Disordered FGF23 and Mineral Metabolism in Children with CKD

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Summary

Background and objectives In children with CKD, information is limited regarding the prevalence and determinants of fibroblast growth factor 23 excess and 1,25-dihydroxyvitamin D deficiency across the spectrum of predialysis CKD. This study characterized circulating concentrations of fibroblast growth factor 23 and 1,25-dihydroxyvitamin D, and investigated their interrelationships and associations with GFR and secondary hyperparathyroidism in children with CKD who were enrolled in the Chronic Kidney Disease in Children observational cohort study.

Design, setting, participants, & measurements Plasma fibroblast growth factor 23 concentrations and determinants of mineral metabolism were measured in 464 children ages 1–16 years with predialysis CKD. GFR was measured by plasma disappearance of iohexol in 70% of participants and estimated by the Chronic Kidney Disease in Children estimating equation using serum creatinine and cystatin C concentrations in the remainder of the participants. Participants were grouped according to CKD stage and by 10-ml/min categories of GFR.

Results Median GFR for the cohort was 45 ml/min per 1.73 m2 (interquartile range=33–57; range=15–109). Plasma fibroblast growth factor 23 concentration was above the normal range in 67% of participants (with higher levels observed among participants with lower GFR) before higher levels of serum parathyroid hormone and phosphorus were observed. Plasma fibroblast growth factor 23 levels were 34% higher in participants with glomerular disease than in participants with nonglomerular disease, despite similar GFR. Serum phosphorus levels, adjusted for age, were significantly lower at GFR of 60–69 ml/min per 1.73 m2 than higher GFR, but thereafter they became higher in parallel with fibroblast growth factor 23 as GFR declined. Serum 1,25-dihydroxyvitamin D concentrations were lower in those participants with low GFR values, high fibroblast growth factor 23 levels, 25-hydroxyvitamin D deficiency, and proteinuria. Secondary hyperparathyroidism was present in 55% of participants with GFR<50 ml/min per 1.73 m2.

Conclusion In children with predialysis CKD, high plasma fibroblast growth factor 23 is the earliest detectable abnormality in mineral metabolism, and levels are highest in glomerular diseases.


Introduction

Advanced CKD in children results in disordered bone and mineral metabolism and associated bone deformities, growth failure, and cardiovascular disease that severely diminish quality of life and lifespan (1). The evolution of such abnormalities during the early stages of CKD in children, however, is incompletely characterized. Thus, too little is known regarding the optimal therapies to use and their timing, which limits our ability to prevent such abnormalities or mediate their severity.

Secondary hyperparathyroidism in advanced CKD is attributed to deficiency of 1,25-dihydroxyvitamin D [1,25(OH)2D] combined with hyperphosphatemia, leading to disordered turnover and mineralization of bone. These abnormalities are now considered novel risk factors for cardiovascular disease and mortality in both children and adults with CKD. Deficiency of 1,25(OH)2D occurs early in the course of progressive CKD in adults and children (2–5), and recent data suggest that excess circulating fibroblast growth factor 23 (FGF23) is the primary mechanism and, therefore, the initiating event in the development of secondary hyperparathyroidism (6,7).

FGF23 is a bone-derived circulating hormone that acts to inhibit renal phosphate reabsorption and suppress the renal synthesis of 1,25(OH)2D (8–10). In adults with CKD, plasma FGF23 concentrations increase progressively as GFR declines before the development of hyperphosphatemia (6,7), and increased FGF23 levels are associated with CKD progression (11–13), left ventricular hypertrophy (14,15), and premature death (16,17). In children, however, information is limited regarding the prevalence and determinants of FGF23 excess and 1,25(OH)2D deficiency across the spectrum of predialysis CKD and their potential association with...
adverse renal and cardiovascular outcomes. Prior single-center studies of FGF23 and mineral metabolism in childhood CKD have been limited by small sample size (18,19), heterogeneous study populations that include dialysis and transplant patients (5,20), and imprecise estimates of GFR (21,22).

In the present study, we characterized circulating concentrations of FGF23 and 1,25(OH)2D and investigated their interrelationships and associations with GFR and secondary hyperparathyroidism in children with predialysis CKD who were enrolled in the Chronic Kidney Disease in Children (CKiD) observational cohort study (23).

Materials and Methods
Participants
We studied 464 children with predialysis CKD who were enrolled in CKiD from June of 2005 to June of 2011. Study details were published (23). Briefly, eligible participants ages 1–16 years with an estimated GFR between 30 and 90 ml/min per 1.73 m2 determined by the original Schwartz equation (24) were enrolled from 48 pediatric nephrology sites in the United States and Canada. Recipients of solid organ transplants were excluded. The Institutional Review Board at each site approved the study protocol, and informed consent was obtained from each patient and parent or guardian (NCT00327860; May 18, 2006).

For the present cross-sectional investigation, we obtained mineral and hormone data from a study visit that occurred 3–6 months after the enrollment visit (n=359) or at the second annual study visit (n=105). At the enrollment visit, GFR was measured by plasma disappearance of iohexol (25) (n=331) or estimated by the CKiD estimating equation using serum creatinine and cystatin C concentrations (26); at the second annual study visit, GFR was estimated. In 331 participants who underwent iohexol GFR measurement, median values for estimated and measured GFR were virtually identical (45 and 44 ml/min per 1.73 m2, respectively). Plasma C-terminal FGF23 concentrations were measured in duplicate by second generation ELISA (Immutopics Int., San Clemente, CA). We recruited a separate cohort of 42 healthy children (mean age=12±4 years) whose median FGF23 was 57 RU/ml (25th and 97.5th percentiles: 17 and 101 RU/ml). Thus, we defined 101 RU/ml as the upper limit of the normal range in these healthy children. This value is comparable with 105 RU/ml, which is considered the upper limit of normal in healthy adults (7), and 108 RU/ml, which is the median 90th percentile value in 172 healthy children (11.0±4.5 years old) (27). Serum concentrations of 25-hydroxyvitamin D (25OHD) were measured in duplicate by chemiluminescence immunoassay (DiaSorin LIAISON 25-OH Vitamin D TOTAL Assay) (28,29); inter- and intra-assay coefficients of variation (CVs) are 11.2% and 8.1%, respectively. 1,25(OH)2D was measured by radioimmunoassay (30); CVs are 12.6% and 9.8%, respectively. Specimens for parathyroid hormone (PTH), FGF23, and vitamin D metabolites were stored at −80°F until measurements were made. Serum concentrations of PTH, calcium, and phosphorus were determined in the CKiD Central Biochemistry Laboratory at the University of Rochester. Intact PTH was measured by chemiluminesmetric assay (CV<5%, n=451 participants; Advia Centaur System; Bayer Healthcare LLC; CV<5%, n=13; PTH Stat; Roche Diagnostics, Indianapolis, IN). Calcium was measured using the arsenazo dye end point method and phosphorus was measured using the phosphomolybdate reaction. Serum calcium concentrations were corrected for serum albumin concentrations: corrected calcium=measured calcium+0.8×(4.0−serum albumin). Urine phosphorus and creatinine concentrations were determined in voided morning specimens by autoanalyzer (Beckman Coulter AU400; Beckman Coulter, Inc., Brea, CA).

Statistical Analyses
We summarized continuous variables as mean±SD or median and interquartile range (IQR) for skewed data, for the overall cohort and participants grouped by CKD stage (stage 2, GFR=60 ml/min per 1.73 m2; stage 3a, GFR=45–59 ml/min per 1.73 m2; stage 3b, GFR=30–44 ml/min per 1.73 m2; stage 4, GFR=15–29 ml/min per 1.73 m2). We expressed categorical variables as frequencies and proportions. For statistical analyses, values of FGF23 and PTH were natural log-transformed to satisfy normality assumptions. We compared mean (median) values of biochemical parameters between CKD stages and across seven finer categories of GFR (≥70, 60–69, 50–59, 40–49, 30–39, 20–29, and ≤20 ml/min per 1.73 m2) using one-way ANOVA or the Kruskal–Wallis test, as appropriate. We used simple linear and multivariable regression analyses to examine associations between estimated GFR and FGF23, 1,25(OH)2D, and other parameters of mineral metabolism. Because serum phosphorus concentrations vary with age in healthy children (31), we expressed the phosphorus value for each participant as a z score relative to age-matched values in 493 healthy children 1–20 years old (31). A P value<0.05 was considered statistically significant. Analyses were performed using STATA 12 (Stata Corp, College Station, TX).

Results
Study Population
Characteristics of 464 participants for the entire cohort and grouped by CKD stage are shown in Tables 1 and 2. The median age was 11.7 years (IQR=8–15), and 39% were girls. The median GFR for the cohort was 45 ml/min per 1.73 m2 (IQR=33–57 ml/min per 1.73 m2), and the range was 15–109 ml/min per 1.73 m2; 2% of participants had CKD stage 1, 20% of participants had CKD stage 2, 28% of participants had CKD stage 3a, 31% of participants had CKD stage 3b, and 19% of participants had CKD stage 4. CKD was caused by nonglomerular disease (obstruction/reflux, hypoplasia/dysplasia, cystic disease, and other) in 80% of participants and glomerular disease (FSGS, hemolytic uremic syndrome, and other) in 20% of participants; 21% of participants reported taking phosphate binding agents, 38% of participants reported taking active vitamin D sterols, and 5% of participants reported taking nutritional vitamin D supplements.

Mineral Ion and Hormone Data for the Cohort and by CKD Stage
For the overall cohort, mean serum concentrations of corrected calcium, phosphorus, 1,25(OH)2D, and median PTH

were within normal ranges (Table 2). In contrast, the median plasma FGF23 level of 138 RU/ml (IQR=9–210) was 2.4 times higher than the median value of 57 RU/ml in 42 healthy children of comparable age (12±4 years); 67% of participants had FGF23 excess, defined as a value >101 RU/ml, and 58% of participants were either vitamin D-insufficient (25OHD<16 to <30 ng/ml; 38%) or -deficient (25OHD<15 ng/ml; 20%) (32). Median urine fractional urinary excretion of phosphate (FEPi) was 16.4% (IQR=11.6–23.2).

Compared with values in CKD stage 2, median plasma FGF23 concentration and urine FEPI were significantly higher in CKD stage 3a and higher stages, whereas serum phosphorus, phosphorus z score, and serum PTH concentrations were significantly higher in CKD stage 3b and higher stages (Table 2). Mean serum concentrations of 1,25(OH)2D were significantly lower at CKD stage 4 (Table 2). Thus, when grouped by CKD stages, higher values of plasma FGF23 and urine FEPI were the earliest significant abnormalities in mineral metabolism observed.

Mineral Ion and Hormone Data by GFR Group

To more closely examine the differences in mineral metabolism with lower levels of GFR, we grouped participants into seven GFR groups spanning 10 ml/min per 1.73 m2. Participants with GFR≥70 ml/min per 1.73 m2 served as the reference group for statistical comparison.

Calcium, Phosphorus, and PTH. Median serum-corrected calcium and phosphorus concentrations did not differ significantly according to GFR (Figure 1A). Because serum phosphorus levels decrease with advancing age in healthy children, we examined serum phosphorus z scores scaled to age-adjusted values in healthy children (31). At GFR of 60–69 ml/min per 1.73 m2, mean phosphorus z score was 0.68 SDs below the mean of the healthy reference population (31) (P<0.001). At lower levels of GFR, phosphorus z scores were progressively higher (0.39 SD per each 10-ml/min per 1.73 m2 decrement in GFR), reaching a maximum value of 1.37 SD (P<0.001) (Figure 2). Median serum PTH concentrations were progressively higher as GFR declined, with values being significantly higher than those values in the reference group (GFR=70 ml/min per 1.73 m2) at GFR=40–49 ml/min per 1.73 m2 and below (P<0.05) (Figure 1A).

FGF23, 25OHD, and 1,25(OH)2D. Median plasma FGF23 concentrations were progressively higher as GFR declined, with values being significantly higher than those values in the reference group at GFR=60–69 ml/min per 1.73 m2 and below (P<0.05) (Figures 1B and 2). Median serum 25OHD levels were slightly but not significantly lower with declining GFR. Median 1,25(OH)2D concentrations were lower as GFR declined, and values were significantly lower at GFRs of 30–39 and 20–29 ml/min per 1.73 m2 (P<0.05) (Figure 1B) compared with the reference group. At GFR<20 ml/min per 1.73 m2, 1,25(OH)2D values were slightly higher; however, four of six individuals in this group were taking active vitamin D sterols.

We calculated the percentage of participants with high plasma FGF23 concentrations (FGF23>101 RU/ml), hyperparathyroidism (serum PTH>65 pg/ml), and hyperphosphatemia (serum phosphorus>1.96 SD for age)
### Table 2. Mineral metabolism by CKD stage

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Stage 2 (GFR=60 ml/min per 1.73 m²)</th>
<th>Stage 3a (GFR=45–59 ml/min per 1.73 m²)</th>
<th>Stage 3b (GFR=30–44 ml/min per 1.73 m²)</th>
<th>Stage 4 (GFR=15–29 ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>464</td>
<td>103</td>
<td>127</td>
<td>145</td>
<td>89</td>
</tr>
<tr>
<td>GFR, ml/min per 1.73 m²</td>
<td>45 [33, 57]</td>
<td>71 [64, 80]</td>
<td>51 [48, 55]</td>
<td>38 [34, 42]</td>
<td>26 [24, 28]</td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>9.4±0.4</td>
<td>9.4±0.4</td>
<td>9.4±0.4</td>
<td>9.3±0.4</td>
<td>9.3±0.4</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>4.6±0.8</td>
<td>4.4±0.7</td>
<td>4.4±0.7</td>
<td>4.6±0.8a</td>
<td>4.9±0.8b,c,d</td>
</tr>
<tr>
<td>Serum phosphorus z score, SD</td>
<td>0.1±1.5</td>
<td>0.4±1.2</td>
<td>-0.2±1.3</td>
<td>0.2±1.5b</td>
<td>0.9±1.8b,c,e</td>
</tr>
<tr>
<td>Serum iPTH, pg/ml</td>
<td>51 [30, 84]</td>
<td>37 [26, 54]</td>
<td>48 [26, 70]</td>
<td>55 [33, 95]b</td>
<td>74 [47, 181]b,c,d</td>
</tr>
<tr>
<td>Serum 25OHD, ng/ml</td>
<td>27±12</td>
<td>27±10</td>
<td>27±11</td>
<td>29±12</td>
<td>25±12</td>
</tr>
<tr>
<td>Serum 1,25(OH)₂D, pg/ml</td>
<td>30±11</td>
<td>33±11</td>
<td>32±10</td>
<td>30±12</td>
<td>25±10b,c,e</td>
</tr>
</tbody>
</table>

Data are means ± SD or medians [25th, 75th percentiles]. Differences between CKD stages were tested using one-way ANOVA. *P* value represents pairwise tests of significance using the Sidak procedure. Analyses of FGF23 and PTH were performed using log-transformed values. iPTH, immunoreactive parathyroid hormone; FGF23, fibroblast growth factor 23; 25OHD, 25-hydroxyvitamin D, 1,25(OH)₂D, 1,25-dihydroxyvitamin D; FEPi, fractional urinary excretion of phosphate calculated as (urine phosphorus×serum creatinine/urine creatinine×serum phosphorus)×100.

*P<0.05 versus stage 2.

*P<0.01 versus stage 2.

*P<0.001 versus stage 3a.

*P<0.05 versus stage 3b.

*P<0.01 versus stage 3b.

*P<0.001 versus stage 3b.

*P<0.01 versus stage 3b.

*P<0.001 versus stage 3b.

*P<0.01 versus stage 3b.

*P<0.001 versus stage 3b.

GFR, glomerular filtration rate; iPTH, immunoreactive parathyroid hormone; FGF23, fibroblast growth factor 23; 25OHD, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; FEPi, fractional urinary excretion of phosphate calculated as (urine phosphorus×serum creatinine/urine creatinine×serum phosphorus)×100.
within each 10-ml/min GFR group (Figure 3). Plasma FGF23 was high in >50% of participants whose GFR was 60–69 ml/min per 1.73 m² or lower, whereas hyperparathyroidism was present in only 18% of this GFR group, being 50% only when the GFR was 30–39 ml/min per 1.73 m² or lower. The prevalence of hyperphosphatemia remained low until the GFR declined to 20–29 ml/min per 1.73 m² (prevalence was 29%).

**Glomerular Versus Nonglomerular Disease**

We compared indices of mineral metabolism between participants with glomerular and nonglomerular disease. Those participants with glomerular disease were 3 years older, but GFR, serum calcium, and PTH concentrations as well as phosphorus z scores were comparable between the groups (Table 3). By contrast, plasma FGF23 concentration \(P=0.01\) and urine protein to creatinine ratio \(P<0.001\) were higher, and serum concentrations of 25OHD, 1,25(OH)₂D, and albumin were lower \(P<0.001\) in participants with glomerular versus nonglomerular disease. In the glomerular group, proteinuria was associated with plasma FGF23 (coefficient=0.05; 95% confidence interval, 0.01 to 0.09; \(P=0.01\) in analyses adjusted for GFR, phosphorus z score, age, and sex; no association was found in the nonglomerular group \(P=0.90\).
For the entire cohort, bivariate analysis revealed that higher log plasma FGF23 was most strongly associated with decreasing GFR ($r = 0.44$, $P < 0.001$). Higher log serum immunoreactive PTH ($r = 0.32$, $P < 0.001$), phosphorus z-score ($r = 0.27$, $P < 0.001$), serum phosphorus ($r = 0.25$, $P < 0.001$), and lower 1,25(OH)$_2$D ($r = 0.21$, $P < 0.001$) were also significantly associated with decreasing GFR. Serum 25OHD, age, and sex were not associated with GFR. Higher levels of proteinuria were significantly associated with lower serum 25OHD concentrations ($r = -0.34$, $P < 0.001$).

### Determinants of FGF23

By multivariable linear regression analysis, log plasma FGF23 concentration was significantly associated with GFR, serum phosphorus z-score, glomerular disease, active vitamin D use, Hispanic ethnicity, and girls (Table 4). Specifically, for each 10-ml/min per 1.73 m$^2$ decrease in GFR, plasma FGF23 increased by 14%, and for each 1 SD increase in serum phosphorus z-score, FGF23 increased by 6%. At a given level of GFR and serum phosphorus, plasma FGF23 concentrations were 34% higher in children with glomerular disease, 18% higher in children receiving active vitamin D supplements, 26% lower in Hispanics, and 15% higher in girls.

### Determinants of 1,25(OH)$_2$D, 25OHD, and PTH

By multivariable analysis, lower serum 1,25(OH)$_2$D concentrations were significantly associated with lower GFR and serum 25OHD levels, higher FGF23 concentrations, proteinuria, and younger age (Table 4). Higher log serum PTH concentrations were significantly associated with lower GFR, serum 25OHD, and corrected calcium levels (Table 4).

### Urine FEPi

In bivariate analysis, higher values of urine FEPi were strongly associated with lower GFR ($r = -0.57$, $P < 0.001$), higher log FGF23 ($r = 0.27$, $P < 0.001$), and higher log PTH ($r = 0.26$, $P < 0.001$) concentrations.

### Discussion

In the largest examination to date of mineral metabolism in children with predialysis CKD, we observed that plasma FGF23 concentrations were increased early and progressively as GFR declined, with the increase in FGF23 preceding increases in serum PTH and phosphorus and decreases in serum 1,25(OH)$_2$D concentrations. In participants grouped by CKD stage, plasma FGF23 concentrations were significantly higher in CKD stages 3 and 4 relative to CKD stage 2, findings similar to those findings reported in children (5,18,19,21) and adults (6,7,33) with...
Because we studied a large number of children across a broad range of GFR, we subdivided participants more finely into seven GFR categories of 10 ml/min each. Plasma FGF23 levels were significantly higher as early as GFR=60–69 ml/min per 1.73 m² (i.e., late stage 2 CKD). Indeed, at this level of GFR, FGF23 levels were above the reference range in 53% of participants. These data provide evidence that, in children with predialysis CKD, high plasma FGF23 is the earliest detectable abnormality in mineral metabolism, similar to findings in adults with CKD (6,7).

Multivariable regression analysis revealed that the principal metabolic determinants of the increase in FGF23 levels were declining GFR, increasing age-adjusted serum phosphorus concentrations (phosphorus \( z \) score), and glomerular disease as etiology of CKD. In the overall cohort, FGF23 was positively correlated with phosphorus \( z \) score. However, as shown in Figure 2, in the GFR=60–69 ml/min per 1.73 m² group, the earliest increase in FGF23 was associated with the lowest phosphorus \( z \) score; at lower GFR levels, both FGF23 and phosphorus \( z \) score increased progressively in parallel. These findings are similar to the findings reported in the

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**Table 3.** Mineral metabolism in glomerular and nonglomerular disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glomerular</th>
<th>Nonglomerular</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>94</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>15 [13, 16]</td>
<td>11 [8, 14]</td>
<td>(&lt;0.001^a)</td>
</tr>
<tr>
<td>GFR, ml/min per 1.73 m²</td>
<td>47 [32, 63]</td>
<td>44 [33, 56]</td>
<td>0.31^a</td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>9.3±0.4</td>
<td>9.4±0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>4.4±1.0</td>
<td>4.6±0.8</td>
<td>0.02^a</td>
</tr>
<tr>
<td>Serum phosphorus ( z ) score, SD</td>
<td>0.13±1.9</td>
<td>0.08±1.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Serum iPTH, pg/ml</td>
<td>49 [29, 114]</td>
<td>52 [30, 82]</td>
<td>0.98^a</td>
</tr>
<tr>
<td>Plasma FGF23, RU/ml</td>
<td>165 [95, 271]</td>
<td>131 [90, 194]</td>
<td>0.01^a</td>
</tr>
<tr>
<td>Serum 25OHD, pg/ml</td>
<td>19±12</td>
<td>29±11</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Serum 1,25(OH)(_2)D, pg/ml</td>
<td>26±12</td>
<td>31±11</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>4.0±0.7</td>
<td>4.4±0.3</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Urine FEpi, %</td>
<td>15.4 [10.7, 23.0]</td>
<td>16.9 [12.2, 23.3]</td>
<td>0.23^a</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio, mg/mg</td>
<td>0.95 [0.35, 2.61]</td>
<td>0.32 [0.14, 0.85]</td>
<td>(&lt;0.001^a)</td>
</tr>
</tbody>
</table>

Data are means±SD or medians [25th, 75th percentiles]. Mean (median) values were compared using \( t \) tests. FEpi calculated as \((\text{urine phosphorus} / \text{serum creatinine}) / (\text{serum phosphorus} / 100)\).

\(^{a}\)Mean (median) values were compared using Wilcoxon rank sum tests.

\(^{b}\)25OHD and 1,25(OH)\(_2\)D were measured in 83 participants with glomerular disease and 293 patients with nonglomerular disease.

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**Table 4.** Multivariable regression analysis of determinants of fibroblast growth factor 23, 1,25-dihydroxyvitamin D, and parathyroid hormone

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Regression Coefficient</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in log plasma FGF23, RU/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, 10 ml/min per 1.73 m²</td>
<td>-0.15</td>
<td>-0.19 to -0.11</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Serum phosphorus ( z ) score, SD</td>
<td>0.06</td>
<td>0.02 to 0.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Glomerular diagnosis</td>
<td>0.29</td>
<td>0.13 to 0.44</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Active vitamin D use</td>
<td>0.16</td>
<td>0.03 to 0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>-0.30</td>
<td>-0.48 to -0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Girls</td>
<td>0.14</td>
<td>0.26 to 0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, yr</td>
<td>-0.004</td>
<td>-0.02 to 0.01</td>
<td>0.59</td>
</tr>
<tr>
<td>Change in serum 1,25(OH)(_2)D, pg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, 10 ml/min per 1.73 m²</td>
<td>1.22</td>
<td>0.62 to 1.82</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Serum 25OHD, 10 ng/ml</td>
<td>2.46</td>
<td>1.52 to 3.41</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Plasma FGF23, 10 pg/ml</td>
<td>-0.06</td>
<td>-0.11 to -0.02</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum phosphorus ( z ) score, SD</td>
<td>0.44</td>
<td>-0.26 to 1.14</td>
<td>0.22</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio, mg/mg</td>
<td>-1.08</td>
<td>-1.62 to -0.53</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>-0.27</td>
<td>-0.53 to -0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Change in log serum PTH, pg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, 10 ml/min per 1.73 m²</td>
<td>-0.15</td>
<td>-0.21 to -0.09</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Serum 25OHD, 10 ng/ml</td>
<td>-0.14</td>
<td>-0.23 to -0.05</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>-0.25</td>
<td>-0.49 to -0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum phosphorus ( z ) score, SD</td>
<td>0.06</td>
<td>-0.01 to 0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum 1,25(OH)(_2)D, pg/ml</td>
<td>0.01</td>
<td>-0.00 to 0.02</td>
<td>0.10</td>
</tr>
</tbody>
</table>

PTH, parathyroid hormone.
work by Isakova et al. (7). They favor the formulation that, with a mild reduction in GFR, the early increase in plasma FGF23 is not dependent on excess phosphorus exposure, as is judged from the serum phosphorus concentration, but, rather, that FGF23 may contribute to the early decrease in serum phosphorus by its phosphaturic effect. Indeed, Wilson et al. (34) first observed mild hypophosphatemia and enhanced capacity to excrete a phosphorus load in adults with mild CKD. Recent data suggest that FGF23 is the primary mediator of this response (6,7,35).

Few studies have tested whether the underlying cause of CKD is a determinant of plasma FGF23 levels. In adults with CKD stages 1 and 2 caused by autosomal dominant polycystic kidney disease, plasma FGF23 concentrations were 4-fold higher than in adults with diabetic or non-diabetic CKD and normal controls (36). An important new finding in the present study is that plasma FGF23 concentrations were significantly higher (by 34%) and serum 25OHD and 1,25(OH)2D levels were significantly lower in children with glomerular disease than in children with nonglomerular disease, despite a lack of difference in GFR between the groups. Loss of vitamin D in the urine has been invoked as a cause of low vitamin D levels in patients with high-grade proteinuria, an association that we observed in the present cohort. However, one would expect that a primary loss of vitamin D and thereby, decrease in serum 1,25(OH)2D levels would lead to a reduction in FGF23 levels. However, we observed higher FGF23 and lower vitamin D concentrations in the glomerular disease group, consistent with the effect of FGF23 to suppress 1,25(OH)2D synthesis and increase the catabolism of both 1,25(OH)2D and 25OHD (9,10,37). Corticosteroid use has been associated with higher levels of FGF23 (5); however, the children with glomerular disease in the present study reported no corticosteroid use. Our finding that phosphorus z scores did not differ between the two groups suggests that a primary difference in phosphate metabolism was not a determinant of the higher FGF23 levels in the glomerular group. Furthermore, the findings of higher FGF23 levels in the glomerular group but no difference in phosphorus z score or FEPi between the groups suggest that participants with glomerular disease may have been relatively resistant to the phosphaturic effect of FGF23.

We observed that serum 1,25(OH)2D concentrations were significantly lower in participants with a GFR of 30–39 ml/min per 1.73 m2 (i.e., CKD stage 3b) and lower. At this level of GFR, ~50% of participants were receiving treatment with active vitamin D analogs, which could have obscured a decrease in 1,25(OH)2D levels at earlier stages of CKD. Our finding that plasma FGF23 was a significant independent predictor of serum 1,25(OH)2D concentrations is consistent with the formulation that, as GFR declines, FGF23 contributes to deficiency of 1,25(OH)2D by suppressing its renal production (6). The independent association between lower serum 25OHD and 1,25(OH)2D concentrations suggests that vitamin D deficiency further contributes to impaired 1,25(OH)2D production.

Secondary hyperparathyroidism was present in 43% of participants in the overall cohort and 55% of those participants with GFR<50 ml/min per 1.73 m2, despite little change in serum calcium levels and a low prevalence of hyperphosphatemia. These findings suggest that serum PTH levels should be monitored in children beginning in CKD stage 3a, irrespective of serum calcium and phosphorus levels. The independent association between higher serum PTH and lower serum 25OHD concentrations suggests that vitamin D deficiency further contributes to hyperparathyroidism in CKD. We observed vitamin D insufficiency or deficiency in 58% of participants, a prevalence comparable with the prevalence in the general pediatric population (38–40) and children with predialysis CKD (41–43).

A major strength of the present study is the recruitment of a large cohort of children with predialysis CKD from multiple pediatric nephrology centers across North America, in whom the underlying cause of CKD is representative of CKD in children. Furthermore, GFR was directly measured in 70% of participants, and the estimating equation used in the remainder was shown to be highly accurate. The study has some limitations. The data are cross-sectional; thus, causal relationships among the variables cannot be defined. GFR was determined simultaneously with hormone measurements in one quarter of the children, and in the remainder of the children, GFR was determined 3–6 months before hormone measurements. Over this time period, however, GFR is predicted to decline by <1 ml/min per 1.73 m2 given that the composite rate of GFR decline in the CKiD cohort is approximately 2 ml/min per 1.73 m2 per year (44). We did not measure intact FGF23, although prior work has shown good correlation between the two assays in CKD. We did not measure soluble Klotho and thus cannot address the question of whether early CKD is associated with Klotho deficiency (45,46). At lower levels of GFR, more participants received active vitamin D sterols, possibly obscuring the true prevalence of 1,25(OH)2D deficiency.

In summary, the present study of children with CKD expands our knowledge of the prevalence of abnormalities of FGF23 and indices of mineral metabolism across a broad range of precisely determined GFRs. Longitudinal follow-up of this cohort will provide an opportunity to further evaluate changes in FGF23 that occur with progressive CKD and the impact of those changes on patient outcome.

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Disclosures

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