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Association of FGF23 with Incident Sepsis in Community-Dwelling Adults: A Cohort Study

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Abstract

Background Fibroblast growth factor 23 (FGF23) is a hormone that regulates vitamin D activity. Higher circulating FGF23 concentrations have been associated with an increased risk of infection-related hospitalization, but the association of FGF23 with risk of sepsis remains unclear.

Methods We examined the association of FGF23 with incident sepsis events in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national longitudinal cohort of black and white adults ≥45 years of age. Using a case-cohort design, we measured baseline FGF23 in 703 sepsis cases and in 991 participants randomly selected from the REGARDS cohort. We defined sepsis as the presence of a serious infection plus two or more Systemic Inflammatory Response Syndrome criteria. We identified first sepsis hospitalizations during 2003–2012 by adjudicated medical record review. Cox proportional hazards models were used to examine associations of FGF23 with incident sepsis, adjusting for age, sex, race, income, education, smoking, body mass index, physical activity, chronic pulmonary disease, eGFR, urine albumin-creatinine ratio, and high-sensitivity C-reactive protein. We also examined whether associations differed by age, race, sex, and CKD by testing interaction terms.

Results Higher FG23 concentrations were associated with greater risk of sepsis (hazard ratio [HR] per doubling of FGF23, 1.37; 95% CI, 1.22 to 1.54) in models adjusted for sociodemographic and clinical variables. After further adjusting for eGFR, urine albumin-creatinine ratio, and high-sensitivity C-reactive protein, the association was attenuated and no longer statistically significant (HR per doubling, 1.01; 95% CI, 0.85 to 1.21). The results did not statistically differ by strata of age, sex, race, or CKD.

Conclusions In community-dwelling adults, higher FGF23 concentrations were not independently associated with higher risk of sepsis.

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Introduction

Fibroblast growth factor 23 (FGF23) plays a central role in the regulation of phosphorus and vitamin D metabolism. The primary site of action of FGF23 is the kidney, where it suppresses synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25 $[OH]_2D$), by inhibiting the expression of the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and by inducing the expression of 24-hydroxylase, the primary catabolic pathway for vitamin D (1).

Increased secretion of FGF23 by bone cells is important for the maintenance of phosphorus balance in the setting of phosphorus excess (like high dietary phosphorus intake or kidney disease). However, sustained elevation in circulating FGF23 concentrations may have long-term consequences. Numerous epidemiologic studies have shown that higher FGF23 concentrations are associated with all-cause and cardiovascular mortality, independently of other factors (1–6). In addition, experimental data show that FGF23 enhances inflammation and impairs innate mmunity (7).

Sepsis is the syndrome of a serious infection complicated by systemic and organ dysfunction, often leading to shock and death (8,9). Higher FGF23 is associated with greater risk of infection-related hospitalization in individuals with CKD (10) and in older community-dwelling adults (11). However, it is unclear if FGF23 is associated with more serious infections complicated by sepsis.

In this study, we examined the association of plasma FGF23 concentrations with risk of incident sepsis in participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. We hypothesized that higher circulating FGF23 concentrations would be associated with increased incidence of sepsis, independently of potential confounders.

Materials and Methods

The REGARDS study is a national, population-based, longitudinal cohort study designed to examine underlying causes for racial and regional differences in

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stroke. Details of the study design have been reviewed elsewhere (12). Briefly, the study was designed to provide an approximately equal representation of men and women and oversampled individuals who were black and individuals living in the Southeastern United States. Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants' sociodemographics; cardiovascular risk factors; and use of antihypertensive, antiglycemic, and cholesterol-lowering medication. After this call, health professionals conducted an in-home study visit that included an electrocardiograph recording, BP, height, weight measurements, an inventory of medications, and collection of blood and urine samples. Overall, 30,239 individuals were enrolled between January 2003 and October 2007 (42% black, 55% women). Follow-up was conducted by computer-assisted telephone interviews every 6 months for suspected medical events (or reported by proxy in case of participants unable to respond).

The REGARDS study protocol was approved by the institutional review boards governing research in human subjects at the participating centers, and all participants provided written informed consent.

Primary Exposure

The primary exposure was baseline plasma FGF23, measured in previously collected samples from the in-home visit that were stored at −80°C after a single thaw using a commercially available C-terminal ELISA (Immutopics, Santa Clara, CA), with coefficients of variation <10%.

Outcome of Interest

The outcome of interest was first sepsis hospitalization. Methods for ascertaining sepsis in REGARDS have been described elsewhere (13). Using logs from the semiannual follow-ups, we retrieved medical records for all hospitalizations attributed to a serious infection (14). Two trained research personnel independently reviewed each hospital record to confirm the presence of a serious infection as a major reason for hospital presentation and to identify pertinent physiologic measures and laboratory assay test results from the first 28 hours of hospitalization, a period designed to encompass the initial emergency department visit and one full day in the hospital. We defined sepsis events as hospitalizations with two or more Systemic Inflammatory Response Syndrome criteria (8). In sensitivity analyses, we repeated the analysis limited to sepsis events with a Sequential Organ Failure Assessment (SOFA) score of two or more (9). We identified sepsis events occurring during 2003–2012.

Covariates of Interest

Age, sex, race, body mass index (BMI), waist circumference, smoking history, annual family income, and educational attainment were determined by self-report. Systolic and diastolic BP were defined as the average of two seated measures taken after a 5-minute rest. History of coronary heart disease was defined as having any of the following: evidence of myocardial infarction on the baseline electrocardiograph, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous coronary intervention), or self-reported history of myocardial infarction. Diabetes was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration of ≥126 mg/dl or higher, or a nonfasting blood glucose concentration of ≥200 mg/dl. Chronic pulmonary disease was defined as use of pulmonary medications, including β-agonists; leukotriene inhibitors; inhaled corticosteroids; combination inhalers; and other pulmonary medications such as ipratropium, cromolyn, aminophylline, and theophylline. High-sensitivity C-reactive protein (hsCRP) was measured by particle-enhanced immunonephelometry (BNII nephelometer; Dade Behring). eGFR was determined from isotope dilution mass spectrometry–traceable serum creatinine measurements using the CKD–Epidemiology Collaboration equation. Urine albumin measured by the BNII ProSpec nephelometer (Siemens AG) and urine creatinine measured by the rate Jaffé method (Roche/Hitachi, Basel, Switzerland) were used to calculate the urine albumin-creatinine ratio (ACR). CKD was defined as an eGFR <60 ml/min per 1.73 m^2 or an ACR ≥30 mg/g.

Derivation of Case Cohort

We used a case-cohort study design to provide an unbiased estimate of the relative hazard of an outcome(s) without requiring measurement of biomarkers in all REGARDS participants (15). Cases included participants who developed incident sepsis. The subcohort sample (comparison group) was selected using stratified sampling to ensure sufficient representation among demographic groups. All participants with at least one follow-up contact (n=29,653) were categorized into 20 strata based on age (45–54, 55–64, 65–74, 75–84, ≥85 years), race (black or white), and sex (male or female). In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% female, 50% male, 20% age 45–54, 20% age 55–64, 25% age 65–74, 25% age 75–84, and 10% age ≥85. Weights were calculated to allow upweighting of cohort random sample participants and cases back to the original sample. The subcohort was sampled without regard to FGF23 status or sepsis outcomes. For the sepsis cases, due to finite resources, we selected a 50% random sample of all REGARDS participants who developed sepsis for measurement of FGF23 in stored plasma samples.

Statistical Analyses

Descriptive statistics were used to compare participant characteristics within the cohort random sample overall and across quartiles of FGF23, using appropriate weights to account for the stratified sampling design. After confirming the proportionality of hazards, Cox regression models for case-cohort studies were used to estimate the hazard ratio (HR) of incident sepsis as a function of baseline FGF23 (16). Model 1 was adjusted for age, sex, race, region of recruitment, annual family income, and educational attainment. Model 2 was adjusted for covariates in model 1 and current smoking, BMI, diabetes status, physical activity, and chronic pulmonary disease. Model 3 was adjusted for covariates in model 2 and eGFR, log-transformed ACR, and log-transformed hsCRP. In all models, FGF23 was analyzed in quartiles, with the lowest quartile serving as the referent group and on a continuous scale after log base 2 transformation (interpreted as "per doubling" of FGF23). We examined for effect modification by age (≥69 versus <69 years), race, sex, and CKD status by testing the statistical significance of a multiplicative interaction term in the models (modeling FGF23 as

Table 1. Baseline characteristics of the study population by quartiles of baseline fibroblast growth factor 23 concentrations in the random subcohort

Characteristics	Overall	Quartile 1 (<53 RU/ml)	Quartile 2 (53–70 RU/ml)	Quartile 3 (70.1–101 RU/ml)	Quartile 4 (>101 RU/ml)
Weighted *N*	27,959	6874	7238	6780	7067
Age, yr	65.0 (64.5 to 65.6)	62.2 (61.2 to 63.2)	64.3 (63.3 to 65.3)	66.4 (65.3 to 67.4)	67.3 (66.3 to 68.4)
Male sex	45	58	46	46	30
Black	41	46	37	45	36
BMI, kg/m^2	29.2 (28.7 to 29.6)	28.4 (27.6 to 29.1)	29.1 (28.3 to 29.9)	29.7 (28.9 to 30.5)	29.4 (28.5 to 30.4)
SBP, mm Hg	127.2 (126.1 to 128.4)	127.9 (125.2 to 130.6)	126.6 (124.7 to 128.6)	127.5 (125.0 to 129.9)	126.7 (124.8 to 128.9)
DBP, mm Hg	76.3 (75.7 to 76.9)	77.8 (76.4 to 79.1)	76.8 (75.5 to 78.1)	76.2 (74.7 to 77.7)	74.5 (73.3 to 75.7)
< HS graduate	12	11	10	12	16
Income <20K/yr	16	14	11	18	21
Smoking (current)	14	12	9	14	21
Exercise (none)	34	31	29	31	43
Comorbidities					
Diabetes	21	17	15	22	28
CHD	17	13	11	16	27
COPD	9	4	9	10	12
eGFR, ml/min per 1.73 m^2		93.3 (91.1 to 95.6)	87.1 (84.9 to 89.2)	80.2 (77.8 to 82.6)	69.1 (66.0 to 72.2)
<60 ml/min per 1.73 m^2	10	2	5	8	23
ACR, mg/g	7.1 (4.5–14.4)	6.4 (4.2–11.7)	6.6 (4.2–11.3)	7.6 (5.1–14.4)	9.3 (4.9–26.6)
≥30 mg/g	13	8	8	15	20
hsCRP, mg/L	2.2 (0.9–4.9)	1.6 (0.7–3.9)	2.0 (0.9–4.1)	2.4 (1.0–5.2)	2.8 (1.1–6.3)

Values are presented as means (95% CIs), median (interquartile range), or proportions. BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HS, high school; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ACR, urine albumin-creatinine ratio; hsCRP, high-sensitivity C-reactive protein.

Table 2. Hazard ratios (95% CIs) of incident sepsis as a function of baseline fibroblast growth factor 23 concentrations

Measure	Quartile 1 (<53 RU/ml)	Quartile 2 (53–70 RU/ml)	Quartile 3 (70.1–101 RU/ml)	Quartile 4 (>101 RU/ml)	Per Doubling of FGF23
N	233	255	243	260	991
Events	107	118	181	297	703
Model 1[a]	Reference	1.08 (0.76 to 1.53)	1.55 (1.10 to 2.16)	2.32 (1.65 to 3.27)	1.37 (1.22 to 1.54)
Model 2[b]	Reference	0.96 (0.66 to 1.40)	1.25 (0.86 to 1.82)	1.62 (1.10 to 2.37)	1.21 (1.06 to 1.39)
Model 3[c]	Reference	0.81 (0.54 to 1.21)	0.95 (0.63 to 1.43)	0.97 (0.62 to 1.51)	1.01 (0.85 to 1.21)

[a]Model 1 is adjusted for age, sex, race, region of recruitment, annual family income, and educational attainment.
[b]Model 2 is adjusted for variables in model 2 plus current smoking, body mass index, diabetes status, physical activity, and chronic pulmonary disease status.
[c]Model 3 is adjusted for variables in model 3 and eGFR, log-transformed urine albumin-creatinine ratio, and log-transformed high-sensitivity C-reactive protein.

a categoric variable in quartiles). A two-tailed *P* value <0.05 was considered statistically significant, except for analyses in which interaction terms were tested, where a *P* value <0.10 was considered statistically significant.

Results

Study Population Characteristics

After excluding 95 participants who had missing FGF23 data or who had a history of sepsis at baseline, we included a total of 703 individuals who developed sepsis during follow-up (cases) and 991 individuals in the random subcohort.

Table 1 depicts the overall characteristics of participants in the random subcohort and by quartile of baseline FGF23. The study sample had a median age of 65 years (95% CI, 64 to 66). Participants with higher FGF23 concentrations were more likely to be black; have higher BMI, lower educational achievement, and lower income; were more likely to be currently smoking, physically inactive, and have a history of diabetes; and had higher ACR, lower eGFR, and higher hsCRP concentrations.

Associations of FGF23 with Sepsis

Table 2 depicts associations of baseline FGF23 concentrations with incident sepsis in Cox proportional hazard regression models. There was a graded increase in the HR of incident sepsis with increasing quartiles of FGF23 in the analysis adjusted for age, sex, race, geographic region of residence, annual family income, and educational attainment (FGF23 <53 RU/ml, reference; FGF23 53–70 RU/ml, HR, 1.08; 95% CI, 0.76 to 1.53; FGF23 70.1–101 RU/ml, HR, 1.55; 95% CI, 1.10 to 2.16; FGF23 >101 RU/ml, HR, 2.32; 95% CI, 1.65 to 3.27 RU/ml). The relationship was attenuated but remained statistically significant when further adjusted for demographic and clinical variables (model 2). However, in the fully adjusted model that added eGFR, ACR, and hsCRP, the association between FGF23 and incident sepsis was no longer statistically significant (FGF23 <53 RU/ml, reference; FGF23 53–70 RU/ml, HR, 0.81; 95% CI, 0.54 to 1.21; FGF23 70.1–101 RU/ml, HR, 0.95; 95% CI, 0.63 to 1.43; FGF23 >101 RU/ml, HR, 0.97; 95% CI, 0.62 to 1.51 RU/ml). eGFR and ACR were the two variables most responsible for attenuation of the effect estimate. Similar results were observed when FGF23 was examined on a continuous scale. In the fully adjusted model that adjusted for kidney function at baseline, the association between higher FGF23 and incident sepsis was no longer significant (HR, 1.01; 95% CI, 0.85 to 1.21).

In a sensitivity analysis limiting sepsis events to those with a SOFA score of two or more (Supplemental Table 1), the results were similar: there was a significant association of higher FGF23 with greater risk of sepsis in multivariable models adjusted for sociodemographic and clinical factors, but this association was attenuated and no longer significant after adjusting for measures of kidney function at baseline.

Stratified Analyses

We performed several analyses stratified by age, sex, race, and CKD (Table 3). There were no significant differences in the association of FGF23 with incident sepsis in analyses stratified by any of these variables, with the *P* value for interaction >0.10 for all analyses.

Discussion

In this study of community-dwelling adults, there was no statistically significant association of higher FGF23 concentrations with greater risk of sepsis in multivariable-adjusted analyses that accounted for kidney function. Further, we did not find that the association of FGF23 with sepsis differed by age, sex, race, or CKD status.

Several lines of evidence support the notion that FGF23 affects innate immunity. Because FGF23 inhibits the production of CYP27B1—the enzyme that catalyzes the conversion of 25(OH)D to $1,25(OH)_2D$—elevated FGF23 concentration can reduce $1,25(OH)_2D$-dependent synthesis of cathelicidin, an important antimicrobial peptide that acts against several bacteria, viruses, and fungi; can disrupt biofilm; promotes phagocytosis; and induces chemotaxis of other immune cells to sites of infection (7,17–19). In addition, elevated FGF23 concentrations have been shown to limit leukocyte recruitment, neutrophil chemotaxis, and impair host defense in animal models of CKD (20,21). Consistent with these data, prior studies have shown that higher FGF23 concentrations were associated with higher risk of hospitalization for infection in individuals with ESKD and in community-dwelling adults. In contrast, we found no statistically significant association of FGF23 with risk of sepsis in REGARDS participants.

The reasons for these discrepancies are unclear. One possible explanation is that we investigated incident sepsis, whereas prior epidemiologic studies examined hospitalizations for infection. Because the former includes the most

Table 3. Hazard ratios (95% CIs) of incident sepsis as a function of baseline fibroblast growth factor 23 concentrations stratified by sex, race, age, and presence or absence of CKD

Measure	Quartile 1 (<53 RU/ml)	Quartile 2 (53–70 RU/ml)	Quartile 3 (70.1–101 RU/ml)	Quartile 4 (>101 RU/ml)	Per Doubling of FGF23	*P* Value for Interaction
Women						0.93
N	82	122	125	169	498	
Events	36	49	85	170	340	
Model 1[a]	Reference	1.08 (0.61 to 1.91)	1.74 (1.01 to 2.99)	2.32 (1.38 to 3.91)	1.35 (1.18 to 1.56)	
Model 2[b]	Reference	0.99 (0.52 to 1.92)	1.17 (0.60 to 2.25)	1.36 (0.74 to 2.51)	1.17 (0.97 to 1.39)	
Model 3[c]	Reference	0.98 (0.48 to 1.98)	1.08 (0.51 to 2.30)	0.97 (0.46 to 2.02)	1.02 (0.81 to 1.29)	
Men						
N	151	133	118	91	493	
Events	71	69	96	127	363	
Model 1[a]	Reference	1.04 (0.65 to 1.67)	1.42 (0.91 to 2.22)	2.72 (1.66 to 4.46)	1.51 (1.22 to 1.87)	
Model 2[b]	Reference	0.98 (0.58 to 1.64)	1.39 (0.84 to 2.29)	2.49 (1.41 to 4.39)	1.45 (1.14 to 1.83)	
Model 3[c]	Reference	0.73 (0.42 to 1.28)	0.94 (0.54 to 1.65)	1.19 (0.61 to 2.32)	0.96 (0.70 to 1.30)	
Black						0.38
N	134	120	128	115	497	
Events	41	42	53	93	229	
Model 1[a]	Reference	1.38 (0.79 to 2.44)	1.35 (0.79 to 2.29)	3.65 (2.12 to 6.29)	1.39 (1.19 to 1.63)	
Model 2[b]	Reference	1.26 (0.68 to 2.34)	1.14 (0.62 to 2.08)	2.99 (1.59 to 5.65)	1.20 (0.99 to 1.46)	
Model 3[c]	Reference	1.04 (0.54 to 1.98)	0.76 (0.37 to 1.58)	1.99 (0.98 to 4.02)	1.32 (1.03 to 1.70)	
White						
N	99	135	115	145	494	
Events	66	76	128	204	474	
Model 1[a]	Reference	0.94 (0.59 to 1.49)	1.63 (1.03 to 2.56)	1.98 (1.27 to 3.09)	1.36 (1.14 to 1.61)	
Model 2[b]	Reference	0.88 (0.53 to 1.46)	1.41 (0.85 to 2.35)	1.43 (0.85 to 2.39)	1.33 (1.12 to 1.56)	
Model 3[c]	Reference	0.74 (0.43 to 1.28)	1.17 (0.67 to 2.03)	0.79 (0.44 to 1.45)	0.95 (0.76 to 1.19)	
Age ≥69						0.44
N	79	105	119	155	458	
Events	38	59	97	150	344	
Model 1[a]	Reference	1.22 (0.69 to 2.17)	1.83 (1.06 to 3.16)	2.43 (1.39 to 4.21)	1.51 (1.22 to 1.87)	
Model 2[b]	Reference	0.94 (0.54 to 1.64)	1.43 (0.86 to 2.37)	1.76 (1.02 to 3.02)	1.13 (0.95 to 1.35)	
Model 3[c]	Reference	0.85 (0.47 to 1.55)	1.04 (0.57 to 1.89)	1.02 (0.52 to 1.99)	0.92 (0.72 to 1.17)	
Age <69						
N	154	150	124	105	533	
Events	69	59	84	147	359	
Model 1[a]	Reference	1.08 (0.68 to 1.72)	1.55 (0.98 to 2.44)	2.81 (1.78 to 4.43)	1.31 (1.14 to 1.51)	
Model 2[b]	Reference	0.98 (0.53 to 1.81)	1.41 (0.77 to 2.59)	1.71 (0.93 to 3.14)	1.39 (1.13 to 1.73)	
Model 3[c]	Reference	0.67 (0.34 to 1.32)	0.88 (0.45 to 1.72)	0.84 (0.41 to 1.70)	1.20 (0.93 to 1.55)	
CKD[d]						0.84
N	22	40	56	101	219	
Events	25	28	64	140	257	
Model 1[a]	Reference	0.90 (0.37 to 2.21)	1.19 (0.53 to 2.69)	1.61 (0.78 to 3.34)	1.19 (0.97 to 1.46)	
Model 2[b]	Reference	0.75 (0.28 to 2.03)	1.04 (0.41 to 2.64)	1.37 (0.57 to 3.26)	1.19 (0.93 to 1.51)	
Model 3[c]	Reference	0.80 (0.28 to 2.31)	0.77 (0.27 to 2.20)	0.83 (0.28 to 2.45)	0.96 (0.69 to 1.33)	
No CKD						
N	198	207	171	149	725	
Events	78	85	105	140	408	
Model 1[a]	Reference	1.13 (0.75 to 1.73)	1.58 (1.04 to 2.39)	2.09 (1.34 to 3.27)	1.38 (1.14 to 1.67)	
Model 2[b]	Reference	1.01 (0.64 to 1.59)	1.36 (0.88 to 2.12)	1.57 (0.97 to 2.52)	1.16 (0.94 to 1.43)	
Model 3[c]	Reference	0.85 (0.54 to 1.36)	1.07 (0.66 to 1.73)	1.04 (0.62 to 1.76)	1.01 (0.82 to 1.26)	

[a]Model 1 is adjusted for age (except for age-stratified models), sex (except for sex-stratified models), race (except for race-stratified models), region of recruitment, annual family income, and educational attainment.
[b]Model 2 is adjusted for variables in model 2 plus current smoking, body mass index, diabetes status, physical activity, and chronic pulmonary disease status.
[c]Model 3 is adjusted for variables in model 3 and eGFR, log-transformed urine albumin-creatinine ratio, and log-transformed high-sensitivity C-reactive protein.
[d]CKD defined as an eGFR <60 ml/min per 1.73 m^2 or an albumin-creatinine ratio ≥30 mg/g at the baseline visit.

severe clinical presentations leading to organ dysfunction, whereas the latter includes a variety of presentations with lower acuity, it may be that FGF23 is an independent marker of infection risk in general but not those infections that lead to sepsis. In addition, sepsis events were adjudicated using detailed hospital record review in REGARDS, whereas hospitalization due to infection was identified using International Classification of Diseases, Ninth Revision (ICD-9) coding from discharge summaries in other studies (10,11).

It is notable that eGFR and ACR were the primary variables that attenuated the association of FGF23 with sepsis risk in multivariable models. Low eGFR and high ACR are among the strongest risk factors for elevated FGF23 and have been linked to higher risk of sepsis. These results suggest the link between higher FGF23 and infection in this and prior studies is, at least in part, driven by kidney disease, and underscores the importance of adjusting for measures of kidney function when assessing the association of FGF23 with infectious outcomes.

Our study had several limitations. Because of the nature of the analysis, the results are observational. Next, serum FGF23 concentrations were measured at a single time point, which may have led to exposure misclassification for some study participants because FGF23 concentrations may have changed between the time they were measured and the occurrence of the sepsis event. In addition, the method used to capture sepsis, through a sequential process of screening records by ICD codes and then relying on physician documentation of suspected infections, is not perfectly sensitive. Next, we measured total (C-terminal) FGF23 in this study. Associations of free or intact FGF23 may differ from associations of total FGF23 with sepsis.

These limitations notwithstanding, our study had many strengths. First, to our knowledge, this is the first study to evaluate the association of FGF23 concentrations with incidence of sepsis in community-dwelling adults. Second, given that this study measured FGF23 at the relatively healthy baseline of participants in a population-based cohort, the study minimizes potential indication bias and reverse causality that can be introduced in measuring FGF23 during acute illness (22). Third, the study minimizes misclassification of the outcome by adjudicating sepsis events through independent chart review of clinical data rather than relying solely on ICD codes. Fourth, the large amount of data collected by the REGARDS baseline study visit allows ample adjustment for multiple, relevant cofounders in the analysis.

In conclusion, higher FGF23 concentrations were not independently associated with higher risk of sepsis in community-dwelling adults after accounting for kidney function. These results suggest that FGF23 does not play a major role in the development of sepsis and, as such, is not likely an important target for reducing risk of sepsis in the community.

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Author Contributions

O. Gutiérrez was responsible for funding acquisition and provided supervision; O. Gutiérrez, S. Judd, and H. Wang were responsible for formal analysis; O. Gutiérrez and S. Paul wrote the original draft; O. Gutiérrez and H. Wang conceptualized the study and were responsible for investigation and methodology; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000942020/-/DCSupplemental.

Supplemental Table 1. Hazard ratio (95% confidence interval) of incident sepsis (defined using SOFA criteria) as a function of baseline fibroblast growth factor 23 concentrations.

References

1. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359: 584–592, 2008
2. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA* 305: 2432–2439, 2011
3. Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L, Larsson TE: Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. *Kidney Int* 83: 160–166, 2013
4. Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L, Larsson TE: Serum FGF23 and risk of cardiovascular events in relation to mineral metabolism and cardiovascular pathology. *Clin J Am Soc Nephrol* 8: 781–786, 2013
5. Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, Ujszaszi A, Kiss I, Rosivall L, Kosa J, Lakatos P, Kovesdy CP, Mucsi I: Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. *J Am Soc Nephrol* 22: 956–966, 2011
6. Gutiérrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, Sarwar A, Hoffmann U, Coglianese E, Christenson R, Wang TJ, deFilippi C, Wolf M: Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 119: 2545–2552, 2009
7. Bacchetta J, Salusky IB, Hewison M: Beyond mineral metabolism, is there an interplay between FGF23 and vitamin D in innate immunity? *Pediatr Nephrol* 28: 577–582, 2013
8. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM,

Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 41: 580–637, 2013
9. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315: 801–810, 2016
10. Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK: Low vitamin D and high fibroblast growth factor 23 serum levels associate with infectious and cardiac deaths in the HEMO study. *J Am Soc Nephrol* 27: 227–237, 2016
11. Nowak KL, Bartz TM, Dalrymple L, de Boer IH, Kestenbaum B, Shlipak MG, Garimella PS, Ix JH, Chonchol M: Fibroblast growth factor 23 and the risk of infection-related hospitalization in older adults. *J Am Soc Nephrol* 28: 1239–1246, 2017
12. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G: The reasons for geographic and racial differences in stroke study: Objectives and design. *Neuroepidemiology* 25: 135–143, 2005
13. Wang HE, Donnelly JP, Griffin R, Levitan EB, Shapiro NI, Howard G, Safford MM: Derivation of novel risk prediction scores for community-acquired sepsis and severe sepsis. *Crit Care Med* 44: 1285–1294, 2016
14. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303–1310, 2001
15. Barlow WE, Ichikawa L, Rosner D, Izumi S: Analysis of case-cohort designs. *J Clin Epidemiol* 52: 1165–1172, 1999
16. Onland-Moret NC, van der A DL, van der Schouw YT, Buschers W, Elias SG, van Gils CH, Koerselman J, Roest M, Grobbee DE, Peeters PH: Analysis of case-cohort data: A comparison of different methods. *J Clin Epidemiol* 60: 350–355, 2007
17. Turner J, Cho Y, Dinh NN, Waring AJ, Lehrer RI: Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. *Antimicrob Agents Chemother* 42: 2206–2214, 1998
18. Kamen DL, Tangpricha V: Vitamin D and molecular actions on the immune system: Modulation of innate and autoimmunity. *J Mol Med (Berl)* 88: 441–450, 2010
19. Nijnik A, Hancock RE: The roles of cathelicidin LL-37 in immune defences and novel clinical applications. *Curr Opin Hematol* 16: 41–47, 2009
20. Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstädt HJ, Meersch M, Unruh M, Zarbock A: FGF23 signaling impairs neutrophil recruitment and host defense during CKD. *J Clin Invest* 126: 962–974, 2016
21. Yang K, Peretz-Soroka H, Wu J, Zhu L, Cui X, Zhang M, Rigatto C, Liu Y, Lin F: Fibroblast growth factor 23 weakens chemotaxis of human blood neutrophils in microfluidic devices. *Sci Rep* 7: 3100, 2017
22. Schnedl C, Fahrleitner-Pammer A, Pietschmann P, Amrein K: FGF23 in acute and chronic illness. *Dis Markers* 2015: 358086, 2015

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