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Treatment of Pediatric Chronic Kidney Disease-Mineral and Bone Disorder

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Abstract

a) Purpose of review—In this paper, we review the pathogenesis and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD), especially as it relates to pediatric CKD patients.

b) Recent findings—Disordered regulation of bone and mineral metabolism in CKD may result in fractures, skeletal deformities, and poor growth, which is especially relevant for pediatric CKD patients. Moreover, CKD-MBD may result in extra-skeletal calcification and cardiovascular morbidity. Early increases in fibroblast growth factor 23 (FGF23) levels play a key, primary role in CKD-MBD pathogenesis. Therapeutic approaches in pediatric CKD-MBD aim to minimize complications to the growing skeleton and prevent extra-skeletal calcifications, mainly by addressing hyperphosphatemia and secondary hyperparathyroidism. Ongoing clinical trials are focused on assessing the benefit of FGF23 reduction in CKD.

c) Summary—CKD-MBD is a systemic disorder that has significant clinical implications. Treatment of CKD-MBD in children requires special consideration in order to maximize growth, optimize skeletal health, and prevent cardiovascular disease.

Keywords

Chronic Kidney Disease; CKD-Mineral and Bone Disorder; Children; Pathogenesis; Treatment of CKD-MBD

Pediatric Chronic Kidney Disease–Mineral and Bone Disorder

In pediatric patients with chronic kidney disease (CKD), disordered regulation of bone and mineral metabolism may be especially detrimental, resulting in fractures, skeletal deformities, and, most pertinently, poor growth. Such disordered regulation may be

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Compliance with Ethical Guidelines

Conflict of Interest

Mark Hanudel declares no conflict of interest.

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Human and Animal Rights and Informed Consent

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characterized by abnormalities in phosphate, calcium, parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D3, or 1,25D), and/or fibroblast growth factor 23 (FGF23) metabolism, that lead to the different subtypes of renal osteodystrophy. The term “renal osteodystrophy” specifically refers to alterations in bone morphology associated with CKD, which can be characterized by the histomorphometric parameters of bone turnover, mineralization, and volume (1). Traditionally, the different types of renal osteodystrophy have been classified on the basis of bone turnover and mineralization (2). Both osteitis fibrosa and mixed disease are characterized by increased turnover, but osteitis fibrosa has normal mineralization, whereas mixed disease has abnormal mineralization. Both osteomalacia and adynamic disease are characterized by decreased turnover, with abnormal mineralization in osteomalacia and acellularity in adynamic disease. Renal osteodystrophy is one measure of the skeletal component of the systemic disorder termed CKD-mineral and bone disorder (CKD-MBD). CKD-MBD describes a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcification (1).

In children, growth is one of the most important markers of health, as well as one of the most vital clinical outcome measures. Contributed to by renal osteodystrophy, and more broadly CKD-MBD, children with CKD do not grow well. In a cross-sectional study of 5615 pediatric CKD patients included in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) chronic renal failure registry, Seikaly et al assessed the percentages of subjects with short stature, defined as a height standard deviation score of less than -1.88 (equivalent to less than the third percentile) (3). Overall, 37% of subjects had short stature, including 22% of those with an estimated glomerular filtration rate (eGFR) of 50–75 ml/min/1.73m^2, 38% of those with an eGFR of 25–50 ml/min/1.73m^2, 47% of those with an eGFR of 10–25 ml/min/1.73m^2, and 68% of those with an eGFR of <10 ml/min/1.73m^2.

Besides poor linear growth, children with CKD also experience bone-specific morbidity secondary to renal osteodystrophy, including fractures and bone deformities. In a prospective study of 537 pediatric CKD patients included in the CKD in Children (CKiD) cohort, Denburg et al evaluated the incidence of fractures (4). At enrollment, the median age was 11.0 years (interquartile range [IQR] 7.4, 14.5 years); the median eGFR was 47 [34, 59] ml/min/1.73m^2; and the median duration of CKD was 8.5 [4.4, 12.9] years. 16% of subjects reported a prior history of fracture. Over a median follow-up of 3.9 [1.8, 4.9] years, 67 participants (12.5%) reported an incident fracture. The gender-specific fracture rates in this cohort were 2- to 3-fold higher than published general population rates. Because of altered skeletal remodeling, bone deformities are also common in pediatric CKD patients. Renal osteodystrophy may clinically manifest as slipped epiphyses of the femur, humerus, radius, and/or ulna, resulting not only in skeletal deformities, but also pain, abnormal gait, and/or inability to ambulate (5). Genu valgum, genu varum, and pes varus may also occur and, importantly, may persist despite long-term treatment with active vitamin D sterols.

To assess the prevalence of renal osteodystrophy in the pediatric end-stage renal disease (ESRD) population, Bakkaloglu et al evaluated bone histomorphometry in 161 pediatric

dialysis patients (mean age 14.1 ± 1.2 years) in whom active vitamin D sterol therapy was held for four weeks prior to bone biopsy (6). Using the TMV (turnover, mineralization, volume) classification system, 57% had high bone turnover, 39% had normal bone turnover, and 4% had low bone turnover. Abnormal mineralization, defined by a concurrent increase in osteoid volume and osteoid maturation time, was present in 48% of all subjects, including 58% of those with high bone turnover, 38% of those with normal bone turnover, and 29% of those with low bone turnover. Bone volume was normal in 73% of subjects and increased in 27%. Such high rates of abnormal mineralization were also observed in a subsequent study of 60 pediatric dialysis patients, in which 80% of subjects had defective mineralization, despite treatment with active vitamin D sterols (7).

To assess the prevalence of renal osteodystrophy in the pediatric pre-dialysis population, Wesseling-Perry et al evaluated bone histomorphometry in 52 pediatric non-dialysis patients with CKD stages 2–5 (mean age 12.2 ± 5.2 years) (8). Bone turnover was normal in all subjects with CKD stage 2, but was increased in 13% with CKD stage 3 and in 29% with CKD stage 4/5. Only four subjects in the entire cohort (8%) had decreased bone turnover. On the other hand, abnormal mineralization, defined by a concurrent increase in osteoid volume and osteoid maturation time, was present in 29% of subjects with CKD stage 2, 42% with CKD stage 3, and 79% with CKD stage 4/5. Bone volume was normal or increased in 96% of the entire cohort. This study demonstrated that mineralization defects are the first observed skeletal abnormalities in children with CKD, and that the prevalence of abnormal mineralization and turnover increases with CKD progression. In dialysis patients, such mineralization defects persist despite active vitamin D sterol therapy and may play a role in the pathogenesis of fractures and skeletal deformities.

Whereas bone biopsy is the gold standard for evaluating bone turnover and mineralization, bone quality (structure) may be better assessed with imaging. In adults, dual-energy x-ray absorptiometry (DXA) scans are commonly used to assess bone mineral density. However, in children with CKD, DXA scans have significant limitations, as described by Weber and Mehls (9) and by Bacchetta et al (10). Specifically, DXA scans rely on areal rather than volumetric bone mineral density, resulting in an artificial underestimation of bone density in short people (including growth delayed pediatric CKD patients). Also, DXA scans cannot distinguish between cortical and trabecular bone, which may be differentially affected in CKD. Lastly, DXA scans cannot evaluate trabecular microarchitecture, which is a significant determinant of bone quality. Therefore, some recommend against the use of DXA scans in children with CKD (9). Also, as noted above, when assessed by bone histomorphometry, most pediatric CKD patients have normal or high bone volume. Even so, regarding bone health in children and adolescents with chronic diseases that may affect the skeleton, the International Society for Clinical Densitometry (ISCD) pediatric task force recommends that, “In patients with primary bone disease or at risk for secondary bone disease, a DXA should be performed when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture, and the DXA results will influence that management” (11). Whether this recommendation is specifically applicable to children with CKD remains to be determined.

Other imaging modalities used to assess bone mineral content in children include quantitative computed tomography (QCT), peripheral quantitative computed tomography (pQCT), and quantitative ultrasonography (12). QCT assesses the volume and density of bone in both the axial and appendicular skeleton; however, it's clinical value is limited by cost, radiation exposure, and lack of standardization. pQCT is more readily available and involves less radiation exposure. pQCT bone mineral density measurements correlate with circulating mineral metabolism factors, including PTH, in pediatric CKD patients (13,14). The ISCD pediatric task force recommends that pQCT "can be used clinically in children where appropriate reference data and expertise are available" (11). Quantitative ultrasonography is easy to perform, does not involve radiation exposure, and has been shown to diagnose secondary hyperparathyroidism better than DEXA in children with CKD (15); however, the results generated may be difficult to apply clinically. Moreover, there remains a paucity of studies assessing the impact of these imaging techniques in children with CKD, and studies that define the associations between these imaging results and bone histology are needed.

Pathogenesis of CKD-MBD

CKD-MBD pathogenesis involves a complex interplay among the kidney, bone, and parathyroid glands. As functional nephrons are lost and GFR declines, a cascade of maladaptive events develops that results in bone disease, extra-skeletal calcification, and adverse cardiovascular outcomes. Different factors have been implicated in the pathogenesis of this maladaptive response, but the primary trigger remains to be defined. In the early stages of CKD, FGF23 levels increase while phosphate and PTH remain within normal ranges (16,17). With progression of CKD, phosphate retention increases levels of phosphaturic hormones FGF23 (18,19) and PTH (20); decreases 1,25D levels (20) in order to lessen enteral phosphate absorption; and decreases ionized calcium levels via increased binding. Elevated FGF23 levels further decrease 1,25D levels via renal 1α-hydroxylase suppression (21) and 24-hydroxylase induction (22). Decreased 1,25D levels reduce intestinal calcium absorption, and low 1,25D and low ionized calcium both further increase PTH levels, resulting in secondary hyperparathyroidism (23). Although different experimental models of CKD have demonstrated increases in FGF23 before PTH, recently published data seem to challenge the concept of primary increases in FGF23 levels. In a large cohort of over 1000 adults, with generally normal kidney function (99% with eGFR >60 ml/min/1.73m^2), Dhayat et al observed that PTH levels began to increase when eGFR decreased below 126 ml/min/1.73m^2, whereas FGF23 levels only began to increase when eGFR decreased below 102 ml/min/1.73m^2 (24). Although further research is needed to better define the complex relationship among GFR, FGF23, PTH, and 1,25D (25), regardless of the initial sequence of events, FGF23 and PTH levels increase with CKD progression. Increased PTH activity on bone results in increased bone turnover and resorption, which weakens bones and increases both calcium and phosphate, which may promote vascular calcification (26).

In addition to renal phosphate retention contributing to multi-organ adverse effects and precipitating CKD-MBD, primary kidney injury/repair mechanisms may produce circulating factors that directly affect the vasculature, the myocardium, and the skeleton (27).

Specifically, local kidney repair mechanisms involving Wnt (Wingless-related integration site) signaling pathway reactivation produce autoregulatory Wnt inhibitors, including Dickkopf-1 (Dkk1) and sclerostin (27). In animal models of early CKD, increased circulating levels of such Wnt inhibitors were observed in the circulation, with concomitant decreased bone formation rates and vascular calcification; Dkk1 neutralization increased bone formation rates and decreased vascular calcification, demonstrating the effect of circulating Wnt inhibitors on CKD-MBD pathogenesis (28).

Therapeutic approaches in CKD-MBD

Current pediatric renal osteodystrophy treatment paradigms aim to minimize complications to the growing skeleton and prevent the extraskeletal calcifications that define CKD-MBD. Therapeutic approaches focus on the treatment of hyperphosphatemia and secondary hyperparathyroidism.

Hyperphosphatemia

In the pediatric population, the normal ranges of serum phosphate vary substantially by age. In the first six months of life, normal serum phosphate concentrations range from 5.2–8.4 mg/dL, decreasing to 5.0–7.8 mg/dL during the second six months of life, then 4.5–6.5 mg/dL at ages 1–5 years, then 3.6–5.8 mg/dL at ages 6–12 years, then 2.3–4.5 mg/dL in adolescents (ages 13–20 years) (29). In healthy children and in children with CKD, serum phosphate concentrations exhibit circadian variation, decreasing after breakfast, nadiring in the late morning, then increasing in the early afternoon (30). In pediatric CKD patients with serum phosphate levels above range for age, dietary phosphorus restriction is required. In infants, adequate intake (AI) of phosphorus is 100 mg daily for ages 0–6 months, and 275 mg daily for ages 7–12 months (29). The recommended dietary allowances (RDA) for older children are: 460 mg daily for ages 1–3 years, 500 mg daily for ages 4–8 years, and 1250 mg daily for ages 9–18 years (29). In children with CKD stages 3–5 and 5D, when the serum PTH concentration is above the target range for CKD stage (see below) and the serum phosphate concentration exceeds the normal reference range for age, it is suggested that dietary phosphorus intake be reduced to 80% of the AI or RDA (29). After initiation of dietary phosphorus restriction, it is suggested that serum phosphate concentration be monitored at least every 3 months in children with CKD stages 3 to 4 and monthly in children with CKD stage 5 and 5D (29).

Persistent hyperphosphatemia despite dietary phosphorus restriction necessitates the use of phosphate-binding agents. Enteral binders complex with phosphorus in the intestinal tract, limiting phosphorus absorption by blocking passive diffusion across a paracellular gradient. Calcium-based phosphate binders are widely prescribed and are effective in lowering serum phosphate levels (31). However, the benefit of calcium-based phosphate binders must be weighed against the possible adverse effects of hypercalcemia and/or vascular calcification. In a cohort of 16 young adult dialysis patients (aged 20–30 years old), Goodman et al found that 14 (87.5%) had evidence of coronary artery calcification (compared to only 5% of age-matched controls), and that subjects with coronary artery calcification had higher calcium intake (nearly double that of subjects without calcification), higher serum phosphate, and

higher calcium-phosphate cross-product (26). Subsequent studies have demonstrated the association between calcium intake and the development of vascular calcifications. In a study of adult patients with CKD stages 3 and 4, Hill et al found that calcium carbonate supplementation of 1500 mg daily resulted in a positive calcium balance of 500 mg daily (32). Moreover, calcium kinetics demonstrated a positive net bone balance that was less than the overall calcium balance, suggesting soft-tissue deposition (32). Similar balance studies in children with CKD are needed to define the optimal calcium intake for maximal bone growth.

At present, to avoid the development of cardiovascular calcifications, it is suggested that the total dose of elemental calcium provided by calcium-based phosphate binders and by dietary calcium not exceed twice the age-based AI or RDA for calcium (31). In infants, adequate intake (AI) of calcium is 210 mg daily for ages 0–6 months, and 270 mg daily for ages 7–12 months (29). The recommended dietary allowances (RDA) for older children are: 500 mg daily for ages 1–3 years, 800 mg daily for ages 4–8 years, and 1300 mg daily for ages 9–18 years (29). Furthermore, if hypercalcemia for age develops, then the calcium-based phosphate binder dose should be reduced. Age-specific normal ranges of blood total calcium and ionized calcium (iCa) are as follows: 0–5 months 8.7–11.3 mg/dL (iCa 1.22–1.40 mmol/L), 6–12 months 8.7–11.0 mg/dL (iCa 1.20–1.40 mmol/L), 1–5 years 9.4–10.8 mg/dL (iCa 1.22–1.32 mmol/L), 6–12 years 9.4–10.3 mg/dL (iCa 1.15–1.32), and 13–20 years 8.8–10.2 mg/dL (iCa 1.12–1.30 mmol/L) (29).

Given concerns for hypercalcemia and vascular calcification with the use of calcium-based phosphate binders, alternative, non-calcium-based phosphate binders have been developed. These include sevelamer formulations, lanthanum, and iron-based compounds. Sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®) are widely used in pediatric CKD. Sevelamer effectively controls hyperphosphatemia without increasing the incidence of hypercalcemia (33). Moreover, a recent meta-analysis of randomized controlled trials of calcium-based binders vs. non-calcium-based binders, which included 25 trials and approximately 8000 patients, found that the use of calcium-based binders resulted in higher mortality than sevelamer in particular and non-calcium-based binders in general (34). Lanthanum carbonate is another effective, non-calcium-based phosphate binder; however, lanthanum accumulates in bones (35) and, given concern for growth impairment in children, is not recommended for routine use in pediatric CKD.

Iron-based phosphate binders are intriguing given their theoretical ability to both bind enteral phosphorus and deliver iron. In a recent randomized trial of ferric citrate vs. active phosphate binder control in dialysis patients, Lewis et al showed that ferric citrate controlled phosphate levels as well as the active control, but also increased iron parameters, decreased the use of intravenous iron, decreased the use of erythropoiesis-stimulating agents, and blunted a decrease in hemoglobin (36). This medication has yet to be studied in the pediatric population.

Other non-calcium-based phosphate binders include aluminum and magnesium-based compounds. Aluminum containing compounds must be used with caution, given concern for aluminum accumulation in tissues, especially the bone and brain, possibly resulting in bone

disease and encephalopathy. Therefore, in pediatric CKD, it is recommended that aluminum-based phosphate binders only be used in adolescent patients with serum phosphate >7 mg/dL and only for one treatment course not to exceed 4–6 weeks (31). Importantly, in children receiving aluminum-based phosphate binders, concurrent use of citrate-based products should be avoided, as citrate enhances aluminum absorption, increasing the risk of aluminum toxicity (31). Magnesium-based compounds are not widely used, and may predispose patients to hypermagnesemia and diarrhea.

Enteral phosphate binders limit passive, paracellular phosphorus absorption. However, such binder-induced effects lead to upregulation of the intestinal sodium-phosphate Npt2b transporter, increasing active enteral phosphate absorption, offsetting some of the beneficial binder effect (37). In animal studies, compared to wild type mice with CKD, Npt2b knockout mice with CKD had significantly lower serum phosphate concentrations (and a blunted increase in FGF23) (37). Moreover, treating the Npt2b-deficient mice with sevelamer carbonate further reduced serum phosphate levels (37). In studies of adult (38) and pediatric (39) dialysis patients, the addition of nicotinamide—a vitamin B3 (niacin) derivative that inhibits Npt2b activity—to phosphate binder therapy effectively lowered serum phosphate levels. Furthermore, in adult CKD patients, with eGFR 30–74 ml/min/1.73m^2, Rao et al demonstrated that extended release niacin reduced both serum phosphate and FGF23 (40). Therefore, maximal suppression of enteral phosphorus absorption in CKD/ESRD patients may possibly be best achieved using Npt2b inhibitors in combination with binders (41). However, further studies are needed to assess the impact of nicotinamide on phosphate control in children with CKD.

Secondary hyperparathyroidism

The mainstay of secondary hyperparathyroidism treatment is active vitamin D sterols (calcitriol or its analogs). In pediatric patients with CKD stages 2–4, it is recommended that active vitamin D sterols be initiated when serum PTH is above the target range for CKD stage, but only if 25(OH) vitamin D (25D) levels are sufficient (>30 ng/mL), corrected total serum calcium is <10 mg/dL, and serum phosphate is within the age-appropriate range (31). The target range for PTH in CKD stages 2–3 is 35–70 pg/mL, and in CKD 4 is 70–110 pg/mL (29). In pediatric patients with CKD stage 5 (not on dialysis), it is recommended that active vitamin D sterols be initiated when PTH is >300 pg/mL (31), but again only in the absence of hypercalcemia or hyperphosphatemia for age, with a goal of maintaining intact PTH levels in the range of approximately two to nine times the upper normal limit for the assay (2). However, the recommended PTH levels for pediatric ESRD patients remain controversial. In a large observational study of 890 pediatric peritoneal dialysis patients from 24 countries reported to the International Pediatric Peritoneal Dialysis Network Registry, clinical and radiological symptoms increased when PTH exceeded 300 pg/ml, the risk of hypercalcemia increased with levels below 100 pg/ml, and time-averaged PTH concentrations above 500 pg/ml were associated with impaired longitudinal growth (42). Based on these results, the authors recommended a PTH target range of 100–300 pg/ml. However, bone histomorphometry data was not available in this study, and the PTH assays were not standardized.

Calcitriol is a commonly used active vitamin D sterol; however, it is associated with an increased risk of hypercalcemia and hyperphosphatemia. Therefore, vitamin D analogs with less calcemic and/or phosphatemic effects have been developed, including paricalcitol and doxercalciferol; however, regardless of the active vitamin D sterol used, serum calcium, phosphate, and PTH should be assessed frequently, and dosage changes made accordingly; algorithms exist regarding management of vitamin D sterols (31). Increased doses of non-calcium-based phosphate binders may prevent hyperphosphatemia, allowing for higher doses of vitamin D sterols to be used.

Despite the use of active vitamin D sterols to effectively control secondary hyperparathyroidism, bone disease continues to plague children and adolescents with CKD. Indeed, in a large cohort of adults who developed kidney disease in childhood, 37% had clinical symptoms of bone disease and 18% were disabled by bone disease (43). Furthermore, vitamin D sterols may increase FGF23 levels. In a study of pediatric dialysis patients, Wesseling-Perry et al showed that both calcitriol and doxercalciferol suppressed PTH levels but increased circulating levels of FGF23 over fourfold, which was associated with a persistent mineralization defect (44). Although the mechanisms of skeletal mineralization are incompletely understood, FGF23 may inhibit mineralization (45,46). Moreover, higher FGF23 levels are independently associated with increased mortality in the dialysis population (47,48). Given the adverse clinical outcomes associated with higher FGF23 levels, further prospective studies are needed to better assess the long-term risks and benefits of vitamin D sterol treatment.

Another medication used for treatment of secondary hyperparathyroidism is cinacalcet, which acts as a calcimimetic by allosteric activation of the calcium-sensing receptor. Cinacalcet, which is commonly used in adult CKD/ESRD patients, effectively lowers serum PTH (49), as well as FGF23 (50). In pediatric dialysis patients, small studies demonstrated that cinacalcet acutely lowered PTH, lowered serum calcium, and was well-tolerated (51,52). However, the long-term effects of cinacalcet in pediatric patients have not been studied and, as the calcium-sensing receptor is expressed on growth plate cartilage, the effects of cinacalcet on growth must be elucidated before cinacalcet use can be recommended in children.

Lastly, when secondary hyperparathyroidism is severe (persistent serum PTH >1000 pg/mL) and refractory to treatment with vitamin D sterols (or vitamin D sterol treatment is precluded by persistent hypercalcemia and/or hyperphosphatemia), it is suggested that subtotal parathyroidectomy be considered (31). Post-parathyroidectomy, serum calcium and phosphate must be monitored very closely, as “hungry bone syndrome,” a condition characterized by acutely increased skeletal calcium and phosphate uptake, may cause marked hypocalcemia and/or hypophosphatemia. Treatment consists of large doses of active vitamin D and calcium. Phosphate supplementation may worsen hypocalcemia, and is generally not recommended unless serum phosphate is <2.0 mg/dL.

Nutritional vitamin D supplementation

As stated above, in pediatric patients with CKD stages 2–4, it is recommended that active vitamin D sterols be initiated when serum PTH is above the target range for CKD stage, but

only if 25(OH) vitamin D (25D) levels are sufficient (>30 ng/mL). If serum PTH is above the target range for CKD stage, but 25D levels are insufficient (<30 ng/mL), then it is suggested to first replete nutritional 25D stores with vitamin D_2 (ergocalciferol) (31). Indeed, Shroff et al demonstrated that ergocalciferol treatment delays the development of secondary hyperparathyroidism in children with early CKD (53). As with active vitamin D sterols, once ergocalciferol supplementation has been initiated, serum calcium and phosphate should be monitored frequently. If hypercalcemia develops, then vitamin D supplementation should be discontinued. If hyperphosphatemia develops, and nutritional vitamin D supplementation is still required, then intensified phosphate control may allow for continued vitamin D treatment. In ESRD, with less functional renal parenchyma, there is less renal conversion of 25D to active 1,25D, and thus more reliance on extra-renal 25D activation. In these patients, the benefit of nutritional vitamin D supplementation is less clear. Thus, there is controversy regarding the effectiveness of nutritional vitamin D supplementation in advanced CKD (54).

Fibroblast growth factor 23

In adult (19) and pediatric (20) CKD-MBD, elevated FGF23 levels are the first observed biochemical abnormality (Figure 1A). Increased FGF23 levels help to maintain normophosphatemia until late in the CKD course; however, higher FGF23 levels are associated with the development of left ventricular hypertrophy (55), CKD progression (48,56,57; Figure 1B), and mortality (47,48). Currently, there are no specific treatments focused on decreasing FGF23 levels and, as mentioned above, active vitamin D sterol treatment of secondary hyperparathyroidism may have the adverse effect of increasing FGF23. One possible approach to blunting the rise of FGF23 levels in CKD, and possibly decreasing FGF23-associated morbidity and mortality, is early lowering of phosphate levels. To test this hypothesis, the **C**KD **O**ptimal **M**anagement with **BI**nders and **N**icotinamid**E** (COMBINE) study has been initiated (41). This randomized clinical trial will assess, in pre-dialysis CKD patients, whether the early use of phosphate binders, with or without concurrent blockade of the intestinal sodium-phosphate co-transporter NPT2b, decreases serum phosphate and FGF23 concentrations and improves surrogate measures of cardiovascular disease, CKD progression, and inflammation. If the hypotheses of the COMBINE study are confirmed—that early phosphate binder therapy with or without NPT2b blockade improves the outcome measures—then the results may provide the basis for future clinical trials assessing the effects of such novel CKD-MBD treatment paradigms on hard clinical endpoints.

In addition to phosphate and 1,25D, other non-mineral metabolism factors have been recently identified as important determinants of FGF23 production. Notably, inflammation (58,59) and iron deficiency (59–61) may increase FGF23 production in CKD. The identification of such novel factors not only helps to better elucidate important aspects of FGF23 regulation, but may also inform new therapeutic strategies to lower pathologically high FGF23 levels in CKD.

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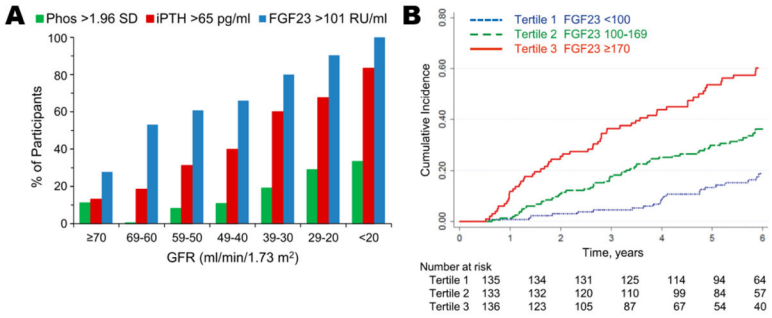

Figure 1.

In pediatric chronic kidney disease (CKD) patients, elevated fibroblast growth factor 23 (FGF23) levels are observed very early in the CKD course (Fig. 1A; 17) and are associated with CKD progression (defined as either dialysis initiation, kidney transplantation, or a 50% reduction in glomerular filtration rate (GFR) from baseline) (Fig. 1B; 57). The association between higher FGF23 levels and CKD progression persists after multivariable adjustment for baseline GFR, proteinuria, blood pressure, glomerular vs. non-glomerular disease, and medication use (angiotensin converting enzyme inhibitors/angiotensin-receptor blockers, vitamin D analogs, and phosphate binders) (57). Used with permission from the American Society of Nephrology.