

Fibroblast Growth Factor-23 and the Long-Term Risk of Hospital-Associated AKI among Community-Dwelling Older Individuals

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Summary

Background and objectives AKI occurs frequently in older persons. Elevated circulating fibroblast growth factor-23 (FGF-23), a known marker of impaired mineral metabolism, may also reflect tubular dysfunction and risk of AKI. This study evaluated FGF-23 as well as traditional markers of kidney disease, namely urine albumin-to-creatinine ratio (UACR) and creatinine-cystatin C estimated GFR (eGFR_{CrCysC}), as risk factors for AKI in elderly individuals.

Design, setting, participants, & measurements Plasma FGF-23, UACR, and eGFR_{CrCysC} were measured in 3241 community-dwelling elderly individuals in the Cardiovascular Health Study. Hospitalization for AKI was defined by International Classification of Diseases, Ninth Revision, Clinical Modification codes. Associations of each biomarker with AKI were evaluated using Cox proportional hazards models adjusted for demographics, cardiovascular risk factors, and biomarkers of kidney function.

Results The mean participant age was 78 years; 60% of participants were women and 16% were African American. The median (interquartile range) values of biomarkers were as follows: FGF-23, 70 RU/ml (53, 99); UACR, 8.88 mg/g (4.71, 20.47); and eGFR_{CrCysC}, 71 ml/min per 1.73 m² (59, 83). Hospitalized AKI occurred in 119 participants over 10.0 years of median follow-up. In fully adjusted analyses, compared with the lowest quartiles, the highest quartiles of FGF-23 (≥ 100 RU/ml) and UACR (≥ 20.9 mg/g) were associated with AKI (FGF-23: hazard ratio [HR], 1.99; 95% confidence interval [95% CI], 1.04 to 3.80; and UACR: HR, 3.35; 95% CI, 1.83 to 6.13). Compared with the highest quartile, the lowest quartile of eGFR_{CrCysC} (< 57 ml/min per 1.73 m²) was associated with AKI with an HR of 2.15 (95% CI, 1.21 to 3.82).

Conclusions FGF-23 adjusted for albuminuria, cardiovascular disease risk factors, and baseline eGFR is independently associated with a higher risk of AKI hospitalizations in community-dwelling elderly individuals. Further studies to understand the nature of this association are warranted.

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Introduction

Community-acquired AKI is an increasingly common reason for hospital admissions in the United States over the past decade (1). Patients hospitalized for AKI are at higher risk of developing ESRD and death (2,3). In addition, 46% of individuals who develop AKI will not fully recover and will be left with CKD, and 58% of patients will be hospitalized again within 1 year (1,2).

Because older persons are at higher risk for AKI (4), identifying AKI risk factors among older persons is particularly important. In a prior publication from the Cardiovascular Health Study (CHS), patient demographics (older age, male sex, nonwhite race), cardiovascular risk factors (serum creatinine, diabetes, hypertension, current smoking), inflammatory biomarkers (C-reactive protein, fibrinogen, albumin, white blood cell count), and subclinical cardiovascular

disease (low ankle-arm index, common and internal carotid intima-media thickness) were identified as risk factors for AKI (5). The urine albumin-to-creatinine ratio (UACR) was not evaluated in this prior analysis.

Fibroblast growth factor-23 (FGF-23) is a phosphaturic hormone that is associated with increased risks of cardiovascular disease and progression to ESRD (6,7). Recent studies suggest that high circulating FGF-23 concentrations may also be due in part to tubular FGF-23 resistance, a state of tubular dysfunction that may also increase risk of AKI (8). Although recent evidence suggests that FGF-23 is elevated at the time of AKI (9), there are no studies of which we are aware that have evaluated whether circulating levels of FGF-23 are a risk factor for AKI incidence. Recent studies have also suggested that estimated GFR based on cystatin C or combined creatinine-cystatin C (eGFR_{CrCysC}) provides a more accurate measure of

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Table 1. Baseline characteristics by quartiles of FGF-23

Characteristic	Fibroblast Growth Factor-23 Quartile			
	1	2	3	4
Range (RU/ml)	<54	54–70	71–100	>100
Participants (<i>n</i>)	824	821	807	789
Demographics				
Age (yr)	77±5	78±5	78±5	79±5
Women	53	57	64	67
African American	23	15	12	14
Prevalent disease				
History of stroke	5	7	5	8
History of heart failure	3	5	7	21
History of coronary heart disease	19	20	25	34
Cardiovascular risk factors				
Hypertension	57	61	63	69
Diabetes	15	20	23	29
Current smoker	5	6	10	10
Body mass index (kg/m ²)	26.3±4.3	26.6±4.2	27.3±4.6	27.6±5.3
Total cholesterol (mg/dl)	200±37	202±38	203±41	203±42
Albumin (g/dl)	3.84±0.30	3.85±0.30	3.82±0.29	3.81±0.31
C-reactive protein (mg/L)	1.90 (0.91, 3.92)	2.21 (0.99, 4.68)	2.87 (1.28, 5.82)	3.14 (1.51, 6.74)
Kidney function				
eGFR _{CrCysC} (ml/min per 1.73 m ²)	77±14	71±15	66±15	56±19
UACR (mg/g)	6.95 (4.29, 14.42)	8.43 (4.52, 17.20)	8.33 (4.72, 18.99)	13.55 (6.15, 55.12)

Data are presented as the mean ± SD, median (interquartile range), or percentage. FGF-23, fibroblast growth factor-23; eGFR_{CrCysC}, creatinine-cystatin C estimated GFR; UACR, urine albumin-to-creatinine ratio.

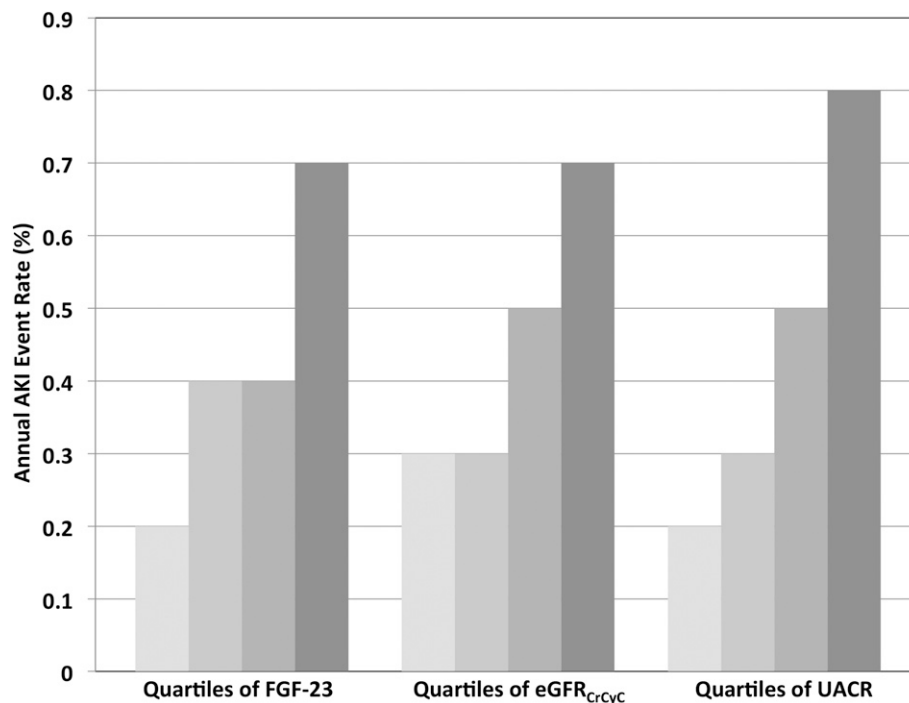


Figure 1. | Annual AKI event rate. The bar chart graphs the annual AKI incidence (number events per person-years at risk) by quartiles of FGF-23, eGFR_{CrCysC}, and UACR. eGFR_{CrCysC}, creatinine-cystatin C estimated GFR; FGF-23, fibroblast growth factor-23; UACR, urine albumin-to-creatinine ratio.

kidney function and may be more strongly associated with cardiovascular outcomes and all-cause mortality (10–15). Two recent studies of middle-aged individuals have also suggested that UACR may be associated with AKI; however, there are few studies that have focused exclusively on elderly individuals or evaluated all three biomarkers (FGF-23, UACR, and eGFR_{CrC_yC}) (2,3,16). We therefore evaluated FGF-23, UACR, and eGFR_{CrC_yC}, three different manifestations of kidney health, as risk factors for AKI hospitalizations in the CHS, a community-dwelling population of older adults. We also evaluated whether the relationships were independent of one another.

Materials and Methods

Study Population

The CHS enrolled 5201 adults aged ≥ 65 into a prospective longitudinal cohort to evaluate risk factors for cardiovascular disease (17,18). Community participants were enrolled between 1989 and 1990 from four communities in the United States (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania) using Medicare eligibility lists. An additional 687 African-American participants were enrolled between 1992 and 1993. Eligible participants had an expectation to remain in the geographic area for 3 years, had no history of cancer, and were able to provide written informed consent. Physical examinations were conducted annually through 1998–1999 and in 2005–2006. Telephone interviews took place semi-annually from 1998 to 1999 and biannually thereafter. All participants provided research access to their complete medical record and Medicare billing claims in follow-up. UACR was measured at the 1996–1997 visit; therefore, this study was restricted to 3406 active enrollees at the 1996–1997 visit. Participants were excluded if samples were not available for FGF-23 measurement ($n=69$), serum creatinine ($n=0$), or cystatin C ($n=0$), or if urine was not available for UACR ($n=92$). Enrollees with prior hospitalizations with AKI between 1989 and 1996 were excluded from the analysis ($n=4$). The final analytic cohort for this analysis comprised 3241 individuals.

Outcome Measure

All administrative discharge summaries were retrieved for the entire CHS cohort from 1996 through 2010. Hospitalization for AKI was defined by hospital discharge International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for AKI, including ICD-9-CM codes for 584 and 584.5–584.9 as the primary diagnosis (19). ICD-9-CM codes for determining AKI have previously been shown to provide very high specificity (97.7%) yet low sensitivity (35.4%) (19).

Exposure Variables

Fasting blood specimens collected in 1996–1997 were collected in EDTA and immediately stored at -70°C . Samples were thawed in 2010 for measurement of FGF-23 (RU/ml). FGF-23 was measured using a C-terminal ELISA kit (Immutopics International, San Clemente, CA) (20). The intra- and interassay reliability was measured with coefficients of variation ranging from 7.4% to 10.6%.

A random urine sample obtained from each participant during the same visit was used to measure UACR. Urine albumin was measured by nephelometry using the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA). Urinary creatinine was measured using a Kodak Ektachem 700 Analyzer (Eastman Kodak Company, Rochester, NY). UACR was calculated in milligrams per gram (21).

The colorimetric method was also used to measure serum creatinine (milligrams per decaliter) using a Kodak Ektachem 700 Analyzer (Eastman Kodak Company). The coefficient of variation for creatinine among monthly controls was 1.94 (1.16, 3.60%). Serum creatinine was calibrated as previously described (22,23). Serum cystatin C concentrations were measured using a BN II nephelometer (Siemens, Munich, Germany). eGFR_{CrC_yC} was calculated using the recently published combined cystatin C and creatinine-based equation (10).

Covariates

Model covariates were abstracted at the 1996–1997 study visit and included demographics (age, sex, race), prevalent cardiovascular disease (clinical diagnosis of prior stroke, heart failure, or coronary heart disease), and cardiovascular risk factors (smoking status [current, former, or never], hypertension [systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medications], diabetes [fasting glucose ≥ 126 mg/dl or use of oral hypoglycemic medications or insulin], total cholesterol, and high sensitivity C-reactive protein).

Statistical Analyses

Because many prior papers in other cohorts and several prior manuscripts from CHS have described characteristics by levels of eGFR_{CrC_yC} or UACR, we elected to describe the cohort by FGF-23 levels. Because there are no established clinical cutpoints for FGF-23, participants were divided into quartiles of FGF-23 and the distribution of covariates across the FGF-23 groups was evaluated. Correlations between FGF-23, UACR, and eGFR_{CrC_yC} were calculated. Time at risk was defined as the elapsed time from the 1996–1997 examination until the first occurrence of AKI. Annual incidence rates for AKI were calculated as the number of events divided by the participants' total time at risk. Natural piecewise cubic spline functions were constructed for FGF-23, UACR, and eGFR_{CrC_yC} with prespecified knots placed at the quartiles of FGF-23, UACR, and eGFR_{CrC_yC}. Nested Cox proportional hazards models were used to estimate the relative hazard of AKI after adjustment for relevant confounding variables. Four sequential models were performed: (1) unadjusted; (2) adjusted for age, sex, and race; (3) additional adjustment for prevalent cardiovascular disease (history of stroke, heart failure, and coronary heart disease) and cardiovascular risk factors (hypertension, diabetes, current smoker, body mass index, total cholesterol, albumin, and C-reactive protein), and (4) additional adjustment for kidney-related variables (log-transformed UACR and eGFR_{CrC_yC} in the FGF-23 model, eGFR_{CrC_yC} and FGF-23 in the UACR model, and FGF-23 and UACR in eGFR_{CrC_yC} model). We repeated the analysis for currently accepted cutpoints for

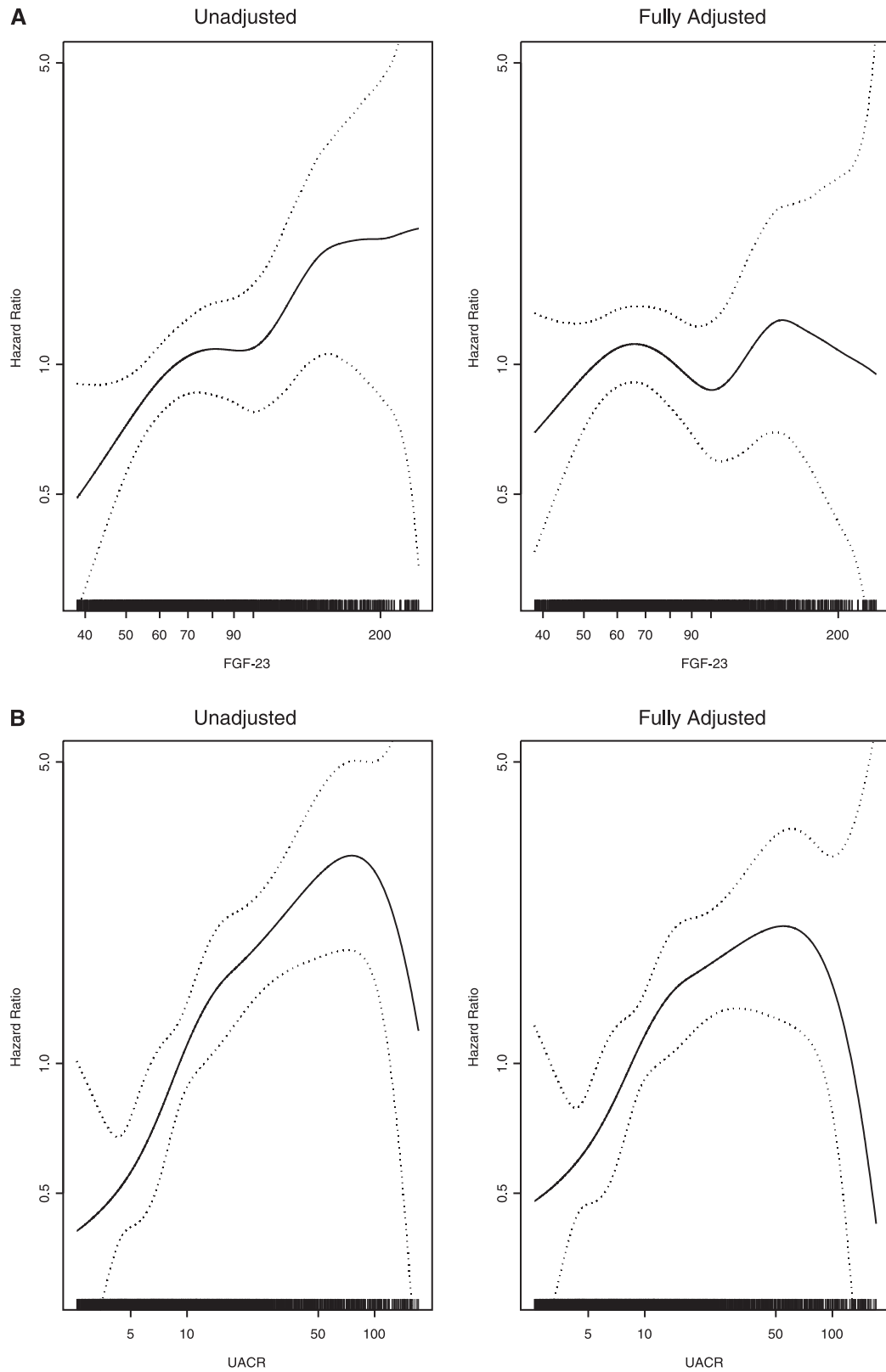


Figure 2. | Association of FGF-23, UACR, and $eGFR_{CrCyc}$ with AKI. Splines plotting the unadjusted and fully adjusted relationship between FGF-23 (A), UACR (B), and $eGFR_{CrCyc}$ (C) and hospitalization with AKI. Knots were placed at the quartiles. Dotted lines represent the 95% confidence intervals.

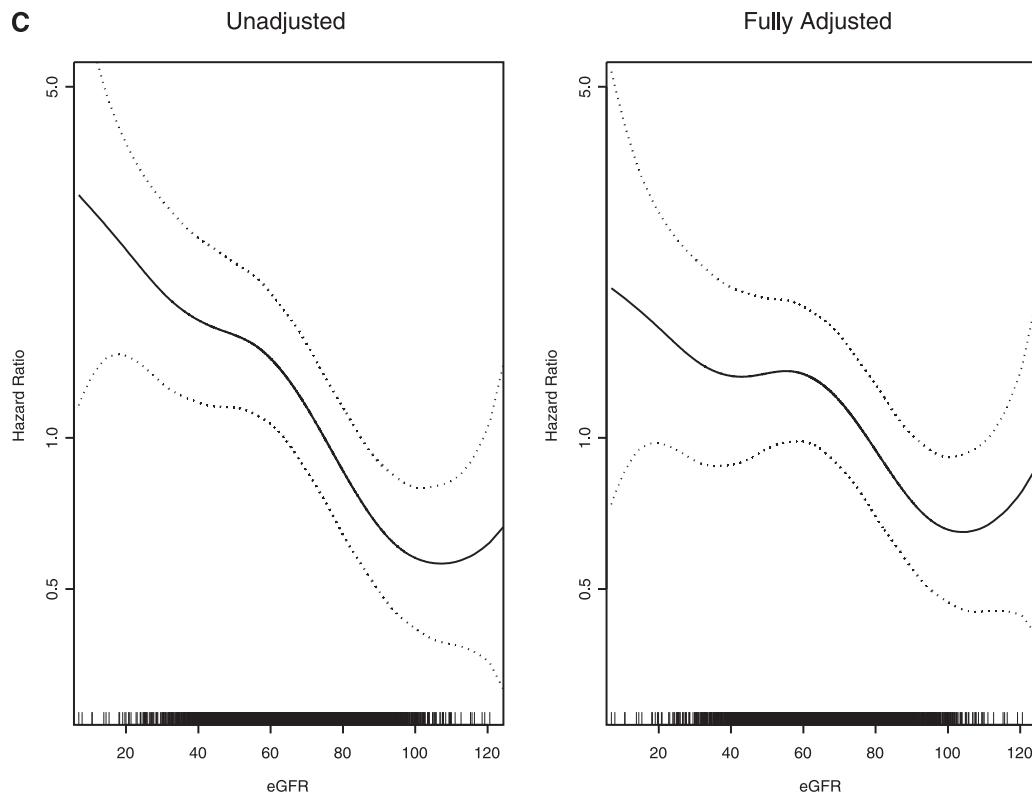


Figure 2. | Continued

eGFR_{CrC_yC} (≥ 60 and < 60 ml/min per 1.73 m²) and UACR (≥ 30 and < 30 mg/g), and given the possibility of competing risk due to mortality, we also evaluated a composite outcome of AKI or death. To test for multicollinearity, we used the variance inflation factor (VIF) and interactions. The proportional hazards assumption was satisfied for all models ($P > 0.20$). We conducted analyses using S-Plus (version 8.0; Tibco, Seattle, WA) and SPSS statistical software (version 16.0.2; SPSS, Inc., Chicago, IL). This research is in compliance with institutional review board approval and compliance with the Declaration of Helsinki.

Results

The mean age of the 3241 participants was 78 ± 5 years; 60% were women and 16% were African American. Median (interquartile range) values for FGF-23, UACR, and eGFR_{CrC_yC} were 70 RU/ml (53, 99), 8.88 mg/g (4.71, 20.47), and 71 ml/min per 1.73 m² (59, 83), respectively. Individuals in the highest quartile of FGF-23 values were older, were more likely to be women and less likely to be African American, were more likely to have a history of prior stroke, heart failure, or coronary heart disease, and had a higher prevalence of cardiovascular risk factors. eGFR_{CrC_yC} was lower and UACR higher in the higher quartiles of FGF-23 (Table 1). The correlations were 0.20 between FGF23 and UACR, -0.41 between FGF-23 and eGFR_{CrC_yC}, and -0.19 between UACR and eGFR_{CrC_yC} (all $P < 0.01$).

The median follow-up was 10.0 years (interquartile range, 5.7, 12.4), during which 119 participants were hospitalized with AKI. Individuals in the highest quartiles

of FGF-23, UACR, and eGFR_{CrC_yC} had a higher incidence of AKI (Figure 1). Figure 2 demonstrates the unadjusted and adjusted splines relating FGF-23, UACR, and eGFR_{CrC_yC} with AKI.

After adjustment for demographic factors, higher FGF-23 was associated with a higher risk of AKI. After additional adjustment for cardiovascular risk factors and kidney-related factors, the second and fourth quartiles were associated with AKI in comparison with the first quartile. There was, however, attenuation after adjustment for UACR and eGFR_{CrC_yC} (Table 2).

Individuals in the highest two quartiles (≥ 9.0 mg/g) of UACR were at higher risk of AKI in unadjusted and adjusted analyses (Table 2), whereas individuals in the lowest two quartiles of eGFR_{CrC_yC} (< 68 ml/min per 1.73 m²) had a higher risk of AKI in both unadjusted and adjusted analyses (Table 2).

When using clinical cutpoints, the unadjusted and fully adjusted hazard ratios for eGFR_{CrC_yC} < 60 ml/min per 1.73 m² compared with ≥ 60 ml/min per 1.73 m² were 2.47 (95% confidence interval [95% CI], 1.70 to 3.58) and 1.65 (95% CI, 1.10 to 2.48), respectively, whereas the unadjusted and fully adjusted hazard ratios for UACR ≥ 30 mg/g compared with < 30 mg/g were 3.06 (95% CI, 2.04 to 4.60) and 1.86 (95% CI, 1.20 to 2.89), respectively. We tested for colinearity using VIFs. The VIFs were 1.32 for FGF-23, 1.46 for eGFR_{CrC_yC}, and 1.25 for UACR; therefore, we had no concerns regarding colinearity. We found no interaction between FGF-23 and ACR ($P = 0.71$) or FGF-23 and eGFR_{CrC_yC} ($P = 0.74$).

Lastly, we evaluated the composite outcome of either AKI or mortality. There were 2023 individuals who reached this outcome; after adjusting for demographics, cardiovascular risk factors, and kidney-related factors, the association with AKI in the second through fourth quartiles of FGF-23 (in comparison with the first quartile) were as follows: 1.07 (0.94, 1.23), 1.12 (0.98, 1.29), and 1.57 (1.36, 1.81).

Discussion

In this study, we demonstrate that higher levels of FGF-23, UACR, and lower eGFR_{CrC_yC} were each independently associated with hospitalization for AKI in community-dwelling elderly individuals. These relationships remained significant after adjustment for demographic, cardiovascular risk factors, as well as each other. These results suggest that different measures of kidney health are all associated with risk of AKI.

Although FGF-23 measured within 24 hours of AKI diagnosis (≥ 0.3 mg/dl or $\geq 50\%$ increase in serum creatinine) has been linked to a higher risk of death or dialysis

(9), to our knowledge, this is the first study demonstrating an association between FGF-23 and hospitalization for AKI. FGF-23 is a phosphaturic hormone that regulates mineral homeostasis (7,24). Recent studies have suggested that FGF-23 is associated with incident cardiovascular disease, left ventricular hypertrophy (LVH), heart failure, progression of kidney disease, and mortality (6,7,25). Therefore, FGF-23 may reflect severity of mineral metabolism risk factors or severity of cardiovascular disease, which in turn are risk factors for AKI.

The theoretical mechanism linking FGF-23 with AKI, through LVH and heart failure, is supported by animal models (26). Mice injected with intravenous FGF-23 developed a significant increase in ventricular wall thickness after 40 $\mu\text{g}/\text{kg}$ q8-hour injections for 5 days (26). In Klotho-deficient mice (coreceptor binding protein for FGF-23), when FGF-23 was elevated, LVH was more likely present than controls (26). Thus, high FGF-23 may result in LVH and heart failure, which in turn are risk factors for AKI.

We also recently demonstrated that high FGF-23 is associated with cardiovascular disease particularly when the

Table 2. Association of FGF-23, eGFR_{CrC_yC}, and UACR with AKI

Characteristic	Quartile			
	1	2	3	4
FGF-23				
Range (RU/ml)	<54	54–70	71–100	>100
Annual event rate, % (no. events/no. at risk)	0.22 (18/824)	0.44 (34/821)	0.40 (29/807)	0.67 (38/789)
Unadjusted	1.00 (ref)	2.09 (1.18 to 3.70)	1.81 (1.00 to 3.28)	3.38 (1.91 to 5.98)
Age, sex, race adjusted	1.00 (ref)	2.47 (1.39 to 4.40)	2.13 (1.17 to 3.88)	4.37 (2.44 to 7.83)
Plus cardiovascular risk factors ^a	1.00 (ref)	2.35 (1.32 to 4.19)	1.79 (0.97 to 3.28)	3.06 (1.67 to 5.63)
Plus other kidney variables ^b	1.00 (ref)	2.08 (1.16 to 3.72)	1.43 (0.77 to 2.65)	1.99 (1.04 to 3.80)
eGFR_{CrC_yC}				
Range (ml/min per m ²)	>80	69–80	57–68	<57
Annual event rate, % (no. events/no. at risk)	0.26 (22/825)	0.25 (19/820)	0.49 (35/803)	0.74 (41/793)
Unadjusted	1.00 (ref)	0.97 (0.52 to 1.81)	2.08 (1.22 to 3.54)	3.47 (2.06 to 5.85)
Age, sex, race adjusted	1.00 (ref)	1.00 (0.53 to 1.87)	2.07 (1.20 to 3.58)	3.29 (1.91 to 5.67)
Plus cardiovascular risk factors ^a	1.00 (ref)	1.04 (0.56 to 1.96)	1.96 (1.13 to 3.41)	2.71 (1.55 to 4.75)
Plus other kidney variables ^c	1.00 (ref)	0.96 (0.51 to 1.80)	1.81 (1.04 to 3.15)	2.15 (1.21 to 3.82)
UACR				
Range (mg/g)	<4.7	4.7–8.9	9.0–20.9	>20.9
Annual event rate, % (no. events/no. at risk)	0.20 (17/825)	0.27 (21/808)	0.49 (34/812)	0.79 (45/796)
Unadjusted	1.00 (ref)	1.52 (0.79 to 2.91)	2.88 (1.59 to 5.22)	5.19 (2.92 to 9.22)
Age, sex, race adjusted	1.00 (ref)	1.59 (0.83 to 3.04)	2.87 (1.58 to 5.21)	4.80 (2.70 to 8.54)
Plus cardiovascular risk factors ^a	1.00 (ref)	1.48 (0.77 to 2.85)	2.59 (1.42 to 4.73)	3.79 (2.08 to 6.92)
Plus other kidney variables ^d	1.00 (ref)	1.56 (0.81 to 3.01)	2.62 (1.44 to 4.79)	3.35 (1.83 to 6.13)

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.

^aAdjusted for age, sex, race, hypertension, diabetes mellitus, smoking, body mass index, prior stroke, prior heart failure, prior coronary heart disease, total cholesterol, and C-reactive protein.

^bFurther adjusted for eGFR_{CrC_yC} and UACR.

^cFurther adjusted for FGF-23 and UACR.

^dFurther adjusted for FGF-23 and eGFR_{CrC_yC}.

fractional excretion of phosphorus is low, suggesting that FGF-23 may mark tubular FGF-23 resistance (8). Therefore, an alternative explanation for our results is that high FGF-23 levels may identify individuals vulnerable to AKI *via* a pathway of tubular damage or lack of tubular reserve (8,27). Lastly, recent studies have shown that FGF-23 levels rise rapidly in response to AKI (28), whereas we show here that high FGF-23 may predate AKI development over months to years. Thus, the relationship may be bidirectional. It remains possible that subtle abnormalities in kidney function and “subclinical” AKI at the time of FGF-23 measurement may reflect greater risk of clinically apparent AKI during long-term follow-up. Future studies are warranted to determine whether these or other mechanisms may explain the association of FGF-23 with future risk of AKI. Although the absence of a linear relationship between FGF-23 and AKI may argue against a causal relationship, we believe that it is difficult to make any definitive conclusions regarding the shape of the relationship, given the low rate of AKI. However, it should be noted that the absolute rate of AKI was higher in the highest quartile of FGF-23 (0.67%) compared with the lower quartiles (0.22%, 0.44%, and 0.40%).

We also confirmed that UACR and eGFR_{CrC_yC} were independently associated with AKI. A prior CHS analysis, lacking urine measures, demonstrated that higher serum creatinine increased the risk of AKI (5). James and colleagues demonstrated that creatinine-based eGFR and proteinuria were associated with AKI defined by administrative billing codes (3). This Canadian population-based study leveraged a single-payer provincial system, but was restricted to 60% of the population with a urine dipstick measurement (average age 57 years) and only 7% had UACR measured. The Atherosclerosis Risk in Communities (ARIC) study (mean age 63 years) also utilized administrative billing codes to capture AKI hospitalizations and noted that both eGFR and UACR were risk factors for AKI in adjusted analyses (2). The Chronic Kidney Disease Prognosis Consortium reported in a meta-analysis that eGFR and UACR were independently associated with incident AKI (appendix, Table 11 in Ganesvoort *et al.* [16]) in the general population; similar results were noted in a stratified analysis by age groups (<65 and >65 years) (16). We expand on results from these prior studies by using the combined cystatin C and serum creatinine eGFR_{CrC_yC}, and therefore providing a more accurate measure of eGFR both as the exposure variable as well as an adjustment variable (10). We also focus exclusively on elderly individuals, the group at highest risk for AKI. Finally, we were able to adjust for a larger set of rigorously ascertained confounding variables in comparison with the CKD Prognosis Consortium.

There are several limitations to our analysis. First, our primary endpoint is hospitalization with AKI defined by ICD-9-CM administrative billing codes as the primary diagnosis. Using the gold standard of a 100% change in serum creatinine for AKI, ICD-9-CM codes for determining AKI were previously shown to provide very high specificity (97.7%) but low sensitivity (35.4%) (19). A prior analysis from the CHS also confirmed the specificity of using ICD-9 codes for diagnosing AKI (5). Therefore the results of these analyses can be generalized to patients with

clinically recognized episodes of AKI requiring hospitalization, but it is uncertain whether they are generalizable to milder episodes of AKI. Other authors, however, have advocated use of these codes; for example, almost all prior studies evaluating this issue, including the US Renal Data System, the study from Alberta, Canada, and the ARIC study, used these methods to identify hospitalizations for AKI (1–3,5). Second, although our study is generalizable to the white or African-American elderly populations in the United States, whether the results generalize to younger populations or other races or ethnicities is uncertain. Third, although we conducted thorough statistical adjustment for known risk factors, both unmeasured and residual confounding remain possibilities. Lastly, FGF-23 was only measured once, as opposed to serially, and UACR was measured using a random sample, rather than a morning sample. Both would most likely have led to misclassification of the exposure variable and dilution of the results to the null (29). The strength of CHS, however, is that it is a large community-based cohort in elderly individuals, and has detailed ascertainment of risk factors at baseline and long-term follow-up to ascertain clinically important outcomes.

In summary, we report that elevated levels of FGF-23, UACR, and eGFR_{CrC_yC} are all associated with a higher risk of hospitalization for AKI among community-dwelling elderly individuals. If these results are confirmed, these measures may identify older persons at higher risk for AKI.

Acknowledgments

R.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None.

References

1. US Renal Data System: *2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Minneapolis, MN, US Renal Data System, 2012
2. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J: Albuminuria and estimated glomerular filtration rate

- independently associate with acute kidney injury. *J Am Soc Nephrol* 21: 1757–1764, 2010
3. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, Tonelli M; Alberta Kidney Disease Network: Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: A cohort study. *Lancet* 376: 2096–2103, 2010
 4. Tomlinson LA, Riding AM, Payne RA, Abel GA, Tomson CR, Wilkinson IB, Roland MO, Chaudhry AN: The accuracy of diagnostic coding for acute kidney injury in England - a single centre study. *BMC Nephrol* 14: 58, 2013
 5. Mittalhenkle A, Stehman-Breen CO, Shlipak MG, Fried LF, Katz R, Young BA, Seliger S, Gillen D, Newman AB, Psaty BM, Siscovick D: Cardiovascular risk factors and incident acute renal failure in older adults: The Cardiovascular Health Study. *Clin J Am Soc Nephrol* 3: 450–456, 2008
 6. 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, Sondheim 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
 7. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, Rifkin D, Siscovick DS, Sarnak MJ, Shlipak MG: Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol* 60: 200–207, 2012
 8. Dominguez JR, Shlipak MG, Whooley MA, Ix JH: Fractional excretion of phosphorus modifies the association between fibroblast growth factor-23 and outcomes. *J Am Soc Nephrol* 24: 647–654, 2013
 9. Leaf DE, Wolf M, Waikar SS, Chase H, Christov M, Cremers S, Stern L: FGF-23 levels in patients with AKI and risk of adverse outcomes. *Clin J Am Soc Nephrol* 7: 1217–1223, 2012
 10. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012
 11. Peralta CA, Katz R, Sarnak MJ, Ix J, Fried LF, De Boer I, Palmas W, Siscovick D, Levey AS, Shlipak MG: Cystatin C identifies chronic kidney disease patients at higher risk for complications. *J Am Soc Nephrol* 22: 147–155, 2011
 12. Shastri S, Katz R, Shlipak MG, Kestenbaum B, Peralta CA, Kramer H, Jacobs DR Jr, de Boer IH, Cushman M, Siscovick D, Sarnak MJ: Cystatin C and albuminuria as risk factors for development of CKD stage 3: The Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 57: 832–840, 2011
 13. Shlipak MG, Coca SG, Wang Z, Devarajan P, Koynier JL, Patel UD, Thiessen-Philbrook H, Garg AX, Parikh CR; TRIBE-AKI Consortium: Presurgical serum cystatin C and risk of acute kidney injury after cardiac surgery. *Am J Kidney Dis* 58: 366–373, 2011
 14. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C: Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 352: 2049–2060, 2005
 15. Vaidya VS, Waikar SS, Ferguson MA, Collings FB, Sunderland K, Gioules C, Bradwin G, Matsouaka R, Betensky RA, Curhan GC, Bonventre JV: Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clin Transl Sci* 1: 200–208, 2008
 16. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J; Chronic Kidney Disease Prognosis Consortium: Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 80: 93–104, 2011
 17. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Wiler PG: The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1: 263–276, 1991
 18. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO: Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol* 3: 358–366, 1993
 19. Waikar SS, Wald R, Chertow GM, Curhan GC, Winkelmayr WC, Liangos O, Sosa MA, Jaber BL: Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol* 17: 1688–1694, 2006
 20. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, Yamamoto T, Hampson G, Koshiyama H, Ljunggren O, Oba K, Yang IM, Miyauchi A, Econs MJ, Lavigne J, Jüppner H: Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med* 348: 1656–1663, 2003
 21. Rifkin DE, Katz R, Chonchol M, Fried LF, Cao J, de Boer IH, Siscovick DS, Shlipak MG, Sarnak MJ: Albuminuria, impaired kidney function and cardiovascular outcomes or mortality in the elderly. *Nephrol Dial Transplant* 25: 1560–1567, 2010
 22. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307–1315, 2004
 23. Shlipak MG, Katz R, Cushman M, Sarnak MJ, Stehman-Breen C, Psaty BM, Siscovick D, Tracy RP, Newman A, Fried L: Cystatin-C and inflammatory markers in the ambulatory elderly. *Am J Med* 118: 1416, 2005
 24. Schoppet M, Hofbauer LC, Brinschelle-Schmal N, Varennes A, Goudable J, Richard M, Hawa G, Chapurlat R, Szulc P: Serum level of the phosphaturic factor FGF23 is associated with abdominal aortic calcification in men: The STRAMBO study. *J Clin Endocrinol Metab* 97: E575–E583, 2012
 25. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, Chonchol M; HOST Investigators: FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol* 22: 1913–1922, 2011
 26. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguilón-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M: FGF23 induces left ventricular hypertrophy. *J Clin Invest* 121: 4393–4408, 2011
 27. Wolf M: Forging forward with 10 burning questions on FGF23 in kidney disease. *J Am Soc Nephrol* 21: 1427–1435, 2010
 28. Christov M, Waikar SS, Pereira RC, Havasi A, Leaf DE, Goltzman D, Pajevic PD, Wolf M, Jüppner H: Plasma FGF23 levels increase rapidly after acute kidney injury. *Kidney Int* 84: 776–785, 2013
 29. Witte EC, Lambers Heerspink HJ, de Zeeuw D, Bakker SJ, de Jong PE, Gansevoort R: First morning voids are more reliable than spot urine samples to assess microalbuminuria. *J Am Soc Nephrol* 20: 436–443, 2009

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