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CLINICAL RESEARCH

25-hydroxyvitamin D, Fibroblast Growth Factor 23, and Risk of Acute Kidney Injury Over 20 Years of Follow-Up

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Introduction: Low serum 25-hydroxyvitamin D levels have been identified as a risk factor for acute kidney injury (AKI) among critically ill patients. Whether low 25-hydroxyvitamin D levels are associated with long-term incidence of hospitalization with AKI in the general population is unknown.

Methods: Among 12,380 participants (mean age, 57 years; 24% black) in the Atherosclerosis Risk in Communities (ARIC) Study who attended visit 2 (1990–1992), we explored the association of serum 25-hydroxyvitamin D with incident hospitalization with AKI. Multivariable Cox models were used to estimate hazard ratios (HRs). We also examined the association of serum fibroblast growth factor 23 (FGF23) with AKI.

Results: During a median follow-up of 24.3 years, 2145 participants had incident hospitalization with AKI (crude incidence rate: 8.3; 95% confidence interval [CI]: 8.0–8.7, per 1,000 person-years). In multivariable Cox models (including adjustment for kidney function), lower 25-hydroxyvitamin D and higher FGF23 levels were each significantly associated with an increased risk of AKI (HR: 1.35; 95% CI: 1.17–1.54, for lowest vs. highest quartile for 25-hydroxyvitamin D, and HR: 1.19; 95% CI: 1.05–1.36, for highest vs. lowest quartile for FGF23). The association was consistent across demographic and clinical subgroups, regardless of whether AKI was the primary diagnosis for hospitalization, and when adjusting for incident chronic kidney disease (CKD) or cardiovascular disease (CVD) as a time-varying covariate.

Conclusion: Among middle- to older-age adults in the community, low 25-hydroxyvitamin D and high FGF23 levels were independently associated with an increased risk of AKI. Future studies should explore underlying mechanisms linking these bone mineral metabolism markers with kidney injury.

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AKI is a serious public health concern causing nearly 4 million hospitalizations annually in the United States.[1,2] Despite declining trends in the rate of overall hospitalizations, the rate of AKI that requires hospitalization has increased more than two-fold over the last decade.[1,2] AKI increases short- and long-term risks of adverse outcomes, including mortality, end-stage kidney disease, longer hospital stay, and lower quality of life.[3–5] Understanding risk factors for AKI in a community setting is important for risk assessment before certain exposures (e.g., surgery and nephrotoxic medications) and identification of potential therapeutic targets to reduce the risk of AKI.[6]

Low serum levels of 25-hydroxyvitamin D have recently attracted attention as a potential risk factor of AKI. Animal models have shown the involvement of vitamin D deficiency in the development of AKI through renal oxidative stress, inflammation, and cell injury.[7–10] Studies of critically ill patients have shown that vitamin D deficiency was highly prevalent among patients with AKI,[11] and low serum levels of 25-hydroxyvitamin D predicted the risk of developing AKI.[12,13] Accordingly, clinical trials are ongoing to test the efficacy of vitamin D supplementation to prevent AKI in critically ill patients (e.g., NCT02962102 and NCT02868827). However, it is unknown whether blood

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levels of 25-hydroxyvitamin D are associated with long-term risk of AKI in the general population.

We hypothesized that low blood levels of vitamin D were associated with a high risk of AKI. To test our hypothesis, we explored the association of serum 25-hydroxyvitamin D with incident hospitalization with AKI using data from the ARIC Study. We also explored the association of a bone mineral marker, FGF23, with the risk of AKI, given the relevant role of FGF23 in vitamin D metabolism.[14]

METHODS

Study Population

The ARIC Study is a prospective cohort study of 15,792 participants aged between 45 and 64 years who were enrolled from four U.S. communities between 1987 and 1989 (visit 1).[15] For the present study, the visit in 1990–1992 (visit 2) was used as the baseline because serum 25-hydroxyvitamin D and FGF23 were first measured in ARIC at this visit. Among 14,348 participants who attended visit 2, we excluded participants who self-identified as of a race/ethnicity other than black or white, as usually done in ARIC due to small sample size (n = 42); those with informed consent restricted to CVD (n = 37), end-stage kidney disease or estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 (n = 18); those missing serum creatinine or cystatin C (n = 1061); those with a previous history of hospitalization with AKI (n = 6); or those who were missing other covariates (n = 804). This left 12,380 participants who were included in the analysis. Written informed consent was obtained from all ARIC participants. The study was conducted in compliance with the Declaration of Helsinki. This study was approved by the institutional review board at each study site (#H.34.99.07.02.A1 at Johns Hopkins University).

Exposures

The primary exposure of interest was serum 25-hydroxyvitamin D. The secondary exposure of interest was serum FGF23. Between 2012 and 2013, ARIC investigators measured serum 25-hydroxyvitamin D and FGF23 using frozen blood samples that were collected at visit 2 and stored at -70°C until they were assayed.[16] The frozen sample was reported to be stable for the measurements of 25-hydroxyvitamin D and FGF23.[16,17] Serum 25-hydroxyvitamin D (coefficient of variation [CV]: 10.9%) was measured as the sum of D2 and D3 using liquid chromatography in tandem with high-sensitivity mass spectrometry (Waters Alliance 32795; Waters, Milford, MA), and calibrated to account for seasonality using the residual approach.[18] Serum intact FGF23 (CV: 16.6%) was measured using a two-site enzyme-linked immunosorbent assay (FGF23 ELISA Kit; Kainos Laboratories, Inc., Tokyo, Japan).

Outcome

The primary outcome was incident hospitalization with AKI defined by the first hospital discharge after visit 2 with a diagnostic code for AKI (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 584.x or ICD-10-CM N17.x) at any position. In ARIC, the reliability of these ICD codes have been reported to be high with a positive predictive value of 92% and negative predictive value of 82%.[19] We also analyzed the incidence of hospitalization with AKI at primary position, assuming that AKI was community-acquired and the primary reason for hospitalization. Participants who were lost-to-follow-up (n = 462), had incident end-stage kidney disease (n = 262), died without hospitalization with AKI (n = 4324), or did not develop AKI by the end of follow-up (December 31, 2017) (n = 5187) were censored. Data on the incident end-stage kidney disease were ascertained through the linkage to the United States Renal Data System.

Covariates

All covariates were assessed at visit 2 except for years of education, which was assessed at visit 1. Age, sex, race, smoking history, alcohol consumption, and years of education were based on self-reported questionnaires. Uses of vitamin D and calcium supplements, and antineoplastic agents were based on medication records at visit 2. Hypertension was defined as taking antihypertensive drugs within the past 2 weeks; systolic blood pressure ≥140 mm Hg; or diastolic blood pressure ≥90 mm Hg. Diabetes was defined as taking antidiabetic drugs within the past 2 weeks; a fasting blood glucose ≥126 mg/dl; or a nonfasting blood glucose ≥200 mg/dl. History of cancer and chronic obstructive pulmonary disease (COPD) were defined by a hospital discharge with ICD-9-CM codes relevant to cancer (140-165, 170-176, 179-209, and 235-239) and COPD (490-492, 494, and 496) between visit 1 and 2. History of coronary heart disease, heart failure, and stroke were defined by self-reported history at visit 1 or incident cases between visits 1 and 2. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[20] Serum parathyroid hormone (CV: 9.7%) was measured using a sandwich immunoassay method (Roche Diagnostics Corporation, Indianapolis, IN) on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation). Serum calcium (CV: 2.4%) and phosphorus (CV: 3.0%) were measured using a colorimetric method on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation).

Statistical Analysis

Baseline characteristics were compared by quartiles of 25-hydroxyvitamin D and FGF23 using chi square tests, analysis of variance, and Kruskal Wallis tests. Incidence rates and 95% CIs were estimated using Poisson regression models. HRs were estimated using multivariable Cox proportional hazard models. Model 1 adjusted for age, sex, and race. Model 2 additionally accounted for body mass index, smoking status (ever vs. never smoke), alcohol use (ever vs. never), education status, medication use (vitamin D, calcium, and antineoplastic agents), hypertension, diabetes, COPD, coronary heart disease, heart failure, stroke, and eGFR. Model 3 further adjusted for bone mineral markers (i.e., parathyroid hormone, phosphorus, calcium, and FGF23 for the analysis of 25-hydroxyvitamin D or 25-hydroxyvitamin D for the analysis of FGF23). The levels of 25-hydroxyvitamin D and FGF23 were categorized according to their quartiles. The highest quartile for 25-hydroxyvitamin D and the lowest quartile for FGF23 served as the reference category.[12,21]

We also treated 25-hydroxyvitamin D and FGF23 as continuous variables modeled as restricted cubic spline, with knots at values corresponding to the 25th, 50th, and 75th percentiles. In addition, we considered two alternative clinical categories for 25-hydroxyvitamin D (deficiency, inadequate, and adequate) according to the Institute of Medicine (<12, 12–19, and ≥20 ng/ml, respectively)[22] and the Endocrine Society (<20, 20–29, and ≥30 ng/ml, respectively).[23]

Several sensitivity analyses were performed. First, we examined the association for 25-hydroxyvitamin D separately by 25-hydroxyvitamin D2 and D3 to account for the influence by the exogenous supplementation of ergocalciferol (D2). Next, because the levels of vitamin D and FGF23 may be markers of poor health that are represented by a high risk of hospitalization, we tested Cox models adjusting for serum albumin and high-sensitivity C-reactive protein as general markers for global health or inflammation in addition to the covariates in model 3. Third, we ran a model further adjusting for incident CKD or CVD as a time-varying covariate. Incident CKD was as defined by >25% decline to eGFR <60 ml/min/1.73 m^2 or hospitalization with CKD diagnosis.[24] Incident CVD was defined as incident coronary heart disease, heart failure, or stroke. Fourth, we tested a model treating eGFR as a time-dependent covariate because a previous study suggested higher risks of kidney disease progression associated with 25-hydroxyvitamin D and FGF23.[25] For this analysis, we used timely updated eGFRs among 10,235 participants who had data on eGFR at either or both visit 4 in 1996–1998 and visit 5 in 2011–2013. Finally, we tested a model adjusting for anemia defined by the World Health Organization (<13 g/dl for men and <12 g/dl for women) in blood samples collected at visit 1 (1987–1989).

Subgroup analyses were performed for the predetermined covariates of age (<60 vs. ≥60 years), sex (male vs. female), race (white vs. black), diabetes (yes vs. no), and eGFR (<60 vs. ≥60 ml/min/1.73 m^2). For subgroup analyses, 25-hydroxyvitamin D and FGF23 were dichotomized at their medians (i.e., < vs. ≥23.9 ng/ml for 25-hydroxyvitamin D and < vs. ≥41.8 pg/ml for FGF23) to obtain reliable estimates. The interaction was statistically assessed using the log-likelihood tests. All statistical analyses were performed using Stata version 15 (StataCorp, Collage Station, TX). A two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Among 12,380 participants included in our analytic sample, the mean age was 56.9 (SD: 5.7) years, 24.0% were black, and 56.8% were female. Participants with lower levels of 25-hydroxyvitamin D were more likely to be black race, female, hypertensive, diabetic, and have a history of stroke; and they were less likely to take vitamin D or calcium supplements. For laboratory data, higher eGFR and lower FGF23 were observed among participants with lower levels of 25-hydroxyvitamin D (Table 1). When baseline characteristics were compared by quartiles of FGF23, participants with higher levels of FGF23 were more likely to be diabetic and have coronary heart disease and stroke, whereas sex and race differences were not evident (Supplementary Table S1). For laboratory data, eGFR was lower and 25-hydroxyvitamin D was slightly higher among those with higher levels of FGF23.

Association of 25-Hydroxyvitamin D With Risk of AKI

During a median follow-up of 24.3 years (interquartile range: 16.4 to 26.2 years), 2145 participants had incident hospitalization with AKI (crude incidence rate per 1000 person-years: 8.3; 95% CI: 8.0–8.7). Figure 1a shows the cumulative incidence of hospitalization with AKI by quartiles of 25-hydroxyvitamin D. Overall, higher risks of AKI were observed in the lowest and second-lowest quartiles of 25-hydroxyvitamin D. In age-, sex-, and race-adjusted Cox proportional models, participants with the lowest quartile had a 50% higher risk of hospitalization with AKI compared to participants with the highest quartile (HR: 1.50; 95% CI: 1.31–1.70] for quartile [Q]1 in model 1) (Table 2). After adjustment for other covariates, the association remained significant, with a 30% greater risk compared

Table 1. Baseline Characteristics by Quartiles of 25-Hydroxyvitamin D: The ARIC Study, 1990–1992[a]

Characteristics	Overall (N = 12,380)	25-hydroxyvitamin D, ng/ml			
		<18.4 (n = 3056)	18.4–23.8 (n = 3082)	23.9–29.5 (n = 3115)	≥29.6 (n = 3127)
Age, mean (SD), yrs	56.9 (5.7)	56.2 (5.6)	57.0 (5.7)	57.1 (5.7)	57.3 (5.7)
Black race	2969 (24.0)	1507 (49.3)	813 (26.4)	433 (13.9)	216 (6.9)
Female	7028 (56.8)	2173 (71.1)	1765 (57.3)	1548 (49.7)	1542 (49.3)
Body mass index, mean (SD), kg/m^2	28.0 (5.4)	29.7 (6.5)	28.3 (5.2)	27.6 (4.8)	26.3 (4.2)
History of smoking	7368 (59.5)	1780 (58.2)	1771 (57.5)	1845 (59.2)	1972 (63.1)
Ever alcohol consumer	9576 (77.4)	2185 (71.5)	2363 (76.7)	2469 (79.3)	2559 (81.8)
≥12 years of education	9795 (79.1)	2312 (75.7)	2408 (78.1)	2521 (80.9)	2554 (81.7)
Medication use					
Vitamin D	152 (1.2)	25 (0.8)	6 (0.8)	35 (1.1)	66 (2.1)
Calcium	909 (7.3)	89 (2.9)	199 (6.5)	254 (8.2)	367 (11.7)
Antineoplastic agents	74 (0.6)	20 (0.7)	14 (0.5)	23 (0.7)	17 (0.5)
Medical history					
Hypertension	3632 (29.3)	1131 (37.0)	944 (30.6)	837 (26.9)	720 (23.0)
Diabetes	1381 (11.2)	516 (16.9)	399 (12.9)	281 (9.0)	185 (5.9)
Cancer	256 (2.1)	64 (2.1)	58 (1.9)	73 (2.3)	61 (2.0)
COPD	120 (1.0)	37 (1.2)	30 (1.0)	32 (1.0)	21 (0.7)
Coronary heart disease	887 (7.2)	205 (6.7)	227 (7.4)	228 (7.3)	227 (7.3)
Heart failure	576 (4.7)	197 (6.4)	156 (5.1)	117 (3.8)	106 (3.4)
Stroke	230 (1.9)	68 (2.2)	70 (2.3)	53 (1.7)	39 (1.2)
Laboratory data, median (IQR)					
eGFR, ml/min/1.73 m^2	96.8 (85.2–106.7)	99 (86.2–110.3)	97.9 (86.3–107.2)	95.6 (84.8–105)	94.7 (83.6–104.4)
FGF23, pg/ml	41.8 (33.9–51.6)	40.8 (32.6–51.1)	41.4 (33.5–51.1)	42.6 (34.8–51.9)	42.6 (34.6–52.6)
25-hydroxyvitamin D, ng/ml	23.9 (18.4–29.6)	14.8 (12.3–16.7)	21.1 (19.8–22.4)	26.5 (25.2–28)	33.8 (31.4–37.6)
Parathyroid hormone, pg/ml	39.4 (31.2–49.5)	45.3 (35.6–57.5)	40.2 (31.9–49.7)	38.5 (30.7–47.8)	35.1 (28.5–43.2)
Calcium, mg/dl	9.3 (9.1–9.6)	9.3 (9.1–9.6)	9.3 (9.1–9.6)	9.3 (9.1–9.6)	9.3 (9.1–9.6)
Phosphorus, mg/dl	3.5 (3.2–3.9)	3.6 (3.2–3.9)	3.5 (3.2–3.9)	3.5 (3.2–3.8)	3.5 (3.2–3.8)

ARIC, Atherosclerosis Risk in Communities study; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; IQR, interquartile range.
[a]Values shown are n (%) unless otherwise stated.

to the risk with the highest quartile (HR: 1.30; 95% CI: 1.14–1.49 in model 2). The additional adjustment for bone mineral markers did not meaningfully change the association (HR: 1.35; 95% CI: 1.17–1.54 in Model 3).

The association was slightly stronger when analyzing hospitalization with AKI at the primary position (e.g., HR: 1.54; 95% CI: 1.07–2.20 for Q4 in model 3) (Table 2). The association was mostly

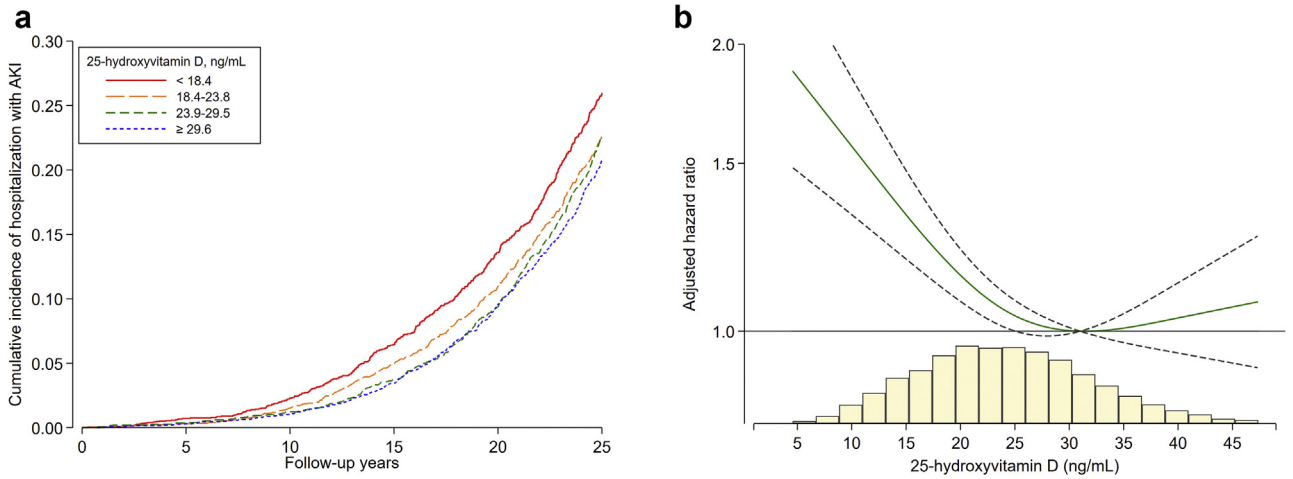

Figure 1. Cumulative incidence and adjusted hazard ratio of hospitalization with acute kidney injury (AKI) for 25-hydroxyvitamin D: the Atherosclerosis Risk in Communities study, 1990–2017. (a) Cumulative incidence of hospitalization with AKI: the level of 25-hydroxyvitamin D was classified according to the quartiles. (b) Adjusted hazard ratio of hospitalizations with AKI in the restricted cubic spline model: The model was adjusted for age, sex, race, body mass index, ever-smoke, ever-drink, education level, medication use of vitamin D, calcium, and antineoplastic agents, diabetes, chronic obstructive pulmonary disease, coronary heart disease, heart failure, stroke, estimated glomerular filtration rate, fibroblast growth factor 23, parathyroid hormone, phosphorus, and calcium. Reference was set at the 80th percentile. The solid green line indicates point estimates, and corresponding upper and lower limits for 95% confidence intervals were presented in dashed lines. The histograms show the distribution of 25-hydroxyvitamin D.

Table 2. The Association of 25-Hydroxyvitamin D With Risk of Hospitalization With AKI: The ARIC Study, 1990–2017[a]

	25-hydroxyvitamin D, ng/ml			
Outcomes	**<18.4**	**18.4–23.8**	**23.9–29.5**	**≥29.6**
AKI at any position				
Events, no.	589	534	518	504
Crude IR (95% CI), per 1000 person-years	9.7 (8.9–10.5)	8.3 (7.6–9.1)	7.9 (7.3–8.6)	7.6 (6.9–8.2)
HR (95% CI)				
Model 1	1.50 (1.31–1.70)	1.16 (1.03–1.32)	1.08 (0.95–1.22)	1 (ref)
Model 2	1.30 (1.14–1.49)	1.10 (0.97–1.24)	1.04 (0.92–1.18)	1 (ref)
Model 3	1.35 (1.17–1.54)	1.12 (0.99–1.28)	1.06 (0.93–1.20)	1 (ref)
AKI at primary position				
Events, n	105	94	70	62
Crude IR (95% CI), per 1000 person-years	1.7 (1.4–2.0)	1.4 (1.2–1.8)	1.1 (0.8–1.3)	0.9 (0.7–1.2)
HR (95% CI)				
Model 1	1.89 (1.34–2.66)	1.56 (1.12–2.16)	1.14 (0.81–1.61)	1 (ref)
Model 2	1.49 (1.05–2.12)	1.39 (1.00–1.94)	1.06 (0.75–1.50)	1 (ref)
Model 3	1.54 (1.07–2.20)	1.44 (1.03–2.01)	1.08 (0.76–1.53)	1 (ref)

AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities study; CI, confidence interval; HR, hazard ratio; IR, incidence ratio; ref, reference.
[a]Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for body mass index; ever-smoke; ever-drink; education level; use of vitamin D, calcium, and antineoplastic medications; diabetes; chronic obstructive pulmonary disease; coronary heart disease; heart failure; stroke; and estimated glomerular filtration rate. Model 3 adjusted for mineral and bone markers (i.e., fibroblast growth factor 23, parathyroid hormone, and phosphorus, calcium) in addition to the covariates in model 2.

unchanged when further adjusting for serum albumin and high-sensitivity C-reactive protein, despite their independent associations with the risk of hospitalization with AKI (Supplementary Table S2). The associations were mostly unchanged with a further adjustment for incident CKD or CVD during follow-up as a time-varying covariate, when treating eGFR as a time-dependent covariate, or when accounting for anemia (Supplementary Table S3).

When 25-hydroxyvitamin D was modeled with a restricted cubic spline, there was no evident risk gradient above 25-hydroxyvitamin D of ∼30 ng/ml, but the AKI risk steadily increased below this range (Figure 1b). Subsequent separate analyses by levels of 25-hydroxyvitamin D2 versus D3 revealed that the association of 25-hydroxyvitamin D was predominantly driven by the level of D3, whereas the level of 25-hydroxyvitamin D2 was not significant in either the low or high range (Supplementary Figure S1).

There were no differences in the association between 25-hydroxyvitamin D and AKI across subgroups of age, sex, race, diabetes, and eGFR (*P*-for-interactions, all >0.05) (Figure 2). We did not observe a significant association in eGFR <60 ml/min/1.73 m^2; however, there were only 331 participants in this category.

When using the cut-points for 25-hydroxyvitamin D levels by the Institute of Medicine, participants with vitamin D deficiency (<12 ng/ml) and inadequate levels (12–19 ng/ml) had 39% and 20% higher risk, respectively, of hospitalization with AKI compared to those with adequate vitamin D (≥20 ng/ml) (HR: 1.39; 95% CI: 1.15–1.69; and HR: 1.20; 95% CI: 1.08–1.33 in model 3, respectively) (Table 3). When using the cut-points from the Endocrine Society, we observed 27% higher risk of AKI among those with vitamin D deficiency (<20 ng/ml) compared to those with adequate vitamin D (≥30 ng/ml) (HR: 1.27; 95% CI: 1.11–1.45) in model 3), whereas the association was not significant for inadequate vitamin D (20–29 ng/ml) (HR: 1.05; 95% CI: 0.94–1.17) (Table 3).

Association of FGF23 With Risk of AKI

Overall, the cumulative incidence of AKI was higher in the highest and second-highest quartiles of FGF23 compared to the lowest quartile (Figure 3a). After adjusting for age, sex, and race, participants with the highest quartile of FGF23 had a 47% higher risk of hospitalization with AKI compared to participants with the lowest quartile (HR: 1.47; 95% CI: 1.30–1.66 in model 1) (Table 4). The association remained significant after adjustment for other covariates (HR: 1.14; 95% CI: 1.01–1.30 in model 2), and in a model additionally accounting for bone mineral markers (HR: 1.19; 95% CI: 1.05–1.36 in model 3). The interaction between 25-hydroxyvitamin D and FGF23 for the risk of hospitalization with AKI based on the covariates in model 3 was not significant (*P* for interaction = 0.56).

The association between FGF23 and AKI was stronger when analyzing risk of hospitalization with AKI at primary position (e.g., HR: 1.67; 95% CI: 1.21–2.31 for the highest vs. lowest quartile in model 3) (Table 4). The associations remained consistent when adjusting for serum albumin and high-sensitivity C-reactive protein (Supplementary Table S2), adjusting for incident CKD or CVD, treating eGFR as a time-dependent covariate, or adjusting for anemia (Supplementary Table S4).

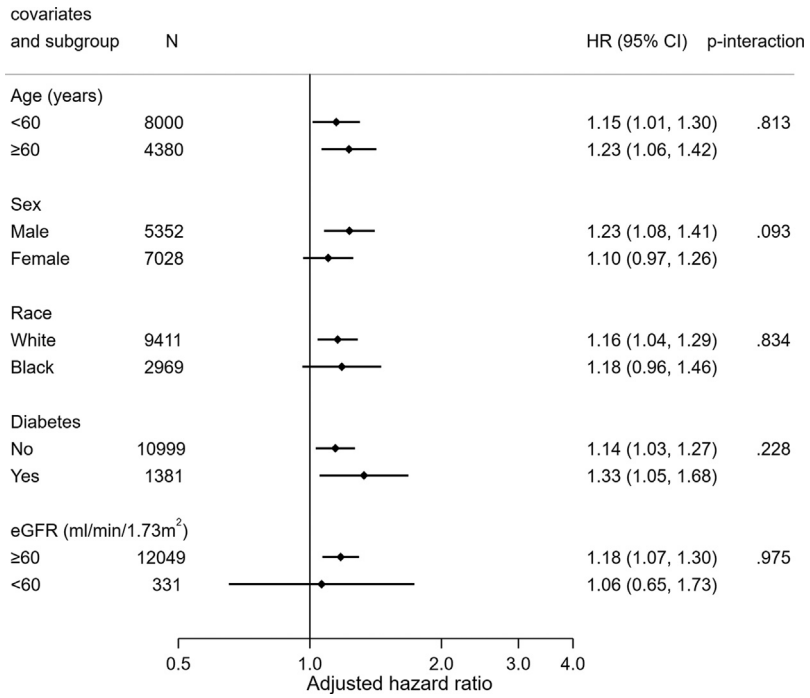

Figure 2. Adjusted hazard ratio of hospitalization with acute kidney injury for 25-hydroxyvitamin D in demographic and clinical subgroups: the Atherosclerosis Risk in Communities ARIC Study, 1990–2017: The hazard ratios (HRs) for 25-hydroxyvitamin D ≥23.9 ng/dl compared to <23.9 ng/dl. The model was adjusted for age, sex, race, body mass index, ever-smoke, ever-drink, education level, medication use of vitamin D, calcium, and antineoplastic agents, diabetes, chronic obstructive pulmonary disease, coronary heart disease, heart failure, stroke, estimated glomerular filtration rate (eGFR), fibroblast growth factor 23, parathyroid hormone, phosphorus, and calcium. CI, confidence interval.

When FGF23 was modeled using restricted cubic spline, the AKI risks appeared to be mostly comparable when FGF23 levels were less than 30 to 40 pg/ml, but AKI risks increased above this range (Figure 3b). The association was consistent across subgroups of age, sex, race, diabetes, and eGFR, without any significant interactions (P for interactions, all >0.05) (Supplementary Figure S2).

DISCUSSION

In this community-based cohort of 12,380 middle- to older-age black and white adults, we found that lower

Table 3. The Association of 25-Hydroxyvitamin D With Risk of Hospitalization With AKI According to the Clinical Classification: The ARIC Study, 1990–2017[a]

	25-Hydroxyvitamin D		
Clinical Classification	**Deficiency**	**Inadequate**	**Adequate**
Institute of Medicine			
Defined range, ng/ml	<12	12-19	≥20
Events/subjects no.	132/703	612/3247	1401/8430
Crude IR (95% CI), per 1000 person-years	9.7 (8.2–11.5)	9.3 (8.6–10.1)	7.9 (7.5–8.3)
HR (95% CI)			
Model 1	1.48 (1.23–1.79)	1.30 (1.17–1.43)	1 (ref)
Model 2	1.36 (1.13–1.65)	1.19 (1.07–1.31)	1 (ref)
Model 3	1.39 (1.15–1.69)	1.20 (1.08–1.33)	1 (ref)
Endocrine Society			
Defined range, ng/ml	<20	20–29	≥30
Events/subjects no.	744/3,950	927/5,532	474/2,898
Crude IR (95% CI), per 1000 person-years	9.4 (8.7–10.1)	8.0 (7.5–8.5)	7.7 (7.0–8.4)
HR (95% CI)			
Model 1	1.40 (1.23–1.59)	1.09 (0.97–1.21)	1 (ref)
Model 2	1.24 (1.09–1.40)	1.03 (0.92–1.15)	1 (ref)
Model 3	1.27 (1.11–1.45)	1.05 (0.94–1.17)	1 (ref)

AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities study; CI, confidence interval; HR, hazard ratio; IR, incident rate; ref, reference.
[a]Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for body mass index; ever-smoke; ever-drink; education stats; use of vitamin D, calcium, and antineoplastic medications; diabetes; chronic obstructive pulmonary disease; coronary heart disease; heart failure; stroke; and estimated glomerular filtration rate. Model 3 adjusted for mineral and bone markers (i.e., fibroblast growth factor 23, parathyroid hormone, phosphorus, and calcium) in addition to the covariates in model 2.

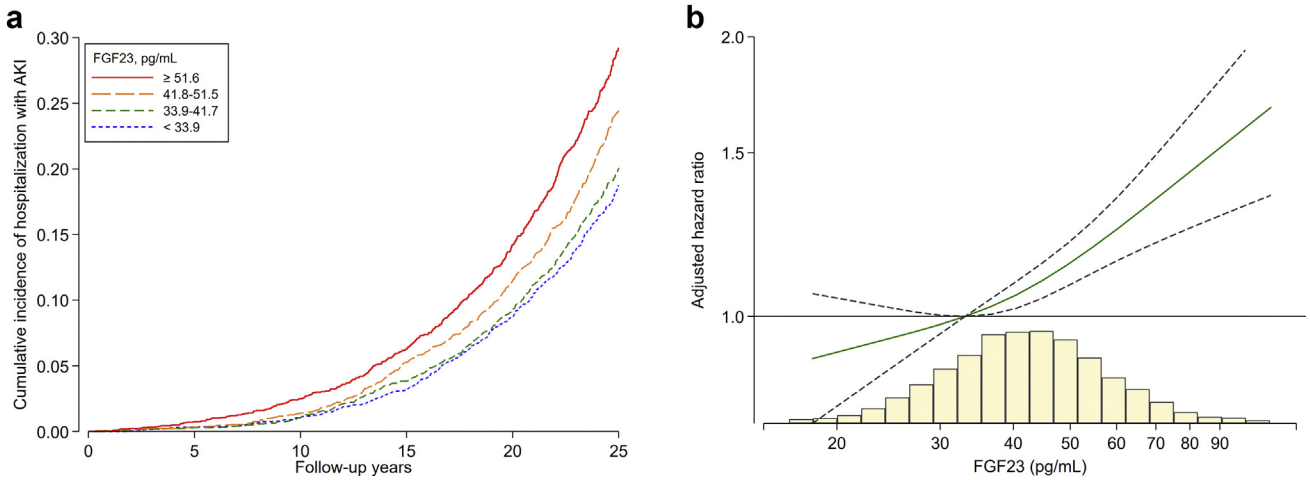

Figure 3. Cumulative incidence and adjusted hazard ratio of hospitalization with AKI for fibroblast growth factor 23 (FGF23): the Atherosclerosis Risk in Communities study, 1990–2017. (a) Cumulative incidence of hospitalization with acute kidney injury (AKI): The level of FGF23 was classified according to the quartiles. (b) Adjusted hazard ratios of hospitalizations with AKI in the restricted cubic spline model. The model was adjusted for age, sex, race, body mass index, ever-smoke, ever-drink, education level, medication use of vitamin D, calcium, and antineoplastic agents, diabetes, chronic obstructive pulmonary disease, coronary heart disease, heart failure, stroke, estimated glomerular filtration rate, 25-hydroxyvitamin D, parathyroid hormone, phosphorus, and calcium. Reference was set at the 20th percentile. The solid green line indicates point estimates, and corresponding upper and lower limits for 95% confidence intervals were presented in dashed lines. The histograms represent the distribution of FGF23.

levels of 25-hydroxyvitamin D were significantly associated with a higher risk of hospitalization with AKI. This association was independent of kidney function, bone mineral biomarkers, and a number of other potential confounders; and it was broadly consistent across subgroups and in sensitivity analyses.

To our knowledge, this is the first study to show the long-term risk of AKI in relation to serum 25-hydroxyvitamin D. Vitamin D deficiency has recently attracted attention as a potential risk factor of AKI, but previous reports were focused on the short-term risk of AKI in hospital settings among critically ill patients.[11–13] Our results extend the literature to the long-term risk of AKI over 20 years of follow-up in the general population. Also, we confirmed that the association of 25-hydroxyvitamin D with AKI was consistent in whites and blacks and in women and men.

The findings in our study and a few previous studies support an etiological involvement of 25-hydroxyvitamin D in the pathophysiology of AKI. A few animal studies reported the pathophysiological link of vitamin D to AKI. For example, rats receiving a vitamin D–free diet showed a more severe form of AKI compared to rats receiving a standard diet.[9] Other

Table 4. The Association of FGF23 With Risk of Hospitalization With AKI: The ARIC Study, 1990–2017[a]

	FGF23, pg/ml			
Outcomes	**<33.9**	**33.9–41.8**	**41.9–51.5**	**≥51.6**
AKI at any position				
Events, no.	449	503	575	618
Crude IR (95% CI), per 1000 person-years	6.9 (6.2–7.5)	7.6 (7.0–8.3)	8.9 (8.2–9.6)	10.2 (9.4–11.0)
HR (95% CI)				
Model 1	1 (ref)	1.08 (0.95–1.23)	1.25 (1.11–1.42)	1.47 (1.30–1.66)
Model 2	1 (ref)	1.06 (0.93–1.20)	1.14 (1.01–1.29)	1.14 (1.01–1.30)
Model 3	1 (ref)	1.07 (0.94–1.22)	1.17 (1.03–1.32)	1.19 (1.05–1.36)
AKI at primary position				
Events, no.	62	70	86	113
Crude IR (95% CI), per 1000 person-years	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.3 (1.1–1.6)	1.8 (1.5–2.2)
HR (95% CI)				
Model 1	1 (ref)	1.10 (0.78–1.54)	1.35 (0.97–1.87)	1.90 (1.39–2.59)
Model 2	1 (ref)	1.10 (0.78–1.54)	1.24 (0.89–1.72)	1.52 (1.11–2.10)
Model 3	1 (ref)	1.13 (0.80–1.59)	1.33 (0.95–1.85)	1.67 (1.21–2.31)

AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities study; CI, confidence interval; FGF23, fibroblast growth factor 23; HR, hazard ratio; IR, incident rate; ref, reference.
[a]Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for body mass index; ever-smoke; ever-drink; education level; use of vitamin D, calcium, and antineoplastic medications; diabetes; chronic obstructive pulmonary disease; coronary heart disease; heart failure; stroke; and estimated glomerular filtration rate. Model 3 adjusted for mineral and bone markers (i.e., 25-hydroxyvitamin D, parathyroid hormone, phosphorus, and calcium) in addition to the covariates in model 2.

studies showed pathophysiological changes in the kidney triggered by vitamin D deficiency, such as increased oxidative stress, inflammation, cell injury, and fibrosis.[7–9] In addition, vitamin D deficiency has been linked to impaired cardiac function and accelerated atherosclerosis,[26] which may cause relative ischemia and hypoxia in the kidney. Also, animal studies suggest that vitamin D deficiency may worsen the progressive loss of kidney function.[27] Thus, our finding of a single remote measure of low 25-hydroxyvitamin D levels increasing the risk of AKI over 20 years may be partly explained by the faster decline in kidney function associated with vitamin D deficiency.[28]

Although our study is observational and does not support causality, whether vitamin D supplementation for those with vitamin D deficiency might reduce the risk of AKI is a reasonable question. Several clinical trials are ongoing to test the efficacy of vitamin D for the prevention of AKI among critically ill patients (e.g., NCT02962102 and NCT02868827). Thus, findings from these studies may provide insights into clinical scenarios where the prevention of AKI is warranted (e.g., targeting vitamin D deficiency vs. regardless of vitamin D level), and the supplementation of vitamin D should be tested (e.g., surgical procedures and use of nephrotoxic medications).

The association of 25-hypdroxyvitamin with the risk of AKI appeared to be nonlinear, which adds to some controversy about what defines vitamin D deficiency. The Institute of Medicine proposes $<$12 ng/ml as deficiency, with 12–20 ng/ml as inadequate, and $\geq$20 ng/ml as adequate.[22] We showed that the risk of AKI was 39% and 20% higher with 25-hydroxyvitamin D $<$12 ng/ml and 12–20 ng/ml, respectively, compared to $\geq$20 ng/ml. Meanwhile, the Endocrine Society uses cut-points of $<$20, 20–29, and $\geq$30 ng/ml,[23] and we showed that participants with $<$20 ng/ml had 27% higher risk of AKI compared to $\geq$30 ng/ml. Although we did not observe significant association for 20–29 ng/ml, in the restricted cubic spline model, the risk of AKI appeared to be higher when 25-hydroxyvitamin D levels were below $\sim$30 ng/ml.

We also found that participants with higher levels of FGF23 had a higher risk of hospitalization with AKI. The association was mostly unchanged after adjusting for serum phosphate, despite the role of FGF23 to reduce phosphate levels by reducing the absorption and increasing the excretion of phosphate in the kidney. Our observation is consistent with a few previous studies investigating the association between FGF23 levels and risk of AKI among critically ill patients[29–32] and among older individuals.[21] Using intact FGF23, the biologically active form of FGF23, we extend the literature to a large cohort of racially diverse middle-aged to older adults.

Potential mechanisms behind the observed association for FGF23 are not well-understood, but may relate to the pleiotropic effects of FGF23 shown in animal studies, such as accelerating renal fibrosis, inflammation, and oxidative stress.[33–35] Unlike vitamin D supplementation, direct interventions to FGF23 are currently more limited.[36,37] However, recent studies suggest some lifestyle factors, such as dietary intake (e.g., phosphorus, high-fat diet) are linked to elevated levels of FGF23.[38,39] Whether changing lifestyle factors might influence the level of FGF23 and subsequent risk of AKI should be evaluated in future investigations.

Study Limitations

Several limitations should be acknowledged. First, the possibility of residual confounding may not be excluded. Recent clinical trials failed to show the effect of supplementation with vitamin D in reducing the risk of CVD[40] or mortality,[41] despite the robust associations in epidemiological studies.[42,43] Second, our outcome ascertainment of AKI relied on diagnostic hospitalization codes, and it is likely that we did not capture some mild cases of AKI. However, severe cases of AKI are especially important due to high medical expenditure and prognostic impact.[44]

Third, 25-hydroxybitamin D was measured once at baseline, and we could not evaluate whether its change over the follow-up period is associated with the risk of AKI. Fourth, we did not measure the level of calcitriol, the biologically active form of vitamin D, although 25-hydroxyvitamin D is often regarded as the best measurement for assessing vitamin D status.[45] We also lacked data on several bone mineral metabolism markers such as vitamin D binding protein, α-Klotho, and ferritin. Fifth, although our cohort was racially diverse and consisted of a wide age range of middle-aged and older adults, the generalizability of our results to other demographics and some clinical populations, such as patients with advanced CKD, should be made with caution.

CONCLUSION

In this community-based cohort, lower levels of 25-hydroxyvitamin D and higher levels of FGF23 were independently associated with incident hospitalization with AKI. These findings suggest the relevance of 25-hydroxyvitamin D and FGF23 in the development of AKI. Future studies should explore underlying mechanisms linking these markers with kidney injury.

DISCLOSURES

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline characteristics by FGF23 quartile: The ARIC Study, 1990-1992

Table S2. Adjusted hazard ratios of hospitalization with AKI for 25-hydroxyvitamin D, FGF23, albumin, and hs-CRP: The ARIC Study, 1990-2017

Table S3. Sensitivity analyses for the association of 25-hydroxyvitamin D with risk of hospitalization with AKI: The ARIC Study, 1990-2017

Table S4. Sensitivity analyses for the association of FGF23 with risk of hospitalization with AKI: The ARIC Study, 1990-2017

Figure S1. Adjusted hazard ratios of hospitalizations with AKI in the restricted cubic spline model by 25-hydroxyvitamin D2 vs. D3: The ARIC Study, 1990-2017

Figure S2. Adjusted hazard ratios of hospitalization with AKI for FGF23 in demographic and clinical subgroups: The ARIC Study, 1990-2017

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