Fibroblast Growth Factor 23 and Inflammation in CKD

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Summary

Background and objectives Levels of fibroblast growth factor 23 (FGF23) and inflammatory markers are commonly elevated in CKD, and each is associated with adverse clinical outcomes. This study tested the hypothesis that FGF23 is independently associated with inflammation in CKD.

Design, setting, participants, & measurements The association between levels of FGF23 and the inflammatory markers IL-6, C-reactive protein (CRP), TNF-α, and fibrinogen was assessed in a cross-sectional analysis of 3879 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study between June 2003 and September 2008.

Results FGF23 correlated directly with IL-6 (r=0.4), CRP (r=0.2), TNF-α (r=0.4), and fibrinogen (r=0.3; P<0.001 for each). In univariate and multivariable-adjusted linear regression analyses, natural log (ln) transformed FGF23 was significantly associated with lnIL-6, lnCRP, lnTNF-α, and fibrinogen (P<0.001 for each). Each unit higher lnFGF23 was associated with severe inflammation, defined as levels of all inflammatory markers in the highest 25th percentile, in univariate (odds ratio [OR], 2.4 [95% confidence interval (CI), 2.0–2.9]) and multivariable-adjusted (OR, 2.0 [95% CI, 1.6–2.5]) logistic regression analyses. Ascending FGF23 quartiles were independently associated with severe inflammation (OR, 5.6 for the highest versus lowest FGF23 quartile [95% CI, 2.3–13.9]; P for trend < 0.001).

Conclusions Higher FGF23 levels are independently associated with higher levels of inflammatory markers in patients with CKD and with significantly greater odds of severe inflammation. Future studies should evaluate whether inflammation modifies the association between FGF23 and adverse outcomes in CKD.


Introduction

Fibroblast growth factor 23 (FGF23) is a phosphate-regulating hormone primarily secreted by osteocytes (1). Levels of FGF23 increase as kidney function declines as a physiologic response to maintain normal serum phosphate levels and neutral phosphate balance (2). Although FGF23 helps to prevent hyperphosphatemia, elevated circulating levels are independently associated with vascular dysfunction (3), left ventricular hypertrophy (4), increased risk for ESRD, and death in patients with CKD (5,6). Recent data indicate that FGF23 contributes directly to the development of left ventricular hypertrophy, suggesting a plausible biologic basis for the observed association between elevated FGF23 and mortality (7). By establishing a direct pathogenic role for FGF23 excess in CKD, these data support the need to explore additional potential mechanisms of FGF23 toxicity that underlie the link between elevated FGF23 levels and adverse clinical outcomes.

CKD is associated with elevated levels of inflammatory markers (8,9), which in turn are associated with atherosclerosis (10), faster rates of CKD progression (11), and increased risk for death (9,12). These observations suggest that inflammation plays an important role in the pathophysiology of cardiovascular disease in CKD. Given the high prevalence of inflammation and FGF23 excess in CKD, and the observations that each predicts risk for adverse clinical outcomes, we hypothesized that elevated levels of FGF23 and inflammation are associated, which could serve as another mechanistic link between FGF23 and adverse outcomes. To date, one small study reported a relationship between higher FGF23 and C-reactive protein (CRP) levels in 145 patients with early CKD (13). We characterized the association between FGF23, CRP, and additional markers of inflammation in a cross-sectional analysis of the Chronic Renal Insufficiency Cohort (CRIC) study of individuals with CKD stages 2–4.

Materials and Methods

Description of the Cohort

The CRIC study is a multicenter, prospective cohort study of risk factors for cardiovascular disease and progression of CKD among individuals with CKD stages 2–4 (14). Adult participants (n=3612) age 21–74...
years with an age-stratified estimated GFR (eGFR) of 20–70 ml/min per 1.73 m² at the screening visit were enrolled. To have adequate representation of ethnic minorities, blacks were oversampled, and the ancillary Hispanic CRIC (HCRCIC) study enrolled 327 additional Hispanic participants (15). Participants were excluded for pregnancy, New York Heart Association class III–IV heart failure, HIV infection, cirrhosis, myeloma, renal cancer, recent chemotherapy or immunosuppressive therapy, polycystic kidney disease, organ transplantation, or previous treatment with dialysis for at least 1 month. The institutional review board at each site approved the study, and all participants provided written informed consent.

Study Population
We evaluated 3879 of the 3939 total CRIC and HCRCIC participants who had baseline plasma FGF23 measured. Data on baseline inflammatory markers were available for nearly all of these participants: IL-6 and TNF-α in 3878 participants, high-sensitivity CRP in 3877, and fibrinogen in 3855. Serum 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D) levels were available in a subset of 1502 and 1527 participants, respectively, at the year 1 follow-up visit.

Data Collection and Measurements
We analyzed the following data that were collected at the baseline visit: demographic characteristics, medical history, smoking status, body mass index (BMI), use of statins, and blood and urinary samples. We evaluated statin use because these agents reduce levels of inflammatory markers in CKD (16). Comprehensive metabolic panels and urinary biochemical panels were measured using standard assays. Urinary fractional excretion of phosphate was calculated as follows:

\[
100 \times \frac{(\text{urine phosphate} \times \text{serum creatinine})}{(\text{serum phosphate} \times \text{urine creatinine})}.
\]

Plasma FGF23 was measured using the second-generation C-terminal assay that detects two epitopes in the C-terminus of FGF23 (Immune [a], San Clemente, CA; coefficient of variation [CV] < 5%). Plasma parathyroid hormone (PTH) was measured using a total PTH assay, which detects both the 1–84 PTH molecule and 7–84 fragments (Scantibodies, Sante, CA; CV < 5%). Serum 25D was quantified using liquid chromatography–mass spectroscopy (CV < 5%), and serum 1,25D was measured by competitive chemiluminescent immunoassay (Heartland Assays, Ames, IA; CV < 12%). Plasma IL-6 and TNF-α were determined by ELISA (R&D systems, Minneapolis, MN; CV < 15%). Plasma high-sensitivity CRP was quantified by particle-enhanced immunonephelometry (Dade Behring–Siemens Healthcare, CV < 5%), and fibrinogen was measured by immunonephelometric reaction (Dade Behring–Siemens Healthcare, CV < 5%). With the exception of the vitamin D assays, all tests were performed in the CRIC Study Central Laboratory at the University of Pennsylvania. Estimated GFR was based on the modified Modification of Diet in Renal Disease (MDRD) equation (17). A subset of 1409 participants had GFR measured directly using 125I iothalamate clearance (iGFR).

Statistical Analyses
Continuous variables were summarized as mean ± SD or median with interquartile range (IQR). Categorical variables were expressed as frequencies and proportions. We analyzed FGF23 on a continuous scale and after categorizing participants into quartiles. Because of their skewed distributions, FGF23, IL-6, CRP, TNF-α, and urinary albumin-to-creatinine ratio (UACR) were natural log (ln)-transformed. We evaluated the associations between FGF23 and other mineral metabolites with markers of inflammation using Spearman correlations. We used separate linear regression models to examine the univariate and multivariable-adjusted association between FGF23 as primary exposure, and individual inflammatory markers (including IL-6, CRP, TNF-α, and fibrinogen) as the dependent variables. Multivariable analyses were adjusted for factors known to be associated with inflammation, including age, sex, race (black versus nonblack), ethnicity (Hispanic versus non-Hispanic), diabetes, current smoking, BMI, use of statins, eGFR, and lnUACR. In secondary analyses, we further adjusted for lnPTH and phosphate levels. To assess whether FGF23 was associated with inflammatory markers independent of vitamin D, we adjusted for 25D and 1,25D separately in the subset of patients in whom these data were available. We also repeated the adjusted analyses in the subcohort of participants with iGFR, substituting iGFR for MDRD eGFR in the multivariable models.

In CKD, elevated BMI is associated with reduced serum phosphate levels (18) and elevated FGF23 levels (19). Therefore, we performed formal tests for interaction between BMI and FGF23 and analyzed models stratified by BMI as lean (<25 kg/m²), overweight (25 to <30 kg/m²) and obese (≥30 kg/m²) (20). Finally, we used logistic regression to determine whether elevated FGF23 levels are independently associated with presence of severe inflammation, defined as being in the highest 25th percentile of plasma concentration of each inflammatory marker (IL-6, CRP, TNF-α, and fibrinogen). We adjusted for the same covariates as in the primary analyses. Two-sided P values < 0.05 were considered to represent a statistically significant difference, unless otherwise noted. We performed analyses using SAS EG, version 9.2 (SAS Institute, Cary, NC).

Results
Baseline characteristics of the 3879 CRIC participants categorized by FGF23 quartiles are presented in Table 1. Compared with lower FGF23 quartiles, participants in the upper quartiles were more likely to be female, to be smokers, and to have diabetes and a higher BMI. In addition to serum creatinine, phosphate, PTH, fractional excretion of phosphate, and UACR, levels of all inflammatory markers (CRP, IL-6, TNF-α, and fibrinogen) increased monotonically while 25D, 1,25D, and eGFR decreased with ascending FGF23 quartiles.

Table 2 presents the correlation coefficients between markers of mineral metabolism and inflammation. Among the mineral metabolites, FGF23 showed the strongest correlation with each inflammatory marker. Only BMI exceeded FGF23 in strength of correlation with CRP, and only eGFR surpassed it for TNF-α. In contrast,
FGF23 was the strongest correlate of IL-6 and fibrinogen levels.

In univariate and multivariable-adjusted linear regression analyses, increasing lnFGF23 and ascending FGF23 quartiles were significantly associated with lnIL-6, lnCRP, lnTNF-α, and fibrinogen (Table 3). The results were qualitatively unchanged in models that further adjusted for lnPTH and phosphate (Table 3), in models that adjusted...
Table 3. Univariate and multivariate linear regression analyses between inflammatory markers as dependent variables and fibroblast growth factor 23 as primary exposure

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
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<th>Adjusted Model A&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>Adjusted Model B&lt;sup&gt;b&lt;/sup&gt;</th>
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<td></td>
<td>Difference (95% CI)</td>
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<td>LnIL-6</td>
<td>0.40 (0.36–0.43)</td>
<td>&lt;0.001</td>
<td>0.29 (0.25–0.33)</td>
<td>&lt;0.001</td>
<td>0.29 (0.25–0.33)</td>
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<tr>
<td>FGF23 quartile 2</td>
<td>0.24 (0.16–0.310)</td>
<td>&lt;0.001</td>
<td>0.14 (0.06–0.21)</td>
<td>&lt;0.001</td>
<td>0.13 (0.05–0.21)</td>
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<tr>
<td>FGF23 quartile 3</td>
<td>0.42 (0.35–0.50)</td>
<td>&lt;0.001</td>
<td>0.25 (0.17–0.34)</td>
<td>&lt;0.001</td>
<td>0.23 (0.15–0.32)</td>
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<tr>
<td>FGF23 quartile 4</td>
<td>0.83 (0.75–0.90)</td>
<td>&lt;0.001</td>
<td>0.57 (0.48–0.65)</td>
<td>&lt;0.001</td>
<td>0.55 (0.46–0.64)</td>
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<tr>
<td>LnCRP</td>
<td>LnFGF23</td>
<td>0.28 (0.23–0.33)</td>
<td>&lt;0.001</td>
<td>0.19 (0.14–0.25)</td>
<td>&lt;0.001</td>
<td>0.22 (0.16–0.27)</td>
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<td>FGF23</td>
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<tr>
<td>FGF23 quartile 2</td>
<td>0.05 (−0.06 to 0.17)</td>
<td>0.34</td>
<td>0.001 (−0.11 to 0.11)</td>
<td>0.99</td>
<td>0.02 (−0.09 to 0.13)</td>
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<td>FGF23 quartile 3</td>
<td>0.24 (0.13–0.35)</td>
<td>&lt;0.001</td>
<td>0.17 (0.05–0.29)</td>
<td>0.004</td>
<td>0.19 (0.07–0.30)</td>
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<td>FGF23 quartile 4</td>
<td>0.59 (0.48–0.70)</td>
<td>&lt;0.001</td>
<td>0.37 (0.24–0.50)</td>
<td>&lt;0.001</td>
<td>0.40 (0.27–0.53)</td>
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<tr>
<td>LnTNF-α</td>
<td>LnFGF23</td>
<td>0.28 (0.25–0.30)</td>
<td>&lt;0.001</td>
<td>0.14 (0.10–0.17)</td>
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<td>0.14 (0.10–0.17)</td>
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<td>FGF23</td>
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<tr>
<td>FGF23 quartile 2</td>
<td>0.22 (0.16–0.28)</td>
<td>&lt;0.001</td>
<td>0.10 (0.03–0.16)</td>
<td>0.002</td>
<td>0.09 (0.03–0.15)</td>
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<td>FGF23 quartile 3</td>
<td>0.40 (0.34–0.46)</td>
<td>&lt;0.001</td>
<td>0.17 (0.11–0.23)</td>
<td>&lt;0.001</td>
<td>0.17 (0.11–0.24)</td>
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<tr>
<td>FGF23 quartile 4</td>
<td>0.59 (0.53–0.65)</td>
<td>&lt;0.001</td>
<td>0.28 (0.21–0.35)</td>
<td>&lt;0.001</td>
<td>0.28 (0.20–0.35)</td>
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<td>Fibrinogen</td>
<td>LnFGF23</td>
<td>0.44 (0.07–0.28)</td>
<td>&lt;0.001</td>
<td>0.13 (0.07–0.18)</td>
<td>&lt;0.001</td>
<td>0.09 (0.03–0.14)</td>
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<td>FGF23 quartile 2</td>
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<td>&lt;0.001</td>
<td>−0.05 (−0.15 to 0.05)</td>
<td>0.40</td>
<td>−0.07 (−0.17 to 0.03)</td>
<td>0.20</td>
</tr>
<tr>
<td>FGF23 quartile 3</td>
<td>0.56 (0.46–0.66)</td>
<td>&lt;0.001</td>
<td>0.12 (0.02–0.23)</td>
<td>0.02</td>
<td>0.09 (0.02–0.20)</td>
<td>0.10</td>
</tr>
<tr>
<td>FGF23 quartile 4</td>
<td>0.98 (0.88–1.08)</td>
<td>&lt;0.001</td>
<td>0.33 (0.22–0.45)</td>
<td>&lt;0.001</td>
<td>0.25 (0.13–0.37)</td>
<td>&lt;0.001</td>
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CI, confidence interval; Ln, log-normal; FGF23, fibroblast growth factor 23; P for trend < 0.0001 for all comparisons.
<sup>a</sup>Model A: Adjusted for age, sex, black race, Hispanic ethnicity, diabetes, current smoking, body mass index, use of statins, estimated GFR, and urinary albumin-to-creatinine ratio.
<sup>b</sup>Model B: Adjusted for model A plus phosphate and parathyroid hormone.
for 25D and 1,25D levels in participants with available levels ($n=1502$), and when we substituted iGFR ($n=1409$) for eGFR (Supplemental Tables A and B).

Significant interaction was detected between BMI and lnFGF23 ($P=0.02$) in the multivariable-adjusted model of lnCRP. In analyses stratified by BMI ($<25$, $25–29.9$, $\geq 30$ kg/m$^2$), unadjusted median levels of CRP increased across FGF23 quartiles and BMI categories in a synergistic pattern: Participants in the highest FGF23 and BMI group had the highest CRP level (Figure 1A). Similar interaction was found between BMI and lnFGF23 ($P=0.04$) in the multivariable-adjusted model of lnTNF-$\alpha$. Although similar analyses of lnIL-6 and fibrinogen did not reach significance ($P>0.05$), unadjusted median levels of IL-6 demonstrated a trend similar to that seen for CRP (Figure 1B).

One hundred thirty-five participants (3.5%) had plasma concentrations of IL-6, CRP, TNF-$\alpha$, and fibrinogen in the highest 25th percentile for each analyte and were thus classified as severely inflamed. LnFGF23 was a strong independent risk factor for severe inflammation in univariate (odds ratio [OR], 2.4 per 1-unit higher lnFGF23 [95% confidence interval (CI), 2.0–2.9]) and multivariable-adjusted (OR, 2.0 per 1-unit higher lnFGF23 [95% CI, 1.6–2.5]) logistic regression analyses. This independent relationship was unchanged in models that further adjusted for lnPTH and phosphate (OR, 2.0 per 1-unit higher lnFGF23 [95% CI, 1.5–2.5]). Figure 2 demonstrates the monotonic higher odds of severe inflammation according to ascending quartiles of FGF23 ($P$ for trend < 0.001 for all models). In contrast, lnPTH and phosphate were not associated with severe inflammation in multivariable-adjusted models (data not shown).

**Discussion**

Among patients with CKD, elevated levels of FGF23 are independently associated with higher levels of CRP, IL-6, TNF-$\alpha$, and fibrinogen and with substantially greater odds of manifesting severe inflammation. The associations were independent of renal function, measures of mineral metabolism, and other factors that are known to be associated with inflammation. Furthermore, among the mineral metabolites we tested, FGF23 was most strongly correlated with each inflammatory marker, and FGF23 but not PTH or phosphate was associated with greater odds for severe inflammation in multivariable models. Given the associations between inflammation, atherosclerosis, and vascular calcification (21), and that some studies have shown association between elevated FGF23 and calcium in CKD and ESRD (22,23), these results provide new insight into another potential mechanism underlying the strong associations between elevated FGF23, cardiovascular disease, and mortality. Further studies are needed to determine whether FGF23 might contribute to atherosclerosis and vascular calcification by stimulating inflammation or whether inflammation might contribute to the development of vascular disease through effects on FGF23.

Our results are consistent with prior reports of a direct association between elevated FGF23 and CRP levels in patients with CKD not yet on dialysis (13), and in patients with ESRD undergoing hemodialysis (24). Our results are

![Figure 1](image_url)

*Figure 1. Median inflammatory marker levels across fibroblast growth factor 23 (FGF23) quartiles and body mass index (BMI) categories.*

(A) C-reactive protein (CRP). (B) IL-6. Q1, FGF23 quartile 1 (<95.8 RU/ml); Q2, FGF23 quartile 2 (95.8 to <145.4 RU/ml); Q3, FGF23 quartile 3 ($\geq 145.5$ to <239.1 RU/ml); Q4, FGF23 quartile 4 ($\geq 239.2$ RU/ml).
also consistent with those of prior studies that reported associations between serum phosphate and inflammatory markers in patients with CKD stages 3–4 (25) and those with ESRD (26). These studies did not measure FGF23; however, given the known correlation between elevated phosphate and FGF23 levels, these findings support the link between FGF23 and inflammation that we observed.

Several mechanisms could underlie the cross-sectional association between elevated levels of FGF23 and inflammatory markers. Elevated FGF23 could stimulate inflammation indirectly by reducing levels of 1,25D. FGF23 reduces circulating levels of 1,25D by inhibiting renal 1-hydroxylase and by stimulating 24-hydroxylase, which accelerates degradation of 1,25D (27,28). Because reduced 1,25D levels are associated with higher IL-6 levels (29), and treatment with vitamin D receptor analogues decreased 1,25D levels associated with higher IL-6 levels (29), and treatment with vitamin D receptor analogues decreased CRP levels in CKD (30), it is possible that FGF23-mediated suppression of 1,25D is pro-inflammatory. Although the lack of change in the associations between FGF23 and inflammatory markers after adjustment for 1,25D levels might be considered contrary to this hypothesis, the vitamin D analyses were partially limited by their different time of measurement.

Another possibility is that FGF23 directly induces inflammation. Our group recently reported that FGF23 is capable of inducing signaling in cells that do not express klotho, the FGF23 co-receptor in the kidney, via activation of FGF receptors, which are present in the liver (7), and adipose tissue (31). Thus, it is possible that FGF23 could induce expression of hepatic-derived inflammatory markers, such as CRP (32), or fat-derived cytokines, such as IL-6 and TNF-α (33,34), through klotho-independent effects. Further studies are needed to investigate whether another off-target effect of FGF23 is to simulate expression of pro-inflammatory cytokines in adipocytes and hepatocytes. Alternatively, because klotho may have anti-inflammatory properties (35) and its renal expression is reduced in patients with CKD (36), klotho deficiency might mediate the association between FGF23 excess and inflammation. Reduced klotho expression may be a mechanism or a consequence of elevated FGF23 levels in CKD (2,37). The main limitations to addressing the role of klotho at present are the lack of a reliable in vivo assay for circulating klotho and incomplete understanding of the relative physiologic effects of soluble klotho versus the cell-based transmembrane form.

A third possibility is that inflammation stimulates FGF23. This form of reverse causality could result from the direct bone resorptive effects of inflammation (38), which could stimulate FGF23 production (39). Alternatively, functional iron deficiency induced by inflammation-mediated secretion of hepcidin, which inhibits intestinal absorption of iron and prevents its release from macrophages and hepatic stores for erythropoiesis (40), could drive increased FGF23 levels. Indeed, iron deficiency induces transcription of FGF23, which is cleaved intracellularly, leading to elevated circulating levels of C-terminal FGF23 but normal intact levels (unless patients carry the activating FGF23 mutation of autosomal-dominant hypophosphatemic rickets) (41,42). Of note, no studies have examined the regulation of FGF23 secretion in osteocytes by disordered iron metabolism in CKD. Future studies should measure both intact and C-terminal FGF23 levels in CKD patients with varying degrees of inflammation and iron deficiency.

We confirmed the strong correlation between obesity and inflammation and demonstrated that BMI modifies the association between lnFGF23 and lnCRP and TNF-α. Adipose tissue produces IL6 and TNF-α (33,34), and IL-6 is a major stimulus of CRP synthesis in hepatocytes (32).
Adipocytes also produce leptin to regulate energy intake and energy expenditure (43). Interestingly, leptin levels are elevated in obesity (44) and in CKD (43,45) and correlate with inflammation and adiposity in CKD (45), suggesting a potential link between inflammation, adiposity, and elevated leptin levels. Furthermore, elevated FGF23 is associated with elevated leptin levels (19), and leptin injection induced secretion of FGF23 in leptin-ablated mice (46), suggesting a potential link between FGF23 and leptin. Thus, we can speculate that leptin may mediate the association between elevated FGF23 and inflammation. Further studies are needed to test this hypothesis.

This study has limitations. The cross-sectional design precludes the establishment of a causal relationship or the direction of the association between FGF23 and inflammation. Although our results and those of a previous study support the hypothesis that FGF23 is associated with inflammation (13), we cannot exclude unmeasured confounders. Although renal function was estimated using the MDRD eGFR formula in the primary analysis, a subanalysis using only participants with eGFR showed similar results. Vitamin D levels were not available in all participants, but adjustments for this confounder in the subset with available levels did not alter the results. We used a single measure of FGF23 and inflammatory markers that may not accurately reflect long-term FGF23 levels and inflammatory status. However, because random misclassification due to biologic variability will lead to underestimation of true associations, this limitation is unlikely to explain our findings. Finally, we defined severe inflammation according to the distribution of values observed in our population (quartiles) rather than on clinically relevant cut-points that are currently unknown in CKD.

In conclusion, the current study shows that higher FGF23 levels are independently associated with higher levels of inflammatory markers in patients with CKD and with significantly greater odds of severe inflammation. Future studies should evaluate whether inflammation modifies the association between elevated FGF23 levels and adverse clinical outcomes in CKD.

Acknowledgments

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Disclosures

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