duncan¹⁰, Joyce Popoola⁵, David V. Milford⁶, Jin Long¹¹, Mary Beth Leonard¹², Mary Fewtrell¹ and Ruksana Shroff ¹³

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.

Lalayannis AD, et al. NDT 2020
Lalayannis AD, et al. 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
- Ultrasound

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

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
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)

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

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