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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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ABSTRACT

Mineral and bone disorder (MBD) is widely prevalent in children with chronic kidney disease (CKD) and is associated with significant morbidity. CKD may cause disturbances in bone remodelling/modelling, which are more pronounced in the growing skeleton, manifesting as short stature, bone pain and deformities, fractures, slipped epiphyses and ectopic calcifications. Although assessment of bone health is a key element in the clinical care of children with CKD, it remains a major challenge for physicians. On the one hand, bone biopsy with histomorphometry is the gold standard for assessing bone health, but it is expensive, invasive and requires expertise in the interpretation of bone histology. On the other hand, currently available non-invasive measures, including dual-energy X-ray absorptiometry and biomarkers of bone formation/resorption, are affected by growth and pubertal status and have limited sensitivity and specificity in predicting changes in bone turnover and mineralization. In the absence of high-quality evidence, there are wide variations in clinical practice in the diagnosis and management of CKD-MBD in childhood. We present clinical practice points (CPPs) on the assessment of bone disease in children with CKD Stages 2–5 and on dialysis based on the best available evidence and consensus of experts from the CKD-MBD and Dialysis working groups of the European Society for Paediatric Nephrology and the CKD-MBD working group of the European Renal Association–European Dialysis and Transplant Association. These CPPs should be carefully considered by treating physicians and adapted to individual patients' needs as appropriate. Further areas for research are suggested.

Keywords: bone, calcium, children, CKD-MBD, dialysis, parathyroid hormone

KEY LEARNING POINTS

What is already known about this subject?

- Chronic kidney disease mineral and bone disorder (CKD MBD) is widely prevalent in children and is associated with pronounced disturbances in the growing skeleton. Although assessment of bone health is a key element in the clinical care of children with CKD, it remains a major challenge for physicians and evidence based guidance is lacking.

What this study adds?

- We present clinical practice points (CPPs) on assessment of bone disease in children with CKD stage 2-5 and on dialysis based on the best available evidence and consensus of European experts from pediatric and adult nephrology.
- Regular clinical examination focusing on skeletal growth and bone/joint evaluation is essential.
- Using trends of serum biomarkers (including calcium, phosphorus, alkaline phosphatase, parathormone and 25 hydroxy vitamin D levels) rather than single laboratory values is of utmost importance to guide therapeutic decisions. Age-specific normal values should be known.
- DXA and all other bone imaging techniques are not routine tools in children with CKD. Plain X-ray can be used in clinical setting to evaluate bone age, bone pain, suspected fractures, slipped epiphyses and deformities. It may be more useful in genetic diseases with specific bone involvement.
- 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 optimising treatment.

What impact this may have on practice or policy?

- The presented CPPs give guidance to physicians on assessment of bone disease in children with CKD in order to adequately manage bone disease and prevent unecessary measures and thereby improve patient outcome.

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Mineral and bone disorder (MBD) is widely prevalent and can cause significant morbidity in children with chronic kidney disease (CKD). It may result in both abnormal bone histology as well as ectopic vascular calcifications [1, 2]. CKD-MBD is a systemic disease comprising vascular and mineral abnormalities as well as abnormalities in bone turnover (from low to high), mineralization (from normal to abnormal) and bone volume (from low to high) [3]. In the growing skeleton, CKD may significantly affect bone modelling and remodelling, manifesting as growth restriction, bone deformities (e.g. genu valgum and genu varum), slipped epiphyses and fractures [1]. These alterations may occur as early as CKD Stage 2 and increase in prevalence and severity as renal function worsens [4–6]. Therefore assessment of bone health is a key element of clinical care in children with CKD but remains a major daily challenge for physicians. Currently, double tetracycline-labelled transiliac bone biopsy with quantitative histomorphometry is the gold standard to assess bone health, but it is expensive, invasive and requires expertise. Therefore it is rarely performed, even in adults with CKD, and far less often in children [7–9]. Furthermore, currently available non-invasive measures of bone health in children, including imaging techniques such as X-ray and dual-energy X-ray absorptiometry (DXA), do not correlate with bone mineral density (BMD) and routinely used biomarkers such as calcium (Ca), phosphate (P), alkaline phosphatase (ALP), parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D] correlate weakly with BMD [10].

Comprehensive guidance on the assessment of bone health in children with CKD is not available, apart from some low-grade recommendations for children in the Kidney Disease: Improving Global Outcomes (KDIGO) 2017 CKD-MBD updated guidelines and the earlier Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [11–13]. Given that there are no randomized trials or meta-analyses and very few prospective studies in children with CKD-MBD, we present clinical practice points (CPPs) [14, 15] rather than a guideline document. These statements on the evaluation of bone health in children with CKD Stages 2–5 and on dialysis are based on the best available evidence and the consensus of experts from the CKD-MBD and Dialysis working groups (WGs) of the European Society for Paediatric Nephrology (ESPN) and the CKD-MBD WG of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Treatment of CKD-MBD is beyond the scope of this document and we refer to existing guidelines where relevant.

MATERIALS AND METHODS

This consensus paper was developed to provide guidance to healthcare professionals on the assessment of renal bone disease in paediatric CKD patients as well as to support high-quality clinical and research practice. Key steps in the development of this consensus document are described here.

Setting up the CPP development group

Two groups were assembled: a core WG and an expert panel. The core group comprised paediatric nephrologists from the CKD-MBD and Dialysis WGs of the ESPN, as well as two representatives of the ERA-EDTA CKD-MBD WG (P.E. and M.H.), who together defined the scope of the project,

formulated the key questions, performed a literature review, conducted the expert panel and drafted the initial and final version of the manuscript based on best available evidence. The expert panel included members of the ESPN CKD-MBD and Dialysis WGs and the ERA-EDTA CKD-MBD WG. All conflicts of interest were declared.

Formulating study questions using the PICO approach

In order to give specific actionable advice, we developed questions in four areas in the diagnosis of CKD-related bone disease including clinical, serological, radiological and histological/histomorphometric parameters. Cardiovascular disease, including ectopic vascular calcification and respective diagnostic methodology, is beyond the scope of this article. In each category, the PICO format was used: the **P**atient (or **P**opulation) to whom the recommendation will apply; the **I**ntervention being considered; the **C**omparison (which may be 'no action' or an alternative intervention); and the **O**utcomes affected by the intervention [16]. The population consisted of children with CKD Stages 2–5D and excluded patients who have a kidney allograft, irrespective of graft function. The interventions considered were the diagnostic tools undertaken to assess bone health, which were compared with the gold standard of bone histomorphometry where available. The outcomes addressed included growth, fractures, bone pain, bone deformities and histomorphometric parameters on bone biopsy.

Literature review and studies included

For evidence retrieval, assessment and synthesis, the PubMed database was searched until 3 March 2020: articles included were randomized clinical trials; prospective uncontrolled or observational studies, irrespective of number of patients; registry data; retrospective studies and case reports with more than five paediatric patients, restricted to human studies in English.

CPPs have been made by the WGs where important clinical and implementation issues arose from discussions of best available evidence or group consensus. CPPs do not have a Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating, as sufficient evidence was not found in this field of bone evaluation in paediatric CKD Stages 2–5D [14, 15].

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.

Evidence and rationale:

Clinical symptoms of CKD-MBD, including limb deformities and pain, or radiological signs of bone disease are noted in ∼15% of children on peritoneal dialysis (PD) [17]. In children with CKD prior to dialysis, the reported fracture rates of 395/10 000 and 323/10 000 person-years in boys and girls were 2.4- and 3-fold higher, respectively, than gender-specific rates reported in a large population-based study of fracture epidemiology in healthy children (162/10 000 person-years for boys and 103/10 000 person-years for girls) [18]. The fracture risk was associated with baseline walking difficulty, Tanner Stages 4–5 of pubertal development, lower height Z-score, higher PTH levels and team sports participation [18]. The only protective factor was P binder use, which significantly decreased fracture risk. Of note, 82% of patients in this study received a Ca-based P binder, suggesting that improved P control and/or the Ca intake from the binder may exert some protective benefit [18]. A similar high prevalence of fractures has been reported in a study of 170 children and young people up to 21 years of age in CKD Stages 2–5D. Eleven of 170 participants (6.5%) had fractures during the study's 1-year follow-up (incidence 556/10 000 person-years). The higher incidence of fractures was likely attributable to the inclusion of participants on dialysis. The fracture sites were the clavicle, tibia, foot, toes and radius. These fractures were sustained in low-impact traumas, such as exercise and falls. Independent risk factors attributed to the higher fracture risk were any period of rapid growth in adolescence, lower Ca and 25(OH)D levels as well as higher PTH levels at baseline [4].

Importantly, CKD-MBD in childhood can lead to important sequelae in adulthood. In 2003, a study of 249 young adults with childhood-onset end-stage kidney disease who were followed into adulthood showed that 37% had symptoms of bone disease (deformities, bone pain, aseptic bone necrosis and atraumatic fractures), 18% were disabled by bone disease and 61% had severe growth restriction [19]. A recent study in children and young adults <30 years of age with CKD Stages 4–5D showed that bone pain was a common problem reported by 58% of the patients and 10% had low-trauma fractures [20], implying that despite improvements in treatment, patients continue to have significant morbidity from MBD.

Children and their caregivers must be asked about the achievement of age-appropriate developmental milestones and the presence and severity of bone pain. Any limitations to

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

A range of monitoring intervals is given depending on the patient's age and degree of CKD. However, the frequency of assessment depends also on the presence and magnitude of abnormalities and progression of CKD. Therefore, even more frequent assessments may be required in individual patients.

[a]Including pain, walking difficulties, fractures, medication and dietary intake (energy, protein, Ca and P).

[b]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.

[c]Including bony deformities (e.g. genu varum or valgus) and gait assessment.

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 frequency of monitoring of these markers depends on the presence and magnitude of abnormalities, age and stage and progression of CKD and concomitant medications. Therefore more frequent assessments may be required in individual patients.
[a]If vitamin D supplementation is required, check levels after 3 months. If normal levels, continue vitamin D supplements and measure levels every 6 months; low levels, consider one repeat course of 'intensive replacement treatment' and repeat levels in 3 months.

routine physical activity should be explored. A history of previous fractures, the site(s) of the fracture(s), the severity of trauma and healing of the fracture(s) must be recorded. A detailed musculo-skeletal examination for the presence of bony deformities and fractures, including careful measurement of the extent of bony deformity (such as genu varus or valgum deformities) and gait assessment is important. A detailed clinical assessment may require multidisciplinary input from paediatric orthopaedic and physiotherapy teams. Ca intake from diet, supplements, if any, and P binders should be regularly assessed and are discussed in detail in other guidelines and reviews [13, 21–23].

Poor growth remains one of the most widely prevalent manifestations of CKD-MBD and has been associated with an increased risk of hospitalization, morbidity and mortality [24]. Fifty percent of children with CKD will not attain their full height potential [25]. The North American Paediatric Renal Trials and Collaborative Studies report that the gender- and age-adjusted height standard deviation scores (SDSs) for males and females at the time of transplantation are −1.77 and −1.68, respectively. The greatest height deficit (−2.2 SDS) is seen in children <5 years of age [26]. The final adult height SDS of 1612 young adults across Europe who received renal replacement therapy in childhood was –1.65 (−2.64 to −0.78), and only 57.4% had attained an adult height within their genetically determined range [27]. Catch-up growth after transplantation is unable to make up for the height deficit in the pre-transplant CKD or dialysis periods but can be improved when steroid-sparing protocols are used [28–30]. Infants and children with CKD should have their height (or supine length for <2 years of age) measured at regular intervals (Table 1) [13, 31]. Measurements should be standardized, with a wall-mounted stadiometer used for older children and a validated infantometer for infants and non-mobile children. Growth velocity must be calculated at 6–12-month intervals [31]. Both height and height velocity should be plotted on age- and gender-specific standardized country-specific or World Health Organization charts. The frequency of measurements should be adjusted to the degree of CKD stage and age of the child [13], based on the prevalence and severity of MBD in more advanced stages of CKD and also at periods of rapid growth, when bone Ca accrual is at its highest and mineralization defects can be common. This is in keeping with a recent guideline from the ESPN CKD-MBD, Dialysis and Transplantation WGs on treatment with growth hormone in children with CKD [31] and the 2008 KDOQI guidelines on the nutritional management of children with CKD [13]. Immobilized patients, those with syndromic/genetic diseases with kidney and bone involvement and inherited disorders like nephropathic cystinosis as a severe phenotype of tubulopathies or primary hyperoxaluria should be evaluated on an individual basis [31–36]. In three recent publications, bone disease, including pain, deformity or fractures, had been reported in up to 70% of cystinosis patients, which is remarkably high compared with CKD-MBD symptoms in children with other underlying kidney diseases [17, 34–36].

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.

Evidence and rationale:

Alterations in P, Ca, PTH and vitamin D metabolism are involved in the pathogenesis of CKD-MBD. However, the first detectable abnormalitiy occuring already in Stage 2 CKD is an increased expression of sclerostin and fibroblast growth factor 23 (FGF23) in osteocytes [37–43]. FGF23 is a phosphaturic hormone that acts on the kidney with its co-factor Klotho by inhibiting sodium-dependent P reabsorption in the proximal renal tubule, whereas sclerostin is a negative regulator of bone remodelling [42]. Thus, in early stages of CKD, increased FGF23 levels maintain P homoeostasis despite declining renal function. In addition, FGF23 suppresses 1,25-dihyroxyvitamin D [1,25$(OH)_2$D] synthesis in the kidney, which promotes hypocalcaemia [41]. The combination of hypocalcaemia, low vitamin D levels, altered expression of Ca-sensing receptor, vitamin D receptor and FGF receptor in the parathyroid gland and decreasing renal P excretory capacity promote the development of secondary hyperparathyroidism (SHPT), which is regularly noted at CKD Stage 3. Since the phosphaturic effects of FGF23 are limited by proximal tubular Klotho deficiency, SHPT becomes an additional adaptive mechanism to maintain P homoeostasis during advanced CKD. In CKD Stages 4 and 5, these adaptations are no longer adequate and hyperphosphataemia develops despite profound elevations in both PTH and FGF23 levels [44].

Table 3. Expected changes in serum PTH, ALP and Ca levels in children with abnormal bone turnover and/or mineralization based on bone histomorphometric findings in children with advanced CKD (adapted from [47–49, 86–88])

Marker	High turnover		Normal turnover		Low turnover	
	Abnormal mineralization	Normal mineralization	Abnormal mineralization	Normal mineralization	Abnormal mineralization	Normal mineralization
PTH	↑↑↑	↑↑	↑↑	N-variable	↑, variable	↓, variable
ALP[a]	↑↑	↑	↑, variable	N-variable	variable	↓, variable
Ca	↓, variable	N-variable	↓, variable	N-variable	↓, variable	↑, variable

[a]ALP levels may be increased in patients receiving treatment with recombinant human growth hormone; N: normal; ↓: reduced; ↑: elevated; ↑↑: moderately elevated; ↑↑↑: severely elevated.

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[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.

There is no ideal biomarker to assess CKD-MBD. All currently available markers have limited sensitivity or specificity to predict intermediate endpoints like alterations in bone (mineralization and turnover) and vessels (vascular calcifications) or hard endpoints like fractures [45]. Several serum parameters have been proposed to monitor CKD-MBD in children, including serum Ca, P, ALP, PTH and 25(OH)D [11, 46–50]. Serum concentrations of Ca, P and ALP vary considerably with age, sex and pubertal stage, even in healthy children [51, 52]. In addition, the complexity and interdependency of all CKD-MBD markers should be taken into consideration. Treatment of CKD-MBD should be based on serial assessment of Ca, P, ALP and PTH levels and interpreted together for therapeutic decision making [11]. We suggest that the frequency of monitoring of these markers should be based on the presence and severity of abnormalities, age, stage and progression of CKD and concomitant medications (Table 2).

There is considerable overlap for bone marker levels between patients presenting with certain bone histomorphometric abnormalities, no clear cut-off values exist and associations are even weaker in predialysis patients compared with those on dialysis. A summary of the associations between commonly used markers of CKD-MBD and the presence of abnormal bone turnover and/or mineralization in children with CKD is provided in Table 3. The above-mentioned limitations should be considered when using this table to assess bone quality in children with CKD based on serum markers.

Markers of bone and mineral metabolism

Age-dependent normal values for various markers of bone and mineral metabolism and CKD stage-dependent PTH target ranges proposed by international guideline committees are given in Table 4. Although ALP values are largely dependent on the assay used, the age- and gender-dependent reference intervals based on thousands of healthy community children and adolescents from a multi-ethnic population are available [52] (Table 4). ALP is synthesized mainly in osteoblasts and indicates bone formation. However, in clinical practice, elevated ALP levels are also used as a biomarker of bone mineralization in children with CKD Stage 5D [47, 49] (Table 3). In contrast, ALP levels are poor predictors of altered bone turnover or mineralization in pre-dialysis patients [50]. Given that bone-specific ALP represents ∼80–90% of total circulating ALP in growing children, total ALP can be used except in patients with severe liver disease, as ALP also originates from hepatocytes [53, 54].

PTH levels can start to rise as early as CKD Stage 2 and are commonly increased in CKD Stage 3 [41] in order to counterbalance calcitriol deficiency, resulting hypocalcaemia and increased P load [50]. SHPT is a hallmark of CKD-MBD and associated with high bone turnover and mineralization defects, bone abnormalities on X-ray, risk of fractures and ectopic calcifications/vascular stiffness [1, 5, 17, 18, 55–60]. However, there are great uncertainties about the optimal PTH target range [61, 62] and recommended values differ widely [7, 45, 46], ranging from 2–3 times the upper limit of normal (ULN) in the European guideline [46] to 2–9 times the ULN in the KDIGO guideline [7] (Table 4). This is at least partly due to methodological challenges. Available second-generation assays have a high interassay variability and cannot discriminate between full-length 'intact' peptide and inactive oxidized PTH or PTH(7–84) fragments [63]. The latter accumulates in advanced CKD and may further contribute to PTH hyporesponsiveness in target organs [64]. The predictive value of PTH in determining high- versus low-turnover bone disease is poor (vide infra). On the other hand, a very recent study in >100 children and young adults with CKD Stages 4 and 5D showed that tibial cortical BMD evaluated by peripheral quantitative computed tomography (pQCT) was negatively associated with PTH and ALP and positively with Ca levels [20]. This study showed that when PTH values were <3 times the ULN, none of the patients had a tibial cortical BMD <−2 SDs [20], confirming earlier recommendations from the European Paediatric Dialysis WG [46]. Novel bone markers such as FGF23 and sclerostin were not included in the CPPs since there is currently no evidence that their assessment is helpful in the clinicial management of CKD-MBD in children.

Combinations of hypercalcaemia and hyperphosphataemia: Combinations of hypercalcaemia and hyperphosphataemia may be associated with vascular calcifications [1, 7, 57–60], whereas hypocalcaemia and hypophosphataemia are associated with impaired bone mineralization in children with CKD [45, 47], as summarized in Table 3. Chronic hypocalcaemia or hypophosphataemia, as seen in children on frequent daily or nocturnal haemodialysis (HD) [65], can result in impaired bone mineralization and rickets and these patients may need high-Ca dialysate and Ca and/or P supplements under regular monitoring. There may be more severe CKD-MBD presenting with multiple fractures and biopsy-proven severe osteomalacia in patients on nocturnal home HD [66]. In addition, patients with P wasting tubulopathies, i.e. nephropahtic cystinosis, may have inadequately low FGF23 and low PTH levels despite advanced CKD and significant metabolic bone disease characterized by hypophosphataemic rickets in infancy, bone pain and deformities, osteomalacia, osteoporosis and fractures [32, 34–36]. Therefore serum Ca and P levels should be monitored regularly depending on CKD stage, underlying renal disease and presence and magnitude of clinical and biochemical abnormalities (Table 2).

Total versus ionized Ca: About half of serum Ca is bound to albumin and proteins and only the 'free' or ionized Ca is biologically active. Albumin-corrected serum Ca and total Ca levels do not correctly estimate serum Ca, particularly in dialysis patients, due to CKD-related alterations in pH, anion gap and circulating plasma proteins [67–69]. Since ionized Ca levels are not influenced by alterations in serum albumin abnormalities [68], we suggest measuring ionized Ca, where available. The International Federation of Clinical Chemistry and Laboratory Medicine recommends using ion-selective electrodes to determine ionized Ca (iCa) in whole blood, plasma and serum samples, as well as rapid analysis of an anaerobic sample placed on ice to counteract pH alteration, which impacts the concentration of iCa. Avoidance of dilution effects of anticoagulant solutions, such as heparin, is also critical [70].

25(OH)D: Low 25(OH)D levels may contribute to hypocalcaemia, SHPT and mineralization defects in children with CKD [18]. Treatment with native vitamin D resulted in the correction of mineralization defects in children with pre-dialysis CKD [71]. Therefore, in line with adult guidelines [72], we suggest that 25(OH)D levels should be monitored regularly to maintain them within normal limits, which has been extensively addressed in recent guidelines from the ESPN CKD and Dialysis WGs [21] (Tables 2 and 4).

Metabolic acidosis: Metabolic acidosis is known to induce the release of bone Ca by a direct physiochemical effect of hydrogen ions on bone, resulting in bone demineralization (osteomalacia and rickets). In addition, it stimulates osteoclastic differentiation and osteoclast-mediated bone resorption, inhibits osteoblastic differentiation and alters the serum concentrations and biological actions of PTH and vitamin D [73–75]. In a large prospective study in paediatric CKD Stages 3–5 patients, metabolic acidosis was significantly associated with elevated serum PTH levels during follow-up. Additionally, children with time-varying serum bicarbonate <8 mmol/L had a significantly higher risk of CKD progression compared with those with a serum bicarbonate of ≥22 mmol/L {adjusted hazard ratio [HR] 2.44 [95% confidence interval (CI) 1.43–4.15]} [76], which is consistent with studies among adult patients [77]. Therefore it is advisable that serum bicarbonate levels should be regularly monitored depending on the stage of CKD and degree of abnormalities and bicarbonate replacement provided (Table 2).

3. Radiological Evaluation of Bone Disease

3.1 Do not perform imaging techniques including DXA, pQCT, high-resolution pQCT (HR-pQCT), magnetic resonance imaging (MRI) or ultrasound in routine clinical practice in children with CKD.

3.2 Perform plain radiography (X-ray) in patients if results are expected to impact on treatment decisions.

Evidence and rationale:

The evidence to recommend a radiological evaluation of bone disease in paediatric CKD is scarce. Conventional X-rays can grossly evaluate bone and notably mineralization. Radiographic signs of severe rickets or late manifestations of SHPT can be observed. X-rays may also be performed in children with bone pains, those with suspected atraumatic fractures and those with genetic diseases with specific bone involvement [1, 32, 33, 35]. In a recent study, 27 of 30 children with nephropathic cystinosis were evaluated by skeletal survey and 64% showed one or more long bone deformity (femoral, tibial bowing or humeral

Table 5. 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

bowing, coxa valga and tibia vara) and 50% showed scoliosis. Thirty-two percent of patients had radiographic evidence of one or more vertebral fractures and 27% had a history of long bone fractures [35]. Bone radiographs are also useful in patients with clinical manifestations suggestive of avascular necrosis, proximal femoral slipped epiphyses or in the assessment of skeletal maturity [12]. Skeletal age can also be determined on an X-ray of the left wrist [78]. In the youngest children and particularly in infants, knee X-ray to evaluate an active metaphyseal area is suggested [79, 80]. Additionally, extraskeletal calcifications can also be visualized [1, 12]. Conventional X-rays are not expensive and are easily available for bone evaluation, but the sensitivity of this examination remains low and the interpretation may vary depending on the expertise of the physician. The benefit:risk ratio in terms of radiation exposure should always be considered.

Although bone imaging techniques, including DXA, pQCT, HR-pQCT, MRI and ultrasound, are interesting for research protocols [18, 81–83], there is no evidence to recommend them as routine screening tools for bone health or fracture risk prediction in paediatric CKD patients. Notably, a lower cortical BMD *Z*-score as assessed by pQCT predicted future fractures in children with CKD Stages 2–5D; the hazard ratio for fractures was 1.75 (95% CI 1.15 − 2.67; P = 0.009) per SDS decrease in baseline BMD [4].

The KDIGO suggests considering DXA imaging in adult patients with CKD who experience bone pain and/or fractures if the results will affect management [11]. There is limited evidence that DXA (lumbar spine and whole-body) and pQCT results are congruent with each other in paediatric CKD [81]. It has yet to be proven if DXA can predict fracture risk in this population in longitudinal prospective studies. A recent study showed that a combination of routine biomarkers was a better predictor of cortical BMD evaluated by pQCT, but BMD measurement by DXA did not correlate with biochemical data or pQCT measures [20].

Thus evidence is scarce for radiological bone evaluation of paediatric CKD-MBD. Before performing bone imaging in the clinical setting, the benefit:risk ratio (and notably in terms of radiation exposure) should always be discussed. Table 5 summarizes the strengths and weaknesses of all the techniques discussed above.

4. Histological Evaluation of Bone Disease

4.1. We suggest considering bone biopsy in children with CKD if the clinical and biochemical findings do not explain underlying bone disease, e.g. severe bone deformity or pain, low-energy fracture, persistent hypercalcaemia or hypophosphataemia, despite optimizing treatment.

4.2. Perform histomorphometric analysis in centres with experience in interpreting paediatric bone biopsies.

Evidence and rationale:

Renal osteodystrophy (ROD), a disorder of bone remodelling, has traditionally been classified according to lesions of bone

Table 6. Bone histomorphometry and PTH levels in children and adolescents on maintenance dialysis

References, Country	Study period	*n*	Population	Histomorphometry	PTH levels and bone turnover
Salusky *et al.* [84], USA		44	PD	39% osteitis fibrosa 25% mild high turnover 11% adynamic bone 9% osteomalacia 16% normal	Bone formation rates correlated positively with PTH levels and negatively with bone aluminium content
Mathias *et al.* [85], USA	July 1988–September 1990	21, M/F: 14/7, 17.5 ± 1.5 years	HD	Osteitis fibrosa: 5 Mild hyperparathyroidism: 3 Adynamic: 6 Mixed: 4 Normal: 3 (4: aluminium bone disease) 16 on CC/CA, 1 on Al, 4 on Al+CC 19 on oral active vitamin D Two site IRMA for intact PTH measurement (*N*: 10–65, Nichols) Conventional 'renal osteodystrophy' (ROD) classification	PTH levels correlated directly with the bone formation rate ($r = 0.84$) and with eroded bone perimeter ($r = 0.67$) and Ca levels ($r = -0.79$, $P < 0.001$) 8/9 patients with serum PTH levels >125 pg/mL had fibrosis (OF and mixed?) All patients having Ca <10 mg/dL and PTH > 125 pg/mL had OF or mixed lesion Ca > 10 and PTH <65 identified aluminum disease (3/3) Based on criteria used, PTH and Ca levels may discriminate high turnover disease from normal and low turnover disease
Goodman *et al.* [86], USA		14 children, 13.4 ± 1.1 years	PD	Before treatment 11 OF 3 Mild Intermittent calcitriol thrice weekly for 12 months After treatment 6 Normal BF 6 Adynamic bone 1 mixed 1 OF Conventional ROD classification Two site IRMA for intact PTH measurement (*N*: 10–65, Nichols)	PTH <200 pg/mL strongly suggest ABD during intermittent calcitriol treatment. Intermittent calcitriol effectively reverse high turnover to normal and there may be a disparity between histology and biochemical parameters. Despite normalization of turnover, serum PTH levels remain persistently high in some subjects.
Salusky *et al.* [48], USA	Retrospective, 1983–92	55, M/F: 29/26, 13 ±5 years, 68 bone biopsies	PD	50% osteitis fibrosa 9% mild high turnover 22% adynamic bone 19% normal Conventional ROD classification Two site IRMA for intact PTH measurement (*N*: 10–65, Nichols) All on active vitamin D, 8 pts on CC+Al, others on CC Conventional ROD classification	Serum PTH > 00 pg/mL and Ca < 10 mg/dL: 85% sensitive and 100% specific for identifying high-turnover disease (excluded all *N* or low turnover disease) Serum PTH < 150 pg/mL and Ca >10 mg/dL: 80% sensitive, 92% specific for identifying low-turnover disease (identified 11 of 14 ABD and excluded all *N* or HT bone disease.
Yalcinkaya *et al.* [87], Turkey	2000, cross-sectional	17, M/F: 8/9, 13.0 ± 3.0 years	PD	47% high turnover 29% adynamic bone 24% mixed No histomorphometry iPTH (IRMA) N: 12–72 Patients were on Ca carbonate and active vitamin D.	Serum PTH >200 pg/mL: 100% sensitive and 66% specific for identifying high-turnover disease Serum PTH <200 pg/mL: 100% sensitive and 92% specific for identifying low-turnover disease

Ziolkowska *et al.* [88], Poland	75% of the patients followed-up between 1993 and 98 Indications: Ca–P disturbances in 8, before GH in the remainder	51, M/F: 29/22, 11.5 ± 2.9	PD [30] or HD [21]	24% high turnover 27% adynamic bone 2% osteomalacia 10% mixed 37% normal IRMA (N: 10–55) Active vitamin D stopped 3 months before BBx Conventional ROD classification	Serum PTH <50 pg/mL: 71% sensitive and 78% specific for identifying low-turnover disease Serum PTH > 200 pg/mL: 75% sensitive and 95% specific for identifying high-turnover disease In patients with normal bone turnover, 69% had PTH level of 50–150 pg/mL
Bakkaloglu *et al.* [47], USA	Bone biopsy undertaken between the years of 1990 and 2005	161	PD	57% high bone turnover 42% normal 1% low TMV classification	PTH < 400 and ALP < 400 provided the highest prediction of normal bone T and M at the highest level (Sens. 72% Specif. 79%) Levels of PTH were higher and serum Ca levels were lower in patients with defective mineralization, irrespective of bone turnover
Wesseling *et al.* [50], USA		52, M/F: 30/22, 13.3 ± 4.4 years	CKD 2–5	High turnover: 29% CKD Stage 4 but not seen in children with Stage 2 Mineralization abnormalities occurred in 42% in Stage 2 in 80% in Stage 4 and exceeding 90% in CKD 5D patients TMV classification first-generation immunometric assay (15–65 pg/mL)	PTH was elevated in 36% of patients with Stage 2, 71% with Stage 3 and 93% with Stage 4/5 CKD, whereas FGF-23 values were elevated in 81% of all patients, regardless of CKD stage Defective skeletal mineralization was associated with lower Ca levels and increased PTH concentrations
Carvalho *et al.* [89], UCLA	2015	22, 10.4 ± 0.7 years (2.0–15.8)	PD	12: high trabecular bone turnover 10: normal to low trabecular bone turnover PTH: 554/122 Ca: 9.2/10.2 Vitamin D off 1 month before BBx All on Ca carbonate	Trabecular bone turnover and osteoid volume correlated with PTH levels ($r = 0.86$, $P < 0.01$ and $r = 0.93$, $P < 0.01$, respectively) Internal cortical osteonal bone formation rate was directly related to ALP ($r = 0.45$, $P < 0.05$) and inversely related to IGF-1 values ($r = -0.55$, $P < 0.01$) and internal cortical porosity was also related to serum ALP levels ($r = 0.57$, $P < 0.01$)
Pereira *et al.* [49], UCLA	As part of research protocols between 1983 and 2006 Histomorphpmetry and microCT	68 bone cores, 50% males, 13.9 ± 0.5 years/14 controls: 15.3 ± 14.2 years	Dx	Normal ($n = 23$) or high ($n = 29$) bone turnover: 76%; adynamic bone: 13% osteomalacia: 11% 37% on active vitamin D Mean PTH in ROD groups: 736/45/293	PTH and ALP correlated with BFR ($r = 0.67$; $P < 0.001$ and $r = 0.38$; $P = 0.004$, respectively) as well as with osteoid accumulation (osteoid thickness: $r = 0.54$; $P < 0.001$ and $r = 0.34$; $P < 0.01$, respectively), whereas serum Ca levels were inversely related to osteoid thickness ($r = 20.43$; $P < 0.001$) BFR did not correlate with any mCT determinations. BV was highly correlated between histomorphometry and mCT Histomorphometric measures of osteoid accumulation correlated with mCT measures of bone mineral density, suggest that skeletal mineralization, in addition to bone volume, may be assessable by high-resolution bone CT in bone cores

turnover and is one component of the bone abnormalities of CKD-MBD. Double tetracycline-labelled transiliac bone biopsy with quantitative histomorphometry is the only way to assess ROD and the three histologic features of bone, namely turnover, mineralization and volume (TMV) that are key parts of the TMV classification [3]. We follow the KDIGO guideline mainly addressing adult CKD patients, suggesting considering a bone biopsy if knowledge of the type of ROD might impact treatment decisions (e.g. initiate or discontinue calcimimetics, calcitriol or vitamin D analogous) and identify a mineralization defect that would alter treatment (e.g. by preferring Ca-based binders and aggressively treating hypophosphataemia and/or vitamin D deficiency) [11]. Bone biopsy findings may also assist specific management in refractory hypercalcaemia, unexplained hypophosphataemia and the presence of unexplained deformities and fractures [6, 7, 9, 11]. Bone biopsy is also indicated in adults with suspected aluminium toxicity, severe progressive vascular calcification, before parathyroidectomy if biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism and may be considered prior to anti-resorptive therapy in patients with advanced CKD and suspected disturbed bone mineralization or disease-associated low bone turnover (e.g. malnutrition, chronic inflammation or diabetes mellitus and low circulating bone turnover markers) [3, 7–9].

Due to the limitations of serum biomarkers to predict bone mineralization and/or turnover in patients with CKD (Tables 3 and 6), the most recent KDIGO guidelines recommend performing a bone biopsy if trends in PTH values are inconsistent or an atypical response to standard therapies for elevated PTH is achieved [11]. Unlike biochemical markers, bone biopsy can distinguish high-turnover osteodystrophy from other forms of bone disease, including mixed osteodystrophy and low bone turnover (adynamic bone disease and osteomalacia), which may improve therapeutic decision making (Tables 3 and 6).

The predominant lesion in bone biopsy in children undergoing dialysis is high bone turnover (~55–60% of patients) [11, 45, 46, 84, 89]. Low-turnover bone disease is only seen half as often in children (18–29% of patients) [85, 87, 88], as summarized in Table 6. However, there are wide variations in results from different parts of the world, possibly explained by differences in the management of CKD-MBD with various PTH targets [47, 50, 90]. Mineralization defects are common in paediatric CKD patients—in a large paediatric bone biopsy series, approximately half of the PD patients displayed increased bone turnover and/or abnormal mineralization [47]. In children, mineralization defects begin early in CKD Stage 2 and have been reported in 29, 80 and >90% of children with CKD Stages 2, 4 and 5D, respectively [50] (Table 6). Therefore the prevalence of impaired mineralization and high bone turnover is greatest at the lowest GFR levels.

In addition to providing a detailed evaluation of trabecular bone, a bone biopsy also allows an accurate evaluation of cortical bone. Recently, increased cortical porosity associated with SHPT was shown in paediatric CKD patients [85]. Loss of cortical integrity in micro-CT data of bone cores may be used for predicting fracture risk. However, bone biopsy is expensive, invasive and requires specific expertise and a certain time for results and thus cannot be used for rapid decision making and is available in only select centres in Europe, with very limited experience in interpreting paediatric bone biopsies. However, the EUROD initiative, led by nephrologists to promote and develop bone biopsy across Europe, may help paediatricians using this tool rationally in children and teenagers with CKD [9]. Although reference values in paediatric populations have been reported [91], ideally age-, gender- and ethnicity-adjusted paediatric reference data would be required for interpreting results. In addition, bone biopsies only provide a quantitative measure of bone health at a single site at a single point in time, assuming that iliac crest remodelling is representative of systemic turnover. So even with the availability of bone biopsy data, we may find that patients do not respond predictably to treatments [92]. In conclusion, we do not recommend bone biopsy for routine care of CKD patients. Bone biopsy in clinical use could be limited to certain cases with inconsistent findings, in which significant additional information for therapeutic decision making is expected from the histological analysis. On the other hand, current understanding of CKD-MBD pathogenesis has largely changed and been significantly enhanced by bone biology studies in biopsy cores. Therefore, in a research setting, the performance of bone biopsies and evaluation with novel techniques will be the only way to validate biomarkers and imaging techniques.

Bone Evaluation in Paediatric CKD: CPPs from the ESPN CKD-MBD and Dialysis WGs and CKD-MBD WG of the ERA-EDTA

RECOMMENDATIONS FOR FUTURE RESEARCH

We recommend the following areas of study to provide future evidence-based recommendations for bone evaluation in children with CKD and on dialysis.

- Determine the prevalence and risk factors for fractures in European children with CKD and on dialysis.
- In a large cohort of children with CKD Stages 3–5D, identify the required amount of Ca intake and the best PTH target range, including second and third-generation assays, which allow normal turnover and mineralization (determined by histology, imaging and biomarker studies) without worsening vascular calcifications (measured by cardiac CT scan and carotid artery intima-media thickness).
- Assess the value of cortical bone evaluation in bone biopsy cores to predict fracture risk.
- Evaluate the sensitivity and specificity of DXA to predict fracture risk in children with CKD Stages 3–5D.
- Validate the clinical utility of trabecular bone score in DXA as a measure of trabecular architecture against transiliac bone biopsy with histomorphometry in CKD and dialysis patients.
- Validate newly proposed circulating CKD-MBD biomarkers by evaluating their protein expression levels in

the bone and simultaneous comparison with bone histomorphometry.
- Identify the link between bone cell maturation and abnormalities in skeletal mineralization in children with CKD.
- Evaluate bone quality and biomechanical competence such as microarchitecture, accumulated microscopic damage and the quality of collagen and the size of mineral crystals in clinical practice by new bone research techniques.

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