Background—Fibroblast growth factor 23 (FGF-23) is a phosphorus-regulating hormone. In chronic kidney disease (CKD), circulating FGF-23 levels are markedly elevated and independently associated with mortality. Left ventricular hypertrophy and coronary artery calcification are potent risk factors for mortality in CKD, and FGFs have been implicated in the pathogenesis of both myocardial hypertrophy and atherosclerosis. We conducted a cross-sectional study to test the hypothesis that elevated FGF-23 concentrations are associated with left ventricular hypertrophy and coronary artery calcification in patients with CKD.

Methods and Results—In this study, 162 subjects with CKD underwent echocardiograms and computed tomography scans to assess left ventricular mass index and coronary artery calcification; echocardiograms also were obtained in 58 subjects without CKD. In multivariable-adjusted regression analyses in the overall sample, increased log FGF-23 concentrations were independently associated with increased left ventricular mass index (5% increase per 1-SD increase in log FGF-23; \( P = 0.01 \)) and risk of left ventricular hypertrophy (odds ratio per 1-SD increase in log FGF-23, 2.1; 95% confidence interval, 1.03 to 4.2). These associations strengthened in analyses restricted to the CKD subjects (11% increase in left ventricular mass index per 1-SD increase in log FGF-23; \( P = 0.01 \); odds ratio of left ventricular hypertrophy per 1-SD increase in log FGF-23, 2.3; 95% confidence interval, 1.2 to 4.2). Although the highest tertile of FGF-23 was associated with a 2.4-fold increased risk of coronary artery calcification (versus <100 U compared with the lowest tertile (95% confidence interval, 1.1 to 5.5), the association was no longer significant after multivariable adjustment.

Conclusions—FGF-23 is independently associated with left ventricular mass index and left ventricular hypertrophy in patients with CKD. Whether increased FGF-23 is a marker or a potential mechanism of myocardial hypertrophy in CKD requires further study.

Key Words: fibroblast growth factor 23 ■ hormones ■ hypertrophy ■ kidney

Chronic kidney disease (CKD) is a growing public health epidemic that is associated with markedly increased risk of cardiovascular disease and mortality.1,2 Although CKD populations manifest a high prevalence of traditional risk factors for atherosclerosis such as hypertension and diabetes mellitus, these classic risk factors do not fully account for the burden of cardiovascular disease in patients with CKD.3–5 Left ventricular hypertrophy (LVH) and diffuse arterial calcification are common manifestations of cardiovascular disease that are powerful independent risk factors for mortality in patients with CKD.6–9 Approximately 40% of patients with predialysis CKD and up to 80% of patients initiating hemodialysis manifest LVH.4,8 Likewise, diffuse arterial calcification begins before patients reach dialysis, and significant disease is present in >60% of new dialysis patients.6,10 Understanding the early mechanisms of LVH and arterial calcification are essential for designing novel therapeutic strategies to attenuate cardiovascular disease in CKD.

Clinical Perspective on p 2552

Elevated serum phosphate concentrations, even within the normal range, are associated with LVH and increased cardiovascular mortality in both CKD and non-CKD populations.11–14 In addition, high phosphate concentrations promote nonatherosclerotic arterial calcification by stimulating metaplasia of vascular smooth muscle cells into an osteogenic
phenotype. These results suggest that disordered phosphorus metabolism is a novel risk factor for cardiovascular disease. However, overt hyperphosphatemia is uncommon outside dialysis, and the small absolute increases in serum phosphate concentrations that were associated with poor clinical outcomes in large epidemiological studies limit the utility as a tool to detect which individual patients with CKD are at greatest cardiovascular risk. Fibroblast growth factor 23 (FGF-23) is a recently discovered hormone that helps maintain normal serum phosphate concentrations in patients with kidney disease by stimulating urinary phosphate excretion and decreasing dietary phosphorus absorption through the inhibition of 1,25-dihydroxyvitamin D \([1,25\text{(OH)}_2\text{D}]\) synthesis. Importantly, circulating concentrations of FGF-23 increase early in the course of kidney disease, long before the development of hyperphosphatemia; thus, a high FGF-23 concentration is among the earliest markers of disordered phosphorus metabolism in CKD.

We recently reported that elevated FGF-23 concentrations at the initiation of dialysis are independently associated with increased risk of future mortality. The results were not confounded by other risk factors and demonstrated a strong “dose-response” type of relationship in that ascending quartiles of FGF-23 were associated with a linear increase in risk of mortality. Furthermore, increased FGF-23 concentrations were much stronger predictors of mortality than elevated serum phosphate concentrations, and the strongest associations between FGF-23 and mortality were observed in the normal range of serum phosphate. These results suggest that increased FGF-23 may represent an early, more sensitive biomarker of disordered phosphorus metabolism than concomitant serum phosphate measurements. Moreover, elevated concentrations of FGF-23 have been shown to nonselectively activate FGF receptors implicated in the development of cardiac hypertrophy and atherosclerosis, suggesting a biological basis for an association between increased FGF-23 and mortality in CKD. However, no studies have examined the relationship between FGF-23 and LVH or coronary artery calcification in patients with predialysis CKD. We conducted a cross-sectional study to test the hypothesis that elevated FGF-23 concentrations are independently associated with left ventricular mass index (LVMI), LVH, and coronary artery calcification in asymptomatic patients with CKD.

Methods

Study Population

The study population consisted of 162 patients with predialysis CKD and 58 patients with preserved kidney function. Consecutive patients with CKD were recruited from outpatient nephrology clinics at the Massachusetts General Hospital, Boston; the University of Maryland, Baltimore; and the Baltimore Veteran’s Administration Medical Center. Patients were eligible for the study if they were ≥30 years of age and had a sustained reduction (≥3 months) in estimated glomerular filtration rate (eGFR) of ≤60 mL · min \(^{-1} \cdot 1.73 \text{m}^2\) based on the simplified Modification of Diet in Renal Disease formula. Exclusion criteria included stage 5 kidney disease (eGFR <15 mL · min \(^{-1} \cdot 1.73 \text{m}^2\)), renal replacement therapy (dialysis or kidney transplant), history of coronary artery bypass grafting, or a history of myocardial infarction within 90 days of enrollment. In addition, to focus the study on patients with early cardiac disease, patients with symptoms consistent with greater than New York Heart Association class 1 heart failure or greater than Canadian Cardiovascular Society class 1 angina were excluded. We also included 58 subjects with preserved kidney function (eGFR >60 mL · min \(^{-1} \cdot 1.73 \text{m}^2\)) to examine the relationship between FGF-23 and myocardial disease in non-CKD patients. These subjects were recruited from inpatient services at the Massachusetts General Hospital; were at least 18 years of age and clinically stable; did not have acute myocardial infarction, known cardiomyopathy or ejection fraction <40%, or known mitral or aortic valve disease; and were scheduled for an echocardiogram for diagnostic purposes per the primary admitting team. All studies were approved by the Institutional Review boards of the Massachusetts General Hospital, University of Maryland School of Medicine, and Baltimore Veteran’s Administration Medical Center, and all patients provided written informed consent.

Clinical Data and Laboratory Results of Interest

Data on demographic characteristics, medical history, current medications, and blood samples were collected in all subjects at the time of enrollment. Blood samples were immediately centrifuged, separated into aliquots, and stored at −80°C for future batched assays. Serum creatinine, calcium, phosphate, and albumin were measured with standard commercial assays. Intact parathyroid hormone concentrations were measured with the Roche Elecsys parathyroid hormone assay (Roche, Indianapolis, Ind). FGF-23 concentrations were measured in duplicate in the Core Laboratory of the Massachusetts General Hospital General Clinical Research Center with a 2-site ELISA that detects 2 epitopes in the carboxyl-terminal portion of FGF-23 (Immutopics, San Clemente, Calif). Serum B-type natriuretic peptide and cardiac C-reactive protein concentrations were measured in CKD patients with the Access 2 Immunoassay System (Beckman Coulter, Inc, Fullerton, Calif) and Siemens Dimension RxL Max (Newark, Del), respectively. Serum was available in 69 CKD subjects for measurement of 1,25(OH)\(_2\)D concentrations using extraction/liquid chromatography–tandem mass spectrometry (Mayo Medical Laboratories, Rochester, Minn). Besides FGF-23 and 1,25(OH)\(_2\)D, all other blood tests in CKD subjects were processed in a central laboratory at the University of Maryland after a single thaw.

Echocardiography

All subjects underwent 2-dimensional transthoracic echocardiograms. In the CKD subjects, the studies were interpreted by a single reviewer at the University of Maryland who was blinded to subjects’ clinical and laboratory data; for the subjects with preserved kidney function, studies were interpreted as part of routine clinical care. Left ventricular ejection fraction was determined using biplane-modified Simpson’s measurements. For the primary analysis, LVMI was calculated with the modified American Society of Echocardiography equation indexed to height. This formula may be preferable to body surface area-indexed formulas in CKD patients because it mitigates the potential effects of extracellular volume overload on weight-based calculations of LVMI. Relative wall thickness was calculated with the following formula: posterior wall thickness plus septal wall thickness divided by end-dias tonic cavity dimension. LVH was defined as LVMI >49.2 g/m\(^2\) for men and >46.7 g/m\(^2\) for women. LVH was further characterized as eccentric hypertrophy if relative wall thickness was ≤0.43 or as concentric hypertrophy if relative wall thickness was >0.43. Normal left ventricular geometry was defined as relative wall thickness ≤0.43 and normal LVMI. To test whether the results were robust to the method of calculating LVMI, body surface area–indexed values were also examined; because the body surface area–indexed and height-indexed results were qualitatively similar, only the latter are presented.

Coronary Artery Calcification

All patients with CKD underwent cardiac computed tomography scans to assess coronary artery calcification. Computed tomography examinations were performed on a 64-slice scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany, at the Massachusetts General Hospital; Brilliance 64, Philips Healthcare, Cleveland, Ohio, at the University of Maryland) using standardized protocols. Calcifications were quantified with dedicated scoring software (Bril-
Table 1. Description of Subjects by Level of Kidney Function

<table>
<thead>
<tr>
<th>Variables</th>
<th>eGFR &gt;60 mL·min⁻¹·1.73 m⁻² (n=58)</th>
<th>eGFR 45–60 mL·min⁻¹·1.73 m⁻² (n=54)</th>
<th>eGFR 30–44 mL·min⁻¹·1.73 m⁻² (n=69)</th>
<th>eGFR &lt;30 mL·min⁻¹·1.73 m⁻² (n=59)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57±17</td>
<td>60±10</td>
<td>64±11</td>
<td>65±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>43</td>
<td>21</td>
<td>32</td>
<td>37</td>
<td>0.10</td>
</tr>
<tr>
<td>Black, %</td>
<td>7</td>
<td>59</td>
<td>43</td>
<td>21</td>
<td>0.10</td>
</tr>
<tr>
<td>eGFR, mL·min⁻¹·1.73 m⁻²</td>
<td>93±23</td>
<td>53±5</td>
<td>37±5</td>
<td>23±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>120±17</td>
<td>135±19</td>
<td>134±20</td>
<td>135±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic</td>
<td>68±13</td>
<td>76±10</td>
<td>76±11</td>
<td>75±13</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic</td>
<td>28±7</td>
<td>32±6</td>
<td>31±7</td>
<td>29±7</td>
<td>0.87</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19</td>
<td>62</td>
<td>52</td>
<td>39</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57</td>
<td>85</td>
<td>93</td>
<td>95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14</td>
<td>6</td>
<td>19</td>
<td>17</td>
<td>0.32</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>0.25</td>
</tr>
<tr>
<td>Tobacco use*</td>
<td>55</td>
<td>66</td>
<td>64</td>
<td>68</td>
<td>0.12</td>
</tr>
<tr>
<td>Medications, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>59</td>
<td>80</td>
<td>75</td>
<td>71</td>
<td>0.01</td>
</tr>
<tr>
<td>Phosphorus binders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Activated vitamin D</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>25</td>
<td>0.001</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.2</td>
<td>1.5±0.2</td>
<td>1.9±0.3</td>
<td>3.0±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.2±0.5</td>
<td>9.1±1.2</td>
<td>9.4±0.5</td>
<td>9.4±0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>3.4±0.5</td>
<td>3.8±1.1</td>
<td>3.9±0.5</td>
<td>3.8±0.6</td>
<td>0.005</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>40 (29–58)</td>
<td>79 (50–135)</td>
<td>64 (41–95)</td>
<td>73 (49–104)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PTH indicates parathyroid hormone. Results are expressed as frequencies, mean±SD, or median (interquartile range) as appropriate.

*Includes current and former smokers.

Statistical Analyses

Baseline characteristics were assessed with standard descriptive statistics. eGFR was examined both on a continuous scale and categorically according to level of kidney function: preserved kidney function (eGFR >60 mL·min⁻¹·1.73 m⁻²), stage 3a CKD (eGFR 45 to 60 mL·min⁻¹·1.73 m⁻²), stage 3b CKD (eGFR 30 to 44 mL·min⁻¹·1.73 m⁻²), or stage 4 CKD (eGFR 15 to 29 mL·min⁻¹·1.73 m⁻²). Coronary artery calcification scores were examined on a continuous scale (log transformed to approximate a normal distribution) and dichotomized by presence (score ≥100 U) or absence (<100 U) of moderate to severe calcification.

Linear regression was used to examine the association between LVMI and baseline demographic, clinical, and laboratory variables. We used multivariable models to examine the relationship between LVMI and FGF-23 concentrations, adjusting for age, gender, race, eGFR, phosphate concentrations, body mass index (BMI), diabetes mellitus, hypertension, and covariates that were significantly (P<0.05) associated with LVMI in univariate analyses. We used ANCOVA to test for different relationships between FGF-23 and LVMI among the CKD and non-CKD populations and conducted prespecified analyses restricted to patients with CKD. We adjusted for exposure to phosphorus binders or activated vitamin D analogs because they may influence FGF-23 concentrations and for serum C-reactive protein and B-type natriuretic peptide concentrations as surrogate markers of inflammation, sodium intake, volume overload, and sympathetic activity, which are nontraditional risk factors for increased LVMI in CKD.

Decreased vitamin D receptor activation by 1,25(OH)₂D has been associated with increased left ventricular mass, and elevated FGF-23 inhibits the synthesis of 1,25(OH)₂D in CKD. Therefore, we also examined the impact of 1,25(OH)₂D on the relationship between FGF-23 and LVMI in CKD, modeling 1,25(OH)₂D as a categorical variable with a separate category for missing values. We tested regression assumptions by examining transformations of LVMI and excluded nonlinear relationships between FGF-23, LVMI, and coronary artery calcification by testing models that included polynomial terms.

Multivariable logistic regression analyses were performed to examine whether increased FGF-23 concentrations were associated with coronary artery calcification scores ≥100 versus <100 U and LVH, adjusted for the same covariates as above. In addition, we examined the likelihood of having concentric or eccentric hypertrophy versus normal left ventricular geometry as a function of log FGF-23 concentrations. For all analyses, FGF-23 was examined both on a continuous scale, using natural log-transformed FGF-23 values to achieve a normal distribution, and in tertiles defined according to its distribution in the overall study sample. Two-tailed values of P≤0.05 were considered statistically significant. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC).

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Tables 1 and 2 depict demographic and laboratory data, coronary artery calcification scores, and echocardiogram
The prevalence of coronary artery calcification was 48% of the patients having scores ≥100 U. Coronary artery calcification scores ranged from 0 to 100 U, % 9 26 16 22 0.13

LVH, % 9 26 16 22 0.13
LVMI, g/m^2.71 35±11 41±11 40±12 41±13 0.02
LVH, % 9 26 16 22 0.13

CAC indicates coronary artery calcification; LVEF, left ventricular ejection fraction. Results are expressed as frequencies, mean±SE, or median (interquartile range) as appropriate.

*Test for trend includes only patients with CKD.

FGF-23 and Left Ventricular Structure
In univariable analyses, increased log FGF-23 concentrations were significantly associated with increased LVMI (9% increase per 1-SD increase in log FGF-23; \( P<0.001 \); Figure 2); the relationship was not modified by the presence of CKD. Other variables that were associated with increased LVMI in univariable analyses included BMI (2% increase per 1-kg/m^2 increase in BMI; \( P<0.001 \)), eGFR (2% increase per 10–mL·min\(^{-1}·1.73 \text{ m}^2 \) decrease in eGFR; \( P<0.001 \)), diabetes mellitus (13% increase compared with none; \( P=0.002 \)), and hypertension (20% increase compared with none; \( P<0.001 \)). When adjusted for age, gender, race, diabetes mellitus, BMI, hypertension, eGFR, and serum phosphate concentrations, a minimal change in the point estimate was found for log FGF-23, which remained significantly associated with in-

\[ \text{PO}_4^{2-} \quad (\text{mg/dl}) \]

\[
\begin{array}{c|c|c|c}
\text{eGFR (ml/min/1.73 m}^2\text{)} & >60 & 45-60 & <30 \\
\text{Log FGF-23} & 7 & 6 & 5 \\
\end{array}
\]

\[ \text{Figure 1. Mean concentrations of log FGF-23 and phosphate according to level of kidney function. Bars represent SDs; shaded areas, normal ranges for each analyte.} \]

\[ \text{Figure 2. Correlation between log FGF-23 and LVM (r=0.27,} \quad P<0.001). \quad \Diamond \text{ Indicates non-CKD subjects; } \blacksquare \text{, subjects with CKD.} \]
creased LVMI (5% increase per 1-SD increase in log FGF-23; \( P=0.01 \)). In the multivariable model, BMI was the only other factor that remained significantly associated with LVMI (\( P<0.001 \)). When examined in tertiles, mean LVMI increased with increasing tertiles of FGF-23 (Table 3), and the step-wise increase in LVMI with increasing tertiles of FGF-23 remained significant in multivariable-adjusted analysis (tertile 1, reference; tertile 2, 5% increase in LVMI; tertile 3, 11% increase in LVMI; \( P \) for linear trend=0.04). In contrast to FGF-23, serum phosphate concentrations were not associated with LVMI or LVH in univariable or multivariable analyses. In analyses restricted to subjects with CKD, log FGF-23 remained independently associated with LVMI (Table 4), and the results were unchanged when further adjusted for vitamin D and phosphorus binder use and serum concentrations of B-type natriuretic peptide, C-reactive protein, and 1,25(OH)\(_2\)D, even though the latter was inversely associated with log FGF-23 (\( P=0.008 \)). In addition, accounting for recruitment site did not alter the results (data not shown).

Increasing log FGF-23 concentrations also were significantly associated with the presence of LVH (odds ratio [OR] per 1-SD increase in log FGF-23, 2.0; 95% confidence interval [CI], 1.4 to 3.0), a result that was virtually unchanged in the fully adjusted analysis (OR per 1-SD increase in log FGF-23, 1.8; 95% CI, 1.2 to 2.9). The prevalence of LVH increased significantly with ascending tertiles of FGF-23 in univariable analysis (Table 3), but this relationship was attenuated after multivariable adjustment (tertile 1, reference; tertile 2: OR, 2.2; 95% CI, 0.7 to 6.8; tertile 3: OR, 2.7; 95% CI, 0.8 to 8.6). In the analyses restricted to subjects with CKD, log FGF-23 was significantly associated with increased risk of LVH independently of traditional risk factors, vitamin D, phosphorus binder use, and serum concentrations of C-reactive protein, B-type natriuretic peptide, and 1,25(OH)\(_2\)D (Table 4).

To further characterize the relationship between increased FGF-23 and LVH, we examined the likelihood of eccentric or concentric hypertrophy versus normal left ventricular geometry as a function of FGF-23 in the CKD patients. Whereas log FGF-23 was not significantly associated with risk of eccentric LVH, log FGF-23 was significantly associated with increased risk of concentric LVH in univariable (OR, 2.4; 95% CI, 1.1 to 5.1) and multivariable-adjusted (OR 3.4; 95% CI, 1.2 to 9.9) analyses.

### FGF-23 and Coronary Artery Calcification

In univariable analyses, increasing age (OR, 1.1 per 1-year increase in age; 95% CI, 1.04 to 1.2), history of coronary artery disease (OR, 7.6; 95% CI, 2.5 to 23), and smoking (OR, 2.9; 95% CI, 1.6 to 5.9) were associated with a significantly increased risk of coronary artery calcification score \( \geq 100 \) versus \(<100 \) U; serum phosphate concentrations were not associated with coronary artery calcification. On a continuous scale, increased log FGF-23 concentrations were not significantly associated with log-transformed coronary artery calcification scores (\( P=0.38 \)) or scores \( \geq 100 \) versus \(<100 \) U (OR per 1-SD increase in log FGF-23, 1.2; 95% CI, 0.8 to 1.7); however, the highest tertile of FGF-23 was associated with 2.4-fold (95% CI, 1.1 to 5.5) greater risk of coronary artery calcification \( \geq 100 \) versus \(<100 \) U compared with the lowest tertile. In fully adjusted models, the point estimate for the highest versus lowest FGF-23 tertile was only

### Table 3. Coronary Artery Calcification Scores and Echocardiographic Characteristics by Tertile of FGF-23

<table>
<thead>
<tr>
<th>FGF-23 Tertile</th>
<th>CAC Score</th>
<th>LVMI, g/m(^2)</th>
<th>LVH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1 (&lt;75 RU/mL)</td>
<td>32 (0–270)</td>
<td>35±8</td>
<td>7</td>
</tr>
<tr>
<td>Tertile 2 (75–150 RU/mL)</td>
<td>121 (0–302)</td>
<td>40±12</td>
<td>21</td>
</tr>
<tr>
<td>Tertile 3 (&gt;150 RU/mL)</td>
<td>117 (14–384)</td>
<td>42±15</td>
<td>25</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcification. Results are expressed as frequencies, mean±SD, or median (interquartile range) as appropriate.

*Test for trend includes only patients with CKD.

### Table 4. Percentage Increase in Mean LVMI and OR of LVH per 1-SD Increase in Log FGF-23 Adjusted for Medication Use and Serum Concentrations of CRP, BNP, and 1,25(OH)\(_2\)D in 162 CKD Subjects

<table>
<thead>
<tr>
<th>Increase in Mean LVMI (95% CI) per 1-SD Increase in Log FGF-23, %</th>
<th>OR (95% CI) of LVH per 1-SD Increase in Log FGF-23</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>( &lt;0.001 )</td>
<td>2.0 (1.2–3.4)</td>
</tr>
<tr>
<td>Multivariable-adjusted model*</td>
<td>0.01</td>
<td>2.3 (1.2–4.2)</td>
</tr>
<tr>
<td>Plus active vitamin D use</td>
<td>0.005</td>
<td>2.2 (1.2–4.3)</td>
</tr>
<tr>
<td>Plus phosphorus binder use</td>
<td>0.003</td>
<td>2.2 (1.2–4.2)</td>
</tr>
<tr>
<td>Plus log CRP</td>
<td>0.005</td>
<td>2.3 (1.2–4.2)</td>
</tr>
<tr>
<td>Plus log BNP</td>
<td>0.006</td>
<td>2.3 (1.1–4.6)</td>
</tr>
<tr>
<td>Plus 1,25(OH)(_2)D†</td>
<td>0.003</td>
<td>2.0 (1.4–3.0)</td>
</tr>
</tbody>
</table>

CRP indicates C-reactive protein; BNP, B-type natriuretic peptide.

*Adjusted for age, gender, race, BMI, eGFR, diabetes, hypertension, and serum phosphate.

†1,25(OH)\(_2\)D was measured in 69 subjects; therefore, 1,25(OH)\(_2\)D was analyzed as a categorical variable with a separate category for missing values.
minimally attenuated, but the association was no longer statistically significant (OR, 2.1; 95% CI, 0.7 to 6.5).

Discussion

In this cross-sectional study of patients with CKD not yet requiring dialysis, increased FGF-23 concentrations were associated with increased LVMI and increased prevalence of LVH independently of such established risk factors as older age, declining eGFR, diabetes mellitus, and hypertension. Importantly, the associations also were independent of serum phosphate concentrations, which were not associated with LVMI or LVH. Although previous studies found hyperphosphatemia to be associated with increased LVMI and LVH, these results suggest that FGF-23 may be superior to serum phosphate measurements as a marker of the early pathophysiological mechanisms that link disordered phosphorus metabolism with cardiovascular disease in CKD, especially when serum phosphate levels are in the normal range. Whether chronically elevated FGF-23 concentrations may also directly promote myocardial hypertrophy in patients with CKD is an intriguing possibility that requires further study.

FGF-23 is a hormone secreted by osteoblasts and osteocytes that acts primarily in renal proximal tubules to increase urinary phosphorus excretion through downregulation of sodium-phosphate cotransporters and to decrease 1,25(OH)2D concentrations through inhibition of renal 25-hydroxyvitamin D-1-α-hydroxylase. Reductions in FGF-23 levels have the opposite effects. The main physiological stimuli of FGF-23 secretion are increased dietary phosphorus intake and increased 1,25(OH)2D levels. In patients with CKD, FGF-23 concentrations are constitutively elevated and increase progressively as kidney function worsens, likely as an appropriate compensation to help maintain normal serum phosphate concentrations in the face of declining nephron mass. By the time patients reach end-stage renal disease, FGF-23 concentrations are often 100- to 1000-fold above the normal range, whereas serum phosphate concentrations are only modestly increased or even normal. Indeed, as demonstrated in Figure 1, serum phosphate concentrations remained within the normal range across the spectrum of eGFR, whereas FGF-23 concentrations were already elevated in early stages of CKD.

Although increased FGF-23 concentrations in advancing CKD appear to be an appropriate compensation to prevent hyperphosphatemia, in the long term, increased FGF-23 may have adverse end-organ effects. In a prospective study of patients with predialysis CKD, elevated FGF-23 concentrations were independently associated with more rapid progression to renal failure, suggesting a direct link between increased FGF-23 and CKD progression. Importantly, the results were independent of serum phosphate concentrations, which were normal in the vast majority of patients. In a more recent prospective cohort study, we observed that increased FGF-23 concentrations at the initiation of hemodialysis were independently associated with increased 1-year all-cause mortality in a dose-dependent fashion. Not only were the results independent of baseline serum phosphate concentrations, but the magnitude of the risk of death associated with the highest concentrations of FGF-23 (OR, 5.7 for highest versus lowest quartile) dwarfed the corresponding risk associated with the highest concentrations of phosphate (OR, 1.2 for highest versus lowest quartile). The results of the present study provide further evidence that markedly elevated FGF-23 concentrations may be toxic in CKD. Furthermore, because LVH is a potent risk factor for cardiovascular mortality in CKD, these results suggest a potential mechanism to explain the link between increased FGF-23 and mortality on dialysis.

FGF receptors, particularly FGFR1, are expressed in adult myocardial cells, and their activation by locally secreted growth factors can stimulate myocardial hypertrophy and interstitial fibrosis. For example, FGF-2 promotes adult cardiac myocyte hypertrophy in vitro, and excess exposure to FGF-2 in animal models results in enhanced myocardial hypertrophy and interstitial fibrosis after infarction. Furthermore, FGF2−/− mice developed significantly less ventricular hypertrophy than wild-type mice after transverse aortic coarctation, suggesting an important role for FGFs in mediating pressure-overload cardiac hypertrophy. Thus, it is intriguing to speculate whether chronic exposure to elevated FGF-23 concentrations in CKD may similarly accelerate myocardial hypertrophy and fibrosis, which characterize uremic cardiomyopathy. For example, at the markedly elevated circulating concentrations seen in patients with CKD, FGF-23 may nonselectively bind to FGF receptors that are normally activated by locally active growth factors such as FGF-2. Indeed, it is intriguing that increased FGF-23 was significantly associated with increased risk of concentric but not eccentric hypertrophy because concentric hypertrophy was observed in animal models of excess FGF-2 exposure described above. Given that FGF-23 concentrations can be lowered in patients with kidney disease using routine clinical interventions that limit dietary phosphorus absorption, whether “treatment” of elevated FGF-23 concentrations with dietary phosphorus restriction or oral phosphorus binders could be a therapeutic target to attenuate the progression of myocardial disease in early kidney disease is an exciting possibility. Of note, although 1,25(OH)2D was inversely associated with FGF-23 in a subset of CKD subjects, adjusting for 1,25(OH)2D did not attenuate the magnitude or strength of the associations between FGF-23 and LVMI or LVH. Although this finding suggests that the relationship between FGF-23 and left ventricular disease may be independent of 1,25(OH)2D, further studies are needed to examine these relationships in more detail.

Vascular calcification is a highly prevalent risk factor for mortality among patients with CKD and is characterized by metaplasia of vascular smooth muscle cells into osteogenic cell types that mineralize surrounding arterial tissue. The univariate association between elevated FGF-23 concentrations and severe coronary artery calcification in this study may reflect a potential link between FGF-23 and diffuse arterial calcification, as has been reported in dialysis patients. However, given that the association was no longer significant after multivariable adjustment and the lack of an association when calcification was examined on a continuous scale, we must interpret these findings with caution, especially because a previous study failed to show an association between FGF-23 and coronary artery calcification.
We acknowledge several limitations of this study. First, the exclusion of CKD subjects with symptomatic heart disease may have limited our ability to detect more robust associations between FGF-23 and LVH and between phosphate and LVH. Nevertheless, this was also an important strength in that we were able to detect an independent association between FGF-23 and increased LVMi despite this potential limitation. Second, the CKD subjects were recruited from outpatient clinics, and the non-CKD subjects were inpatients. This likely introduced more variability into the measurements of the non-CKD subjects, who likely had higher LVMi than if they had been recruited from the outpatient setting. Indeed, non-CKD subjects in this study had wider variation in their FGF-23 concentrations and a higher prevalence of congestive heart failure than the subjects with CKD. However, we would expect these limitations to bias the results to the null, yet we were still able to detect significant associations. Finally, given that these results are cross-sectional, we cannot draw definitive inferences on their direction or causality. Nevertheless, this is the first report to link FGF-23 with LVMi and LVH in CKD, observations that may contribute to the robust association between FGF-23 and mortality. Given the growing worldwide burden of CKD and its strong association with cardiovascular mortality, prospective human studies and laboratory experiments are needed to further explore the effects of FGF-23 on the cardiovascular system in CKD.

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CLINICAL PERSPECTIVE

Chronic kidney disease (CKD) is a growing public health epidemic that is an established risk factor for cardiovascular morbidity and mortality. An emerging body of evidence suggests that, in addition to traditional risk factors, a number of “uremic” factors contribute to the high prevalence of cardiovascular disease in this population. Left ventricular hypertrophy is a common manifestation of cardiovascular disease in CKD that is associated with increased risk of mortality. Fibroblast growth factor 23, a novel phosphate-regulating hormone that is markedly elevated in patients with CKD, is independently associated with increased left ventricular mass index and left ventricular hypertrophy independently of known risk factors in CKD such as age, diabetes mellitus, and hypertension. Given that circulating fibroblast growth factor 23 concentrations are elevated early in the course of kidney failure and that fibroblast growth factors have been implicated in the development of myocardial hypertrophy, this study suggests a novel biological mechanism that may contribute to the accelerated development of myocardial disease in CKD. In addition, given that fibroblast growth factor 23 can be lowered with routine clinical interventions that restrict dietary phosphorus absorption, these results may suggest novel therapeutic strategies for ameliorating the development of left ventricular hypertrophy in millions of patients with CKD.
Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease
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