Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients With Chronic Kidney Disease

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Context  A high level of the phosphate-regulating hormone fibroblast growth factor 23 (FGF-23) is associated with mortality in patients with end-stage renal disease, but little is known about its relationship with adverse outcomes in the much larger population of patients with earlier stages of chronic kidney disease.

Objective  To evaluate FGF-23 as a risk factor for adverse outcomes in patients with chronic kidney disease.

Design, Setting, and Participants  A prospective study of 3879 participants with chronic kidney disease stages 2 through 4 who enrolled in the Chronic Renal Insufficiency Cohort between June 2003 and September 2008.

Main Outcome Measures  All-cause mortality and end-stage renal disease.

Results  At study enrollment, the mean (SD) estimated glomerular filtration rate (GFR) was 42.8 (13.5) mL/min/1.73 m², and the median FGF-23 level was 145.5 RU/mL (interquartile range [IQR], 96-239 reference unit [RU]/mL). During a median follow-up of 3.5 years (IQR, 2.5-4.4 years), 266 participants died (20.3/1000 person-years) and 410 reached end-stage renal disease (33.0/1000 person-years). In adjusted analyses, higher levels of FGF-23 were independently associated with a greater risk of death (hazard ratio [HR], per SD of natural log-transformed FGF-23, 1.5; 95% confidence interval [CI], 1.3-1.7). Mortality risk increased by quartile of FGF-23: the HR was 1.3 (95% CI, 0.8-2.2) for the second quartile, 2.0 (95% CI, 1.2-3.3) for the third quartile, and 3.0 (95% CI, 1.8-5.1) for the fourth quartile. Elevated fibroblast growth factor 23 was independently associated with significantly higher risk of end-stage renal disease among participants with an estimated GFR between 30 and 44 mL/min/1.73 m² (HR, 1.3 per SD of natural log-transformed FGF-23; 95% CI, 1.04-1.6) and 45 mL/min/1.73 m² or higher (HR, 1.7; 95% CI, 1.1-2.4), but not less than 30 mL/min/1.73 m².

Conclusion  Elevated FGF-23 is an independent risk factor for end-stage renal disease in patients with relatively preserved kidney function and for mortality across the spectrum of chronic kidney disease.

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the normal range. However, small studies suggest that an elevated FGF-23 level is an independent risk factor for mortality among patients undergoing dialysis, and for more rapid loss of kidney function in earlier stages of chronic kidney disease. Whether FGF-23 is associated with greater risks of mortality and end-stage renal disease in the much larger population of patients with earlier stages of chronic kidney disease is unknown. We tested the hypothesis that an elevated FGF-23 level is an independent risk factor for death and end-stage renal disease in a large, racially and ethnically diverse, prospective cohort study of individuals with chronic kidney disease stages 2 through 4.

**METHODS**

**Study Population**

The Chronic Renal Insufficiency Cohort (CRIC) Study is a multicenter, prospective observational study of risk factors for cardiovascular disease, progression of chronic kidney disease, and mortality. Three thousand six hundred twelve individuals aged 21 to 70 years with an estimated GFR of between 20 and 70 mL/min/1.73 m² were enrolled between June 2003 and March 2007. Because chronic kidney disease and its associated adverse outcomes are more common in minorities, self-reported blacks were oversampled, and the ancillary Hispanic CRIC study enrolled 327 additional self-reported Hispanic participants through September 2008. Exclusion criteria included inability to consent, institutionalization, enrollment in other studies, pregnancy, New York Heart Association class III to IV heart failure, human immunodeficiency virus, cirrhosis, myeloma, polycystic kidney disease, renal cancer, recent chemotherapy or immunosuppressive therapy, organ transplant, or prior treatment with dialysis for at least 1 month. The protocol was approved by the institutional review board at each study site (eMethods available at http://www.jama.com), and participants provided written informed consent.

**Exposure and Outcomes**

The primary exposure was plasma FGF-23, which was measured in baseline samples from 3879 of the 3939 participants after a single thaw. A central laboratory at the University of Pennsylvania used a second generation C-terminal assay (Immutopics, San Clemente, California) to measure FGF-23 in duplicate with a mean intra-assay coefficient of variation of less than 5%. Results from C-terminal and intact FGF-23 assays are highly correlated, and biologically active FGF-23 is accurately measured by either assay.

There was no significant difference in the mean (SD) estimated GFR between the study population and the 60 participants who were excluded because they had inadequate sample volumes for assay of FGF-23 (45.0 [13.5] vs 42.8 [13.5] mL/min/1.73 m²). Clinical data were collected at the baseline visit by interview and questionnaire, and additional laboratory tests of blood and urine were measured centrally using standard assays (eMethods). Outcomes included all-cause mortality and end-stage renal disease, defined as initiation of dialysis or kidney transplant. Participants were followed up until the occurrence of death, voluntary withdrawal from the study, loss to follow-up, or December 31, 2008, when the database was locked for analysis. More than 90% of the participants were retained during the longitudinal observation period.

**Statistical Analysis**

We used descriptive statistics to compare clinical characteristics according to baseline FGF-23 levels and examined Spearman correlations between FGF-23, estimated GFR, and other laboratory values. We used time-to-event analyses to examine risks of outcomes according to baseline FGF-23 levels, which were expressed as a continuous variable with hazard ratios (HRs) calculated per SD increment of natural log-transformed FGF-23, and in quartiles, with the lowest quartile defined as the reference group. We used Cox proportional hazards regression to examine unadjusted and multivariable adjusted relationships between FGF-23 and outcomes. We hierarchically adjusted for demographic factors (age, sex, race, and ethnicity), estimated GFR (based on the modified Modification of Diet in Renal Disease [MDRD] study equation) and other chronic kidney disease–specific risk factors (urinary albumin-to-creatinine ratio, hemoglobin, and serum albumin), traditional cardiovascular risk factors (systolic blood pressure, body mass index, diabetes, smoking, low-density lipoprotein cholesterol, prior history of coronary artery disease, congestive heart failure, stroke, and peripheral vascular disease) and the use of cardioprotective and renoprotective medications (aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), and levels of mineral metabolites (serum calcium, phosphate and parathyroid hormone). All adjusted models were stratified by study site to account for potential variability in baseline hazards across centers. We used Schoenfeld residuals to confirm the proportionality assumption.

**Stratified and Sensitivity Analyses**

Because reduced kidney function is an independent risk factor for end-stage renal disease and death, we performed prespecified analyses stratified by baseline estimated GFR and tested for interaction with FGF-23. We also performed stratified analyses and tests for interaction with FGF-23 for the individual chronic kidney disease–specific risk factors, cystatin C, traditional cardiovascular risk factors, and other mineral metabolites. Because death precludes the occurrence of future end-stage renal disease, we used competing risk regression in a sensitivity analysis of end-stage renal disease. Twenty participants who died after reaching end-stage renal disease were included in the primary analysis of mortality; however, because incident end-stage renal disease increases the subsequent hazard of death, we per-
Table 1. Baseline Characteristics in All Participants and According to Quartiles of Fibroblast Growth Factor 23

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Participants, [Median, 145.5] (n = 3879)</th>
<th>1. &lt; 95.8 (n = 969)</th>
<th>2. 95.8-145.4 (n = 970)</th>
<th>3. 145.5-239.1 (n = 970)</th>
<th>4. ≥ 239.2 (n = 970)</th>
</tr>
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<tbody>
<tr>
<td>Demographic and clinical</td>
<td></td>
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</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.2 (11.0)</td>
<td>56.6 (11.3)</td>
<td>58.7 (10.9)</td>
<td>59.0 (10.8)</td>
<td>58.3 (10.9)</td>
</tr>
<tr>
<td>Women</td>
<td>1738 (44.8)</td>
<td>350 (36.1)</td>
<td>385 (39.7)</td>
<td>386 (39.8)</td>
<td>456 (47.0)</td>
</tr>
<tr>
<td>Black</td>
<td>1620 (41.8)</td>
<td>404 (41.7)</td>
<td>374 (38.6)</td>
<td>456 (47.0)</td>
<td>456 (47.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>495 (12.8)</td>
<td>72 (7.4)</td>
<td>138 (14.2)</td>
<td>138 (14.2)</td>
<td>147 (15.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3339 (86.1)</td>
<td>731 (75.4)</td>
<td>843 (87.0)</td>
<td>872 (89.9)</td>
<td>893 (92.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1879 (48.4)</td>
<td>291 (30.0)</td>
<td>443 (45.7)</td>
<td>552 (56.9)</td>
<td>593 (61.1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>853 (22.0)</td>
<td>146 (15.1)</td>
<td>209 (21.5)</td>
<td>237 (24.4)</td>
<td>261 (26.9)</td>
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<tr>
<td>Congestive heart failure</td>
<td>376 (9.7)</td>
<td>33 (3.4)</td>
<td>66 (6.8)</td>
<td>100 (10.3)</td>
<td>177 (18.2)</td>
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<tr>
<td>Stroke</td>
<td>385 (9.9)</td>
<td>77 (7.9)</td>
<td>79 (8.1)</td>
<td>117 (12.1)</td>
<td>112 (11.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>258 (6.6)</td>
<td>33 (3.4)</td>
<td>41 (4.2)</td>
<td>74 (7.6)</td>
<td>110 (11.3)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>508 (13.1)</td>
<td>76 (7.8)</td>
<td>97 (10.0)</td>
<td>132 (13.6)</td>
<td>203 (20.9)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)a</td>
<td>32.1 (7.8)</td>
<td>30.6 (6.7)</td>
<td>31.5 (7.0)</td>
<td>32.4 (7.8)</td>
<td>33.9 (9.1)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>128.6 (22.2)</td>
<td>123.6 (19.5)</td>
<td>126.9 (21.6)</td>
<td>131.8 (23.1)</td>
<td>132.0 (23.3)</td>
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<td>Medication use</td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>1651 (42.9)</td>
<td>367 (38.2)</td>
<td>424 (44.1)</td>
<td>427 (44.4)</td>
<td>433 (44.8)</td>
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<tr>
<td>β-Blockers</td>
<td>1899 (49.3)</td>
<td>346 (36.0)</td>
<td>447 (46.5)</td>
<td>516 (53.6)</td>
<td>590 (61.0)</td>
</tr>
<tr>
<td>Statins</td>
<td>2127 (55.2)</td>
<td>432 (44.9)</td>
<td>537 (55.9)</td>
<td>592 (61.5)</td>
<td>566 (58.5)</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>2650 (68.8)</td>
<td>581 (60.5)</td>
<td>690 (71.8)</td>
<td>707 (73.5)</td>
<td>672 (69.5)</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td>270 (7.0)</td>
<td>49 (5.1)</td>
<td>59 (6.1)</td>
<td>66 (6.6)</td>
<td>96 (9.9)</td>
</tr>
<tr>
<td>Active vitamin D</td>
<td>124 (3.2)</td>
<td>14 (1.5)</td>
<td>14 (1.5)</td>
<td>36 (3.7)</td>
<td>60 (6.2)</td>
</tr>
<tr>
<td>Nutritional vitamin D</td>
<td>394 (10.2)</td>
<td>95 (9.9)</td>
<td>110 (11.4)</td>
<td>87 (9.0)</td>
<td>102 (10.5)</td>
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<td>Laboratory results</td>
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<td></td>
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<tr>
<td>Creatinine, mean (SD), mg/dL.</td>
<td>1.8 (0.6)</td>
<td>1.5 (0.4)</td>
<td>1.7 (0.5)</td>
<td>1.9 (0.6)</td>
<td>2.2 (0.8)</td>
</tr>
<tr>
<td>Estimated GFR, mL/min/1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>42.8 (13.5)</td>
<td>52.1 (12.1)</td>
<td>45.5 (11.7)</td>
<td>39.2 (10.9)</td>
<td>34.3 (12.2)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>401 (10.3)</td>
<td>(23.5) (12.0)</td>
<td>(2.8) (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-60</td>
<td>2720 (70.1)</td>
<td>(73.4) (79.2)</td>
<td>(73.4) (79.2)</td>
<td>(54.5) (54.5)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>758 (19.5)</td>
<td>(3.0) (8.9)</td>
<td>(23.8) (42.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uinine albumin-to-creatinine ratio, median (IQR), mg/g</td>
<td>52.1 (8.7-460.9)</td>
<td>14.5 (5.0-121.7)</td>
<td>32.2 (6.5-275.0)</td>
<td>102.9 (15.0-713.2)</td>
<td>212.7 (28.4-1277.3)</td>
</tr>
<tr>
<td>Albumin, mean (SD), g/dL</td>
<td>3.9 (0.5)</td>
<td>4.0 (0.4)</td>
<td>4.0 (0.4)</td>
<td>3.9 (0.5)</td>
<td>3.8 (0.5)</td>
</tr>
<tr>
<td>Cystatin C, mean (SD), mg/L</td>
<td>1.5 (0.5)</td>
<td>1.1 (0.3)</td>
<td>1.4 (0.4)</td>
<td>1.6 (0.4)</td>
<td>2.0 (0.6)</td>
</tr>
<tr>
<td>Calcium, mean (SD), mg/dL</td>
<td>9.2 (0.5)</td>
<td>9.2 (0.4)</td>
<td>9.2 (0.5)</td>
<td>9.2 (0.5)</td>
<td>9.1 (0.6)</td>
</tr>
<tr>
<td>Phosphate, mean (SD), mg/dL</td>
<td>3.7 (0.7)</td>
<td>3.4 (0.5)</td>
<td>3.6 (0.6)</td>
<td>3.8 (0.8)</td>
<td>4.1 (0.8)</td>
</tr>
<tr>
<td>Fractional excretion of phosphate, median (IQR)</td>
<td>26.5 (19.5-36.8)</td>
<td>23.0 (17.8-30.2)</td>
<td>25.1 (18.7-33.9)</td>
<td>27.8 (21.1-38.9)</td>
<td>32.5 (22.8-44.4)</td>
</tr>
<tr>
<td>Parathyroid hormone, median (IQR), pg/mL</td>
<td>54.0 (35.0-89.0)</td>
<td>40.0 (29.0-59.0)</td>
<td>47.4 (32.4-73.2)</td>
<td>62.8 (40.0-105.0)</td>
<td>82.4 (47.0-137.0)</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D, mean (SD), ng/mLb</td>
<td>213.1 (10.8)</td>
<td>22.0 (10.1)</td>
<td>24.0 (11.6)</td>
<td>21.5 (10.8)</td>
<td>16.6 (9.9)</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>12.6 (1.8)</td>
<td>13.5 (1.6)</td>
<td>12.8 (1.7)</td>
<td>12.4 (1.6)</td>
<td>11.8 (1.8)</td>
</tr>
<tr>
<td>LDL, mean (SD), mg/dL</td>
<td>102.6 (35.3)</td>
<td>107.0 (33.1)</td>
<td>102.1 (33.4)</td>
<td>101.3 (36.3)</td>
<td>99.8 (38.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To covert calcium from mg/dL to mmol/L, multiply by 0.25; creatinine from mg/dL to µmol/L, multiply by 88.4; LDL from mg/dL to mmol/L, multiply by 0.0259; and parathyroid hormone from pg/mL to ng/L, multiply by 0.1053. a Body mass index calculated as weight in kilograms divided by height in meters squared. b 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were available in 333 and 332 participants, respectively.
formed an additional sensitivity analysis of mortality in which we censored those 20 participants when they developed end-stage renal disease. Phosphate binders and active vitamin D therapy can modulate FGF-23 levels and are associated with survival. We adjusted for use of these medications and for use of vitamin D supplements and performed a sensitivity analysis that excluded participants who were receiving these agents at enrollment. To test for potential confounding by vitamin D levels, we examined the unadjusted association of FGF-23 with outcomes in the 333 participants with 1,25-dihydroxyvitamin D and 25-dihydroxyvitamin D measurements at baseline and examined this association again among the 1159 participants with these measurements at the 1-year follow-up visit, and then adjusted for demographics and vitamin D levels.

To determine whether the results were robust to alternate measures of kidney function, we repeated the main analysis after substituting MDRD-based estimated GFR with cystatin C and direct iothalamate GFR measurements that were available from 1409 participants. To investigate whether the relationship between FGF-23 and mortality might represent a more accurate capture of residual confounding introduced by imprecision in the measures of renal function, we assessed the speci-
ficity of the FGF-23 results by also examining risk of death according to parathyroid hormone, which correlated with estimated GFR to a similar extent as FGF-23. Finally, because fractional excretion of phosphate (FePi = [urine phosphate × serum creatinine] / [serum phosphate × urine creatinine] × 100%) is a readily available clinical measure of the phosphaturic action of FGF-23 (higher FGF-23 causes increased FePi), we explored the utility of FePi as a surrogate measure of the effect of FGF-23 by substituting it for FGF-23 in the fully adjusted mortality model. Analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, North Carolina). All statistical tests were 2-sided, and P values < .05 were considered significant.

RESULTS

Baseline characteristics are presented in Table 1 for the overall population and by FGF-23 quartiles. The mean (SD) estimated GFR at the baseline visit was 42.8 mL/min/1.73 m² (13.5 mL/min/1.73 m²). Although the mean (SD) serum phosphate level was 3.7 mg/dL (0.7 mg/dL), and 89% of participants had normal phosphate levels (< 4.6 mg/dL), the median FGF-23 level was 145.5 RU/mL (interquartile range [IQR], 96-239 RU/mL), which is more than 3-fold higher than the median of 43 RU/mL (IQR, 29-72 RU/mL) in a population with a low prevalence of chronic kidney disease. Fibroblast growth factor 23 correlated with estimated GFR (r = -0.52; P < .001), cystatin C (r = 0.59; P < .001), serum phosphate (r = 0.35; P < .001), parathyroid hormone (r = 0.37; P < .001), FePi (r = 0.26; P < .001), and hemoglobin (r = -0.36; P < .001). After FGF-23, parathyroid hormone was the next closest correlate of estimated GFR (r = -0.47; P < .001).

FGF-23 and Risks of Clinical Outcomes

During a median follow-up of 3.5 years, 266 participants died (20.3/1000 person-years) and 410 reached end-stage renal disease (33.0/1000 person-years). Median FGF-23 levels were significantly higher in those who died (234; IQR, 142-419 RU/mL) or reached end-stage renal disease (236; IQR, 160-372 RU/mL) than in those who remained event-free (133; IQR, 91-210 RU/mL; P < .001 for each).

Mortality

Unadjusted and multivariable-adjusted HRs for mortality are presented in Table 2 according to baseline FGF-23, expressed as a continuous variable and in quartiles. Adjusting for demographic characteristics, estimated GFR and other chronic kidney disease–specific risk factors did not alter the relationship between elevated FGF-23 levels and risk of death observed in unadjusted analyses. Participants in the highest vs the lowest quartile demonstrated a 4.3-fold greater risk of death, and the intermediate quartiles demonstrated intermediate risks. Further adjustment for traditional cardiovascular risk factors; use of cardio- protective and renoprotective medications; and serum calcium, phosphate, and parathyroid hormone levels minimally attenuated the relationship between FGF-23 and risk of death. In the fully adjusted models, the graded increase in risk of death persisted across

The multivariable-adjusted hazard ratio (95% confidence intervals) of death per unit increment in standard deviation of natural log-transformed fibroblast growth factor 23 (FGF-23) is plotted for the entire cohort and according to strata of baseline covariates. See Figure 1 legend for adjusted variables. To convert calcium from mg/dL to mmol/L, multiply by 0.25; low-density lipoprotein from mg/dL to mmol/L, multiply by 0.0259; and parathyroid hormone from pg/mL to ng/L, multiply by 0.103.
the spectrum of FGF-23 levels (Figure 1), and the effects of estimated GFR and proteinuria on mortality were completely attenuated. In multivariable-adjusted stratified analyses, elevated FGF-23 levels were associated with homogenously greater risk of mortality (Figure 2).

In sensitivity analyses, the results were qualitatively unchanged when we censored at the time of end-stage renal disease; when we substituted cystatin C (HR per SD of natural log-transformed FGF-23, 1.4; 95% CI, 1.2-1.7) or iothalamate GFR instead of the MDRD estimated GFR; when we adjusted for vitamin D levels; when participants treated with phosphate binders, active vitamin D, or vitamin D supplements were excluded; or when use of these medications was included in the multivariable models (eTable 1 available at http://www.jama.com). Unlike FGF-23, neither parathyroid hormone (HR per SD of natural log-transformed parathyroid hormone, 1.1; 95% CI, 0.9-1.3) nor FePi (HR per SD of natural log-transformed FePi, 1.0; 95% CI, 0.9-1.1) was associated with mortality in fully adjusted models that excluded FGF-23.

**End-Stage Renal Disease**

In contrast to mortality, adjustment for estimated GFR and chronic kidney disease–specific risk factors attenuated the unadjusted association between FGF-23 and risk of end-stage renal disease in the primary analysis (Table 2) and when death was treated as a competing risk (eTable 2). In the fully adjusted model, reduced estimated GFR was the strongest predictor of end-stage renal disease, and estimated GFR modified the relationship between FGF-23 and risk of end-stage renal disease (P for natural log-transformed FGF-23 × estimated GFR = .005). Although the median FGF-23 was higher in more advanced chronic kidney disease, elevated levels of FGF-23 were independently associated with greater risk of end-stage renal disease in participants with baseline estimated GFR between 30 and 45 mL/min/1.73 m² and 45 mL/min/1.73 m² or higher but not in those with estimated GFR lower than 30 mL/min/1.73 m² (Figure 3). In contrast, the risk of death according to FGF-23 was homogenously significant across categories of estimated GFR (Figure 3).

**COMMENT**

An elevated level of FGF-23 is an independent risk factor for mortality in a referred population of patients with chronic kidney disease stages 2 through 4. The effect was minimally confounded by other factors known to influence survival and was specific to FGF-23 among the mineral metabolites we analyzed. These results are consistent with prior reports of greater risk of mortality in association with elevated FGF-23 levels in patients undergoing hemodialysis,4,5 recipients of kidney transplants,21 and individuals with a prior history of cardiovascular disease.20 Unexpectedly, FGF-23 was more strongly associated with mortality than traditional cardiovascular disease– and chronic kidney disease–specific risk factors, most notably, reduced estimated GFR and proteinuria. These data emphasize the potential of FGF-23 as a novel risk factor for mortality in chronic kidney disease.

The mechanisms that underlie the association between elevated levels of FGF-23 and mortality are unclear. One possibility is that FGF-23 is an excellent biomarker of toxicity of other factors in the family of disordered mineral metabolism, such as elevated serum phosphate and parathyroid hormone. However, a recent meta-analysis demonstrated the poor relationship between parathyroid hormone and mortality, and the modest effect of elevated serum phosphate.22 In the current study, similar to the few previous studies that performed direct comparisons,4,5,21 FGF-23 was more strongly associated with mortality than other mineral metabolites, and its effect was neither confounded nor modified by phosphate or parathyroid hormone. In addition, increased FePi, which is a measure of the physiological action of FGF-23 on renal phosphate handling,19 was not associated with mortality. These findings suggest that mechanisms beyond mineral metabolism may underlie excess mortality in association with elevated FGF-23.
Another possibility is that an elevated level of FGF-23 is a sensitive marker of the severity of kidney dysfunction that accurately conveys mortality risk associated with chronic kidney disease but that is not directly attributable to FGF-23. This also seems inadequate, however, given the previous report linking elevated levels of FGF-23 with mortality in a predominantly non–chronic kidney disease cohort,20 and our observation of homogeneous risk of mortality across the range of renal function regardless of whether it was quantified using the standard MDRD estimated GFR, iothalamate GFR, or cystatin C. In addition, the specificity of the results for FGF-23 relative to parathyroid hormone, despite their similar correlation with estimated GFR, suggests that the effect of FGF-23 on death may be acting through a mechanistic pathway that is at least partially independent of renal function. Finally, the observation that estimated GFR and proteinuria fell out as insignificant risk factors for mortality in multivariable models that included FGF-23 suggests that rather than simply acting as a biomarker of chronic kidney disease severity, elevated FGF-23 may contribute to the excess mortality that was attributed to chronic kidney disease in previous studies in which FGF-23 levels were unavailable. Although postulating direct toxicity of FGF-23 remains speculative,23 elevated FGF-23 consistently associates with pathophysiologically plausible mechanisms of premature death including left ventricular hypertrophy, endothelial dysfunction, atherosclerosis, and arterial calcification.24-28 Experimental or randomized human studies are needed to assign or refute a direct causal role for FGF-23 in excess mortality.

The relationship between FGF-23 and risk of end-stage renal disease was more complex. In the overall population, FGF-23 was associated with risk of end-stage renal disease until estimated GFR was added to the model. Although this might suggest that an elevated level of FGF-23 is not a risk factor for end-stage renal disease, the relationship between FGF-23 and end-stage renal disease was modified by estimated GFR, which was the most potent determinant of progression to end-stage renal disease. Unlike death, in which events were relatively balanced across the range of estimated GFR, analyses of end-stage renal disease in the overall population were driven primarily by participants with baseline estimated GFR less than 30 mL/min/1.73 m². This group experienced the greatest number of end-stage renal disease events with incidence rates that were approximately 4-fold and 18-fold higher than those with estimated GFR of 30 through 45 and 45 mL/min/1.73 m² or higher, respectively (Figure 3). When the analyses were stratified by kidney function, higher FGF-23 emerged as an independent risk factor for end-stage renal disease in those with estimated GFR higher than 30 mL/min/1.73 m², and the effect size grew with higher estimated GFR. Although these results suggest that FGF-23 testing might help stratify risk of progression to end-stage renal disease in the growing number of patients found to have modestly reduced estimated GFR, confirmation by future studies is needed.

Limitations of the study include the lack of data on cause of death. Although greater risk of cardiovascular mortality is likely given previous reports of FGF-23 and cardiovascular events,29 future studies should examine cause-specific mortality and risk of major cardiovascular events in patients with chronic kidney disease according to FGF-23. Second, vitamin D levels were only available in subsets of participants. However, since adjustment for vitamin D levels or vitamin D treatment did not alter the point estimate for FGF-23 similar to previous studies,4 it is unlikely that vitamin D confounds the relationship between FGF-23 and mortality. Third, we did not study other biomarkers, such as troponin T and brain natriuretic peptide, which have been associated with adverse outcomes in chronic kidney disease.15 Finally, the lack of a validated assay in chronic kidney disease precluded us from measuring circulating levels of the soluble form of klotho, the FGF-23 coreceptor that is expressed in the kidneys and parathyroid glands and that demonstrates antiaging and vascular-protective effects.29,30 Future studies should explore whether reduced expression of klotho due to chronic kidney disease itself31 or secondary to increased FGF-2332 is a potential mediator of FGF-23-associated mortality.

Previous reports of greater risk of mortality in association with elevated FGF-23 levels among patients undergoing dialysis13 established the possibility that FGF-23 may be a novel predictor of adverse outcomes in patients with kidney disease. In the current study, we extend these results to the much larger population of patients with chronic kidney disease stages 2 through 4 in whom treatment of disordered phosphorus metabolism is not recommended because their serum phosphate levels are usually normal. If the results of the current study are confirmed and experimental studies support the hypothesis of direct toxicity of FGF-23, future research should evaluate whether therapeutic or preventative strategies that lower FGF-23 can improve outcomes.

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Online-Only Material: eMethods and eTables 1 and 2 are available at http://www.jama.com.

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