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FGF23 and Left Ventricular Hypertrophy in Children with CKD

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Abstract

Background and Objectives High plasma concentration of fibroblast growth factor 23 (FGF23) is a risk factor for left ventricular hypertrophy (LVH) in adults with CKD, and induces myocardial hypertrophy in experimental CKD. We hypothesized that high FGF23 levels associate with a higher prevalence of LVH in children with CKD.

Design, setting, participants, & measurements We performed echocardiograms and measured plasma C-terminal FGF23 concentrations in 587 children with mild-to-moderate CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study. We used linear and logistic regression to analyze the association of plasma FGF23 with left ventricular mass index (LVMI) and LVH (LVMI ≥95th percentile), adjusted for demographics, body mass index, eGFR, and CKD-specific factors. We also examined the relationship between FGF23 and LVH by eGFR level.

Results Median age was 12 years (interquartile range, 8–15) and eGFR was 50 ml/min per 1.73 m^2 (interquartile range, 38–64). Overall prevalence of LVH was 11%. After adjustment for demographics and body mass index, the odds of having LVH was higher by 2.53 (95% confidence interval, 1.28 to 4.97; $P<0.01$) in participants with FGF23 concentrations ≥170 RU/ml compared with those with FGF23<100 RU/ml, but this association was attenuated after full adjustment. Among participants with eGFR≥45 ml/min per 1.73 m^2, the prevalence of LVH was 5.4%, 11.2%, and 15.3% for those with FGF23 <100 RU/ml, 100–169 RU/ml, and ≥170 RU/ml, respectively ($P_{trend}=0.01$). When eGFR was ≥45 ml/min per 1.73 m^2, higher FGF23 concentrations were independently associated with LVH (fully adjusted odds ratio, 3.08 in the highest versus lowest FGF23 category; 95% confidence interval, 1.02 to 9.24; $P<0.05$; fully adjusted odds ratio, 2.02 per doubling of FGF23; 95% confidence interval, 1.29 to 3.17; $P<0.01$). By contrast, in participants with eGFR<45 ml/min per 1.73 m^2, FGF23 did not associate with LVH.

Conclusions Plasma FGF23 concentration ≥170 RU/ml is an independent predictor of LVH in children with eGFR≥45 ml/min per 1.73 m^2.

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Introduction

Left ventricular hypertrophy (LVH) is the most common cardiovascular abnormality in children with CKD, with a reported prevalence of 17%–49% (1–3). LVH develops early and progresses throughout the course of CKD, and when untreated, poses an increased risk for cardiovascular disease morbidity and mortality (4). Understanding the factors contributing to the development of LVH in children and adolescents with CKD is essential to reducing future cardiovascular risk.

Recent studies have identified fibroblast growth factor 23 (FGF23), a bone-derived circulating peptide, as a novel CKD-related risk factor in the development of LVH. Plasma concentrations of FGF23 increase early and progressively in both children (5) and adults (6) with advancing CKD. High FGF23 is associated with premature death (7,8), cardiovascular events (9), and LVH (10,11), with experimental data favoring a direct pathophysiologic role of FGF23 in promoting LVH *via* an FGF receptor 4 (FGFR4)–dependent pathway (12,13). However, few studies have assessed the role of FGF23 in the development of LVH in children with CKD, and the findings are inconsistent (14,15). In this study, we tested the hypothesis that high plasma concentrations of FGF23 are independently associated with a significantly higher prevalence of LVH in children and adolescents with predialysis CKD. We also assessed whether this relationship was modified by level of GFR.

Materials and Methods

The CKD in Children (CKiD) Study, a prospective observational cohort study, enrolled children aged 1–16 years with eGFR between 30 and 90 ml/min per 1.73 m^2 at 54 pediatric nephrology centers across North America; the study design, methods, and exclusion criteria have been described (16). The study was approved by a Monitoring Board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases, and by the institutional review boards of each participating center. Informed consent was obtained from each participant's parent or guardian and from the participant, when age-appropriate.

Participants

The CKiD Study enrolled 891 participants from January of 2005 to March of 2015. Participants underwent annual study visits at which height, weight, BP, and laboratory values were determined. For this cross-sectional analysis, we included 587 children who underwent initial measurement of plasma FGF23 within 6 months of enrollment and echocardiographic assessment at the subsequent study visit 6–9 months later.

Echocardiographic Assessment

The specific procedure for echocardiographic determination of left ventricular mass and the definition of LVH used in the CKiD Study have been described (2). Briefly, M-mode and Doppler echocardiography were performed at participating centers, and reading and analyses of echocardiographic data were performed by the Cardiovascular Core Imaging Research Laboratory (CCIRL) at Cincinnati Children's Hospital Medical Center. To achieve standardization and uniformity of echocardiographic images across the centers, qualifying recordings were sent to each center and then certified at the CCIRL; left ventricular mass interobserver coefficient of variation (CV) was 4.85%, and intraobserver CV was 4.52%. Left ventricular mass was indexed to height (mass [g]/height $[m]^{2.7}$), to account for body size (17). LVH was defined as left ventricular mass index (LVMI) ≥95th percentile for healthy children and adolescents (18). Because LVMI indexed to height does not fully account for changes due to growth, we also expressed LVMI as a *z*-score on the basis of age and sex (18).

BP Measurement

Casual BP was determined by trained personnel (19) as the average of three measurements obtained by auscultation, using an aneroid sphygmomanometer (Mabis MedicKit 5; Mabis Healthcare, Waukegan, IL). BP was expressed as a *z*-score on the basis of age, sex, and height (20).

Assays

Specimens for FGF23, parathyroid hormone (PTH), and vitamin D metabolites were stored at −80°C until measurements were made. We measured plasma FGF23 concentrations in duplicate by second-generation ELISA, using capture and detection antibodies directed against two different C-terminal epitopes (Immutopics Int., San Clemente, CA); inter- and intra-assay CVs were 11.5% and 5.7%, respectively. The median plasma FGF23 value in healthy children of comparable age was 57 RU/ml (2.5th and 97.5th percentiles, 17 and 101 RU/ml) (5). Serum concentrations of vitamin D metabolites were measured by Heartland Assays (Ames, IA), as described (5). Serum creatinine (enzymatic), intact PTH, calcium, and phosphorus, and urine protein and creatinine concentrations were determined in the CKiD Central Biochemistry Laboratory, University of Rochester (5). Serum calcium concentrations were corrected for serum albumin concentrations: corrected calcium=measured calcium+0.8×(4.0−serum albumin).

Covariates

GFR was estimated using the revised Schwartz equation, and is equal to 0.413×(height [cm]/serum creatinine [mg/dl]) (21). The primary diagnoses of CKD were categorized as either nonglomerular (obstruction/reflux, hypoplasia/dysplasia, cystic disease, pyelonephritis/interstitial nephritis, or other nonglomerular disease) or glomerular (FSGS, familial nephritis, hemolytic uremic syndrome, or other glomerular disease). Duration of CKD was defined as the time (in years) between the date of CKD onset and date of the FGF23 measurement. Because serum phosphorus and hemoglobin concentrations vary with age in healthy children, we expressed these values for each participant as a *z*-score relative to age-matched values in healthy children (22,23).

Statistical Analyses

All analyses presented are cross-sectional, using plasma FGF23 concentration as the primary exposure and the subsequent echocardiographic assessment as the outcome. Secondary exposure variables were phosphorus *z*-score, 25-hydroxyvitamin D (25OHD), 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], and PTH concentrations. Covariate values were obtained concurrently with the FGF23 measurement.

We categorized FGF23 using previously defined tertiles (24): <100 RU/ml (within the normal range), 100–169 RU/ml, and ≥170 RU/ml. We used Kruskal–Wallis tests to compare the distribution of continuous characteristics across FGF23 categories and Pearson chi-squared tests to evaluate the association between categorical characteristics and FGF23 category. We used Wilcoxon rank-sum tests to compare the distribution of continuous characteristics of mineral metabolism between children with LVH and those without LVH. We determined the statistical significance of the trend in prevalence of LVH across FGF23 categories using the Cochran–Armitage trend test, and trend in mean LVMI *z*-score across FGF23 categories using a regression of LVMI *z*-score on FGF23 category.

We used logistic regression to quantify the association of category of FGF23 (100–169 and ≥170, versus reference of <100) on the odds of LVH. Model 1 was unadjusted; model 2 was adjusted for age, sex, race, and body mass index (BMI); model 3 was additionally adjusted for systolic BP (SBP) *z*-score, hemoglobin *z*-score, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), and eGFR. We also analyzed the odds of LVH according to continuous FGF23 concentrations, reported per doubling of FGF23. Similarly, we used linear regression models (*i.e.*, unadjusted; adjustment for age, sex, race, BMI; additional adjustment for SBP *z*-score, hemoglobin *z*-score, ACEI/ARB, and eGFR) to quantify the association of FGF23, either as categories or per doubling of FGF23, on the mean LVMI *z*-score. In our final set of analyses, we stratified the study population by eGFR using the clinically relevant cut-off point of ≥45 ml/min per 1.73 m^2 (CKD stages 2–3a) or <45 ml/min per 1.73 m^2 (CKD stages 3b–4); with this stratification, the number of participants who had LVH was approximately the same in each of the two eGFR categories. We performed similar analyses for each of the secondary exposures (phosphorus *z*-score, 25OHD, $1,25(OH)_2D$, and PTH concentrations). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All tests were two-sided and a *P* value of <0.05 was considered statistically significant.

Results

Characteristics of the 587 participants, overall and by category of plasma FGF23 concentration, are summarized in Table 1. The median age was 12 years (interquartile range [IQR],

8–15), 38% were girls, and the median eGFR was 50 ml/min per 1.73 m^2 (IQR, 38–64). Five percent of participants had CKD stage 1, 27% had stage 2, 30% had stage 3a, 24% had stage 3b, and 14% had stage 4. CKD was caused by nonglomerular disease in 78% of participants. Fifty-four percent of participants reported taking ACEIs or ARBs; 30% took active vitamin D sterols, 40% took nutritional vitamin D supplements, and 17% took phosphate-binding agents.

The median plasma FGF23 concentration was 117 RU/ml (IQR, 80–181). Compared with the lowest FGF23 category (<100 RU/ml), participants in the highest category (≥170 RU/ml) had lower eGFR, lower serum albumin and $1,25(OH)_2D$ concentrations, and lower hemoglobin *z*-scores, and had higher serum phosphorus and PTH concentrations and higher urine protein-to-creatinine concentration ratio (Table 1).

Overall, the median LVMI was 30 g/$m^{2.7}$ (IQR, 25–36) and the median LVMI *z*-score was 0.11 (IQR, −0.74 to 1.04). The prevalence of LVH was 11% (67 out of 587) (Table 2). Children with LVH had higher serum phosphorus concentrations and higher SBP *z*-scores, and had lower serum 25OHD and $1,25(OH)_2D$ concentrations and lower eGFR compared with those without LVH (Table 2).

When stratified by FGF23 concentration, the overall prevalence of LVH was 7% in those with FGF23<100 RU/ml, 13% in those with FGF23 between 100 and 169 RU/ml, and 16% in those with FGF23≥170 RU/ml (P_{trend} <0.01). The mean LVMI *z*-score was −0.05 SD, +0.25 SD, and +0.25 SD in those in the lowest, middle, and highest FGF23 category, respectively.

FGF23 and Odds of LVH

The relationship between FGF23 and left ventricular mass is shown in Table 3. In unadjusted analysis, the odds ratio (OR) of having LVH was significantly higher by 1.98 (95% confidence interval [95% CI], 1.04 to 3.79; $P<0.05$) and 2.41 (95% CI, 1.25 to 4.62; $P<0.01$) in participants with plasma FGF23 in the middle and highest category compared with those with FGF23 in the normal range (<100 RU/ml) (model 1, Table 3). Although the odds of having LVH remained significantly higher in participants with FGF23≥170 RU/ml after adjustment for demographics and BMI (model 2, Table 3), the association was attenuated after full adjustment for SBP *z*-score, hemoglobin *z*-score, and eGFR (model 3, Table 3). Similarly, participants with plasma FGF23 in the middle and highest category had significantly greater mean LVMI z-scores than those with FGF23<100 RU/ml, in unadjusted and partially adjusted models (models 1 and 2, Table 3); however, the association was attenuated after full adjustment (model 3, Table 3).

When plasma FGF23 was modeled as a continuous variable, per doubling of FGF23, we observed similar significant associations with LVH and with LVMI *z*-score in the unadjusted and partially adjusted models (models 1 and 2, Table 3), but attenuation after full adjustment (model 3, Table 3).

We observed a significant interaction between eGFR and FGF23 on LVH ($P_{interaction}$=0.03) and thus examined the prevalence of LVH in participants stratified by eGFR category. In the 361 participants with eGFR≥45 ml/min per 1.73 m^2, the prevalence of LVH was 5%, 11%, and 15% in those with FGF23 in the lowest, middle, and highest FGF23 category (P_{trend}=0.01) (Figure 1). In contrast, in the 223 participants with eGFR<45 ml/min per 1.73 m^2, the prevalence of LVH was similar across FGF23 categories (Figure 1).

The relationships between FGF23 and LVH, stratified by eGFR category, are shown in Table 4. In those with eGFR≥45 ml/min per 1.73 m^2, the odds of having LVH was significantly higher in participants with FGF23≥170 IU/ml compared with those with FGF23<100 RU/ml in unadjusted and fully adjusted models (fully adjusted OR, 3.08; 95% CI, 1.02 to 9.24; $P<0.05$) (model 3, Table 4). Further, each doubling of FGF23 was associated with a two-fold higher odds of having LVH (OR, 2.02; 95% CI, 1.29 to 3.17; $P<0.01$; model 3, Table 4). The higher odds of having LVH in those in the highest FGF23 category remained significant when we additionally adjusted for concentrations of 25OHD (OR, 4.07; 95% CI, 1.11 to 14.9; $P<0.05$); 25OHD did not modify the association of FGF23 with LVH.

By contrast, in those with eGFR<45 ml/min per 1.73 m^2, FGF23 did not associate with LVH in any of the models analyzed (Table 4); however, SBP *z*-score (OR, 1.63; 95% CI, 1.08 to 2.47; $P<0.05$) and BMI (OR, 1.16; 95% CI, 1.04 to 1.30; $P<0.01$) did associate with LVH in the fully adjusted model. When comparing the risk of LVH in the highest versus the lowest FGF23 category, the OR was 3.08 (95% CI, 1.02 to 9.24) with eGFR≥45 ml/min per 1.73 m^2, a value significantly greater than that of 0.39 (95% CI, 0.12 to 1.28) with eGFR<45 ml/min per 1.73 m^2 (Table 4), indicating that eGFR modified the association between FGF23 and LVH.

Mineral Metabolites and Odds of LVH

In children with eGFR≥45 ml/min per 1.73 m^2, each doubling of serum 25OHD concentration was associated with a 60% lower odds of LVH (OR, 0.40; 95% CI, 0.21 to 0.75; $P<0.01$), and each doubling of phosphorus *z*-score was associated with a 39% higher odds of LVH (OR, 1.39; 95% CI, 1.03 to 1.88; $P<0.05$) in fully adjusted analyses (Supplemental Table 1). Associations with LVH were not observed in those with eGFR<45 ml/min per 1.73 m^2, except for the lowest tertile of phosphorus *z*-score, which associated with a 73% lower odds of LVH (OR, 0.23; 95% CI, 0.05 to 0.95; $P<0.05$) (Supplemental Table 1). PTH did not associate with LVH in either eGFR category.

Discussion

In the largest study of children with predialysis CKD to date, we find that among children and adolescents with eGFR≥45 ml/min per 1.73 m^2, higher plasma FGF23 concentrations were independently associated with a higher prevalence of LVH. This association was strongest in participants with FGF23 levels ≥170 RU/ml in whom the odds of LVH was three times higher than in those with FGF23 levels <100 RU/ml. Further, when analyzed as a continuous variable, each doubling of FGF23 was associated with a two-fold higher odds of LVH. The associations were significant before and after adjustment for confounders including hemoglobin level and SBP, the latter a strong independent predictor of LVH in children with CKD (2). By contrast, the association of FGF23 with LVH was attenuated at lower eGFR (<45 ml/min per 1.73 m^2), when high SBP and higher BMI were significant predictors. These findings suggest that in children with eGFR of 45 ml/min per 1.73 m^2 and above, in whom BP can often be normal, FGF23 is an important determinant of left

Table 1. Baseline characteristics of participants by category of plasma FGF23 concentration

Characteristic[a]	Overall Cohort	FGF23<100 RU/ml	FGF23=100–169 RU/ml	FGF23≥170 RU/ml
n	587	238	189	160
Age, yr	12 (8–15)	11 (9–15)	12 (8–15)	12 (8–15)
Female, %	38	35	39	41
Race/ethnicity, %				
White	70	67	73	70
Black	14	15	12	13
Other	17	18	16	17
Systolic BP *z*-score	0.27 (−0.48 to 0.94)	0.25 (−0.53 to 0.88)	0.26 (−0.45 to 0.93)	0.34 (−0.35 to 1.12)
Nonglomerular CKD, %	78	79	81	73
Duration of CKD, yr	9.1 (5.3–13.1)	9.0 (5.3–12.5)	9.1 (5.4–13.5)	9.5 (5.2–13.0)
eGFR, ml/min per 1.73 m^2	50 (38–64)	60 (47–75)	50 (39–61)	39 (27–50)[b]
Body mass index, kg/m^2	18.8 (16.6–22.6)	19.1 (16.9–23.2)	18.7 (16.4–22.8)	18.5 (16.4–21.5)
Height *z*-score	−0.6 (−1.3 to 0.2)	−0.4 (−1.2 to 0.3)	−0.7 (−1.3 to 0.2)	−0.7 (1.4 to −0.01)[c]
Serum albumin, g/dl	4.4 (4.1–4.6)	4.5 (4.3–4.7)	4.3 (4.1–4.6)	4.3 (4.0–4.5)[b]
Hemoglobin *z*-score	−0.62 (−1.95 to 0.55)	−0.16 (−1.33 to 0.77)	−0.70 (−1.88 to 0.62)	−1.56 (−2.81 to −0.18)[b]
Mineral metabolism				
Serum calcium, mg/dl	9.2 (9.0–9.5)	9.2 (8.9–9.5)	9.3 (9.0–9.5)	9.3 (9.0–9.6)[c]
Serum phosphorus, mg/dl	4.4 (4.0–4.9)	4.4 (3.9–4.7)	4.4 (4.0–4.8)	4.6 (4.0–5.2)[d]
Phosphorus *z*-score	−0.3 (−1.1 to 0.6)	−0.4 (−1.3 to 0.3)	−0.3 (−1.1 to 0.5)	0.0 (−0.9 to 1.2)[d]
Serum 25OHD, ng/ml	28 (21–35)	27 (21–35)	28 (22–36)	28 (17–35)
Serum 1,25(OH)D, pg/ml	33 (25–41)	36 (27–42)	34 (26–41)	29 (22–35)[b]
Serum iPTH, pg/ml	48 (32–73)	39 (26–55)	59 (40–83)	69 (42–141)[d]
Urine protein-to-creatinine ratio, mg/mg	0.3 (0.1–1.0)	0.2 (0.1–0.5)	0.4 (0.1–0.9)	0.7 (0.2–1.7)[d]
Medication use				
ACEI/ARB, %	54	56	52	54
Active vitamin D sterols, %	30	16	31	49[b]
Nutritional vitamin D supplements, %	40	29	41	54[b]
Phosphate-binding agents, %	17	12	15	26[d]

FGF23, fibroblast growth factor 23; 25OHD, 25-hydroxyvitamin D; 1,25(OH)D, 1,25-dihydroxyvitamin D; iPTH, intact parathyroid hormone; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

[a]Median (interquartile range) reported for continuous characteristics; percentage reported for categorical characteristics.

[b]$P<0.001$ versus FGF23<100 RU/ml.

[c]$P<0.05$ versus FGF23<100 RU/ml.

[d]$P<0.01$ versus FGF23<100 RU/ml.

Table 2. Comparison of mineral metabolism and other characteristics between participants with left ventricular hypertrophy and those without left ventricular hypertrophy

Characteristic[a]	Left Ventricular Hypertrophy	No Left Ventricular Hypertrophy
n (%)	67 (11)	520 (89)
Mineral metabolism		
FGF23, RU/ml	147 (98–247)	114 (79–175)[b]
Serum calcium, mg/dl	9.3 (9.1–9.5)	9.2 (9.0–9.5)
Serum phosphorus, mg/dl	4.6 (4.2–5.3)	4.4 (4.0–4.8)[b]
Phosphorus *z*-score	0.1 (−0.7 to 1.1)	−0.3 (−1.1 to 0.6)[b]
Serum 25OHD, ng/ml	24 (13–33)	28 (21–35)[c]
Serum $1,25(OH)_2D$, pg/ml	27 (21–34)	34 (25–41)[d]
Serum iPTH, pg/ml	55 (42–107)	48 (32–72)
Systolic BP *z*-score	0.67 (−0.13 to 1.27)	0.20 (−0.54 to 0.88)[d]
eGFR, ml/min per 1.73 m^2	44 (35–58)	52 (39–65)[c]
Hemoglobin *z*-score	−1.25 (−2.49 to 0.29)	−0.55 (−1.89 to 0.55)
Urine protein-to-creatinine ratio, mg/mg	0.61 (0.21–1.40)	0.31 (0.11–0.90)[b]

FGF23, fibroblast growth factor 23; 25OHD, 25-hydroxyvitamin D; 1,25(OH)D, 1,25-dihydroxyvitamin D; iPTH, intact parathyroid hormone.
[a]Median (interquartile range) is reported for continuous characteristics; percentage is reported for categorical characteristics.
[b]$P<0.01$.
[c]$P<0.05$.
[d]$P<0.001$.

ventricular structure, whereas with advanced CKD, factors including hypertension and high BMI are relatively stronger determinants of LVH than FGF23.

Our data showing strong dose-dependent associations of higher FGF23 with greater risk of LVH are consistent with studies in adults with predialysis CKD (10,11,25). Further, our finding that FGF23 is a novel CKD-related cardiovascular risk factor in children is potentially of even greater importance because unlike adults, most children with CKD do not have multiple comorbidities such as preexisting

Table 3. Relationship between FGF23 and left ventricular mass

Model	Relative Odds of Left Ventricular Hypertrophy (95% Confidence Interval)	Mean LVMI *z*-Score (95% Confidence Interval)
Model 1		
FGF23, RU/ml		
<100	Reference	Reference
100–169	1.98 (1.04 to 3.79)[a]	0.30 (0.06 to 0.54)[a]
≥170	2.41 (1.25 to 4.62)[b]	0.29 (0.04 to 0.55)[a]
FGF23, per doubling	1.38 (1.12 to 1.71)[b]	0.14 (0.04 to 0.23)[b]
Model 2		
FGF23, RU/ml		
<100	Reference	Reference
100–169	1.78 (0.90 to 3.52)	0.30 (0.07 to 0.54)[a]
≥170	2.53 (1.28 to 4.97)[b]	0.32 (0.07 to 0.57)[a]
FGF23, per doubling	1.43 (1.13 to 1.81)[b]	0.14 (0.04 to 0.23)[b]
Model 3		
FGF23, RU/ml		
<100	Reference	Reference
100–169	1.31 (0.62 to 2.77)	0.15 (−0.09 to 0.40)
≥170	1.44 (0.66 to 3.17)	−0.02 (−0.29 to 0.25)
FGF23, per doubling	1.13 (0.85 to 1.50)	0.01 (−0.10 to 0.11)

Model 1: unadjusted. Model 2: additionally adjusted for age, sex, race, and body mass index. Model 3: additionally adjusted for systolic BP *z*-score, hemoglobin *z*-score, use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and eGFR. FGF23, fibroblast growth factor 23; LVMI, left ventricular mass index.
[a]$P<0.05$.
[b]$P<0.01$.

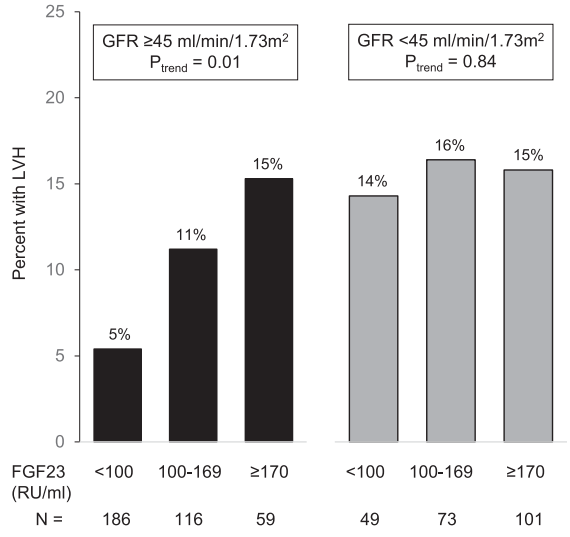

Figure 1. | Higher prevalence of left ventricular hypertrophy associates with higher category of plasma FGF23 concentration in children with GFR ≥45 ml/min per 1.73 m². FGF23, fibroblast growth factor 23; LVH, left ventricular hypertrophy.

advanced cardiac disease, peripheral vascular disease, or diabetes.

A potential mechanism of FGF23-induced cardiac hypertrophy has been recently revealed in a series of experimental studies. Faul *et al.* (11) demonstrated that administration of FGF23 induced hypertrophy of cardiomyocytes *in vitro* and induced LVH in experimental models of CKD *via* a direct FGFR4-dependent mechanism. Administration of the pan-FGF receptor blocker PD173074 not only prevented the development of LVH with induction of CKD in rats, but also reversed LVH and myocardial fibrosis in animals with established CKD (26). Further, blockade of FGFR4 or its genetic ablation prevented the development of LVH, whereas expression of a constitutively active variant of FGFR4 induced LVH, demonstrating that induction of LVH by FGF23 depends on activation of FGFR4 (12). Consistent with this formulation, Leifheit–Nestler *et al.* (13) found that in myocardial autopsy specimens of the left ventricle from individuals with childhood-onset ESRD, LVH was associated with upregulation of FGFR4 and activation of the calcineurin-nuclear factor of activated T cell signaling pathway.

Our findings are consistent with those of Seeherunvong *et al.* (15) who, in a retrospective study of 26 children receiving hemodialysis, found that each 1 SD increase in log-transformed C-terminal FGF23 concentration was associated with a 17% greater LVMI; no association was seen with intact FGF23 (15). The highest FGF23 levels were observed in children with concentric LVH, similar to findings in adults with CKD (10). However, our findings differ from those of Sinha *et al.* (14) in 83 children with CKD stages 2–5, in whom intact FGF23 concentrations were not associated with LVMI (14). There are several differences between the two studies. Sinha *et al.* studied considerably fewer children and measured serum intact FGF23, whereas we measured C-terminal FGF23. Intact FGF23 has significant diurnal variation, higher intraindividual

Table 4. Relationship between plasma FGF23 and left ventricular hypertrophy stratified by level of GFR

Model	Relative Odds of Left Ventricular Hypertrophy (95% Confidence Interval)	
	GFR≥45 ml/min per 1.73 m²	GFR<45 ml/min per 1.73 m²
Model 1		
FGF23, RU/ml		
<100	Reference	Reference
100–169	2.22 (0.94 to 5.25)	1.26 (0.46 to 3.47)
≥170	3.17 (1.22 to 8.22)[a]	1.21 (0.46 to 3.16)
FGF23, per doubling	1.91 (1.32 to 2.77)[b]	1.03 (0.76 to 1.39)
Model 2		
FGF23, RU/ml		
<100	Reference	Reference
100–169	1.98 (0.77 to 5.09)	0.74 (0.24 to 2.26)
≥170	3.18 (1.16 to 8.77)[a]	0.75 (0.27 to 2.11)
FGF23, per doubling	2.10 (1.38 to 3.17)[b]	0.86 (0.60 to 1.24)
Model 3		
FGF23, RU/ml		
<100	Reference	Reference
100–169	2.02 (0.73 to 5.55)	0.44 (0.13 to 1.50)
≥170	3.08 (1.02 to 9.24)[a]	0.39 (0.12 to 1.28)
FGF23, per doubling	2.02 (1.29 to 3.17)[c]	0.68 (0.44 to 1.06)

Model 1: unadjusted. Model 2: additionally adjusted for age, sex, race, and body mass index. Model 3: additionally adjusted for systolic BP *z*-score, hemoglobin *z*-score, and use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. FGF23, fibroblast growth factor 23.

[a]$P<0.05$.

[b]$P<0.001$.

[c]$P<0.01$.

variation (27), and may be less stable if sample processing is delayed by more than 2 hours (28).

As observed in studies of adults with CKD, we found that the association of FGF23 with LVH was independent of SBP, one of the strongest risk factors for higher left ventricular mass in children. Ali *et al.* (29) reported that in normotensive adolescents, FGF23 levels were significantly higher in obese versus nonobese patients and were independently associated with greater LVMI. Those authors speculated that higher FGF23 might be an early marker of cardiac injury in obese adolescents. In the present study, FGF23 was a significant predictor of LVH even after adjustment for BMI.

Clinical and experimental data support an important association between vitamin D and adverse cardiac remodeling (30–32). Ky *et al.* (32) found that higher serum 25OHD and $1,25(OH)_2D$ concentrations associated with lower left ventricular mass in 1431 adult participants from the Chronic Renal Insufficiency Cohort Study. We also observed that higher serum 25OHD concentrations were associated with lower odds of LVH. Unlike the findings of Ky *et al.* (32), we observed no effect modification by vitamin D of the association between FGF23 and LVH.

The major strengths of the present study include a large representative cohort of children with predialysis CKD from multiple pediatric nephrology centers across North America and standardized collection of demographic, clinical, laboratory, and echocardiographic data (16). The study has several limitations. The data do not demonstrate causation or reveal mechanisms that might mediate the association between FGF23 and LVH. We did not measure circulating concentrations of soluble Klotho and thus cannot address the questions of whether Klotho deficiency was present, and if so, if was associated with cardiac structure. Klotho deficiency was implicated in the development of dilated, but not hypertrophic cardiomyopathy in mice with CKD, independently of FGF23 (33). Administration of Klotho was shown to counteract LVH induced by the uremic toxin, indoxyl sulfate, in mice (34). Lower serum Klotho was significantly associated with a higher LVMI in some studies of patients with CKD (34), but was not associated with cardiovascular outcomes, including LVH, in other studies (35) in which FGF23 did significantly associate with future heart failure and atherosclerotic events (35). Nevertheless, the proposed mechanisms by which FGF23 induces cardiac hypertrophy are independent of Klotho (12).

In conclusion, we find that high plasma FGF23 concentration is significantly associated with a higher prevalence of LVH in children with mild-to-moderate CKD (eGFR≥45 ml/min per 1.73 m^2). Interventional studies are needed to determine whether therapeutic strategies that reduce or attenuate the increase in FGF23 can prevent or delay the onset of LVH in children with CKD.

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Disclosures

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