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Associations of FGF23 with change in bone mineral density and fracture risk in older individuals

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TI has received consulting fees from Guidepoint Global and Daiichi Sankyo. JHI has consulted for Astra Zenica and Ardelyx pharmaceuticals. All the other authors declared no competing interests.

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Abstract

Elevated levels of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23) have been linked to greater risk of fractures in some studies, especially among individuals with chronic kidney disease (CKD). We evaluated FGF23 as a risk factor for bone loss and fractures in the Health, Aging, and Body Composition (Health ABC) study, which is a prospective biracial cohort of well-functioning adults aged 70 to 79 years recruited at two clinical centers in the United States. The sample for the bone mineral density (BMD) analysis consisted of 2234 participants who had at least two serial total hip areal BMD measures. The fracture analysis included 2786 participants, 567 of whom sustained a fracture during a median follow up of 4.95 years. Linear mixed-effects models were used for longitudinal measurements of total hip areal BMD and the proportional subdistribution hazard regression model subject to competing risks of death was used for risk of fracture. The median FGF23 was 46.7 (interquartile range [IQR] 36.7 – 60.2) pg/mL. The mean annualized percent change in total hip areal BMD did not vary significantly according to FGF23 quartile in all participants (P for trend=0.70), but the effect was modified by CKD status (adjusted P for interaction < 0.001). Among participants with CKD, the unadjusted mean annualized percent change in total hip areal BMD was greater with higher levels of FGF23 (unadjusted P for trend=0.02), but the trend was attenuated with adjustment for estimated glomerular filtration rate and parathyroid hormone (adjusted P for trend=0.30). FGF23 was not significantly associated with fracture risk in crude (hazard ratio [HR] per doubling of FGF23, 0.97; 95%CI 0.85 – 1.12) or adjusted models (HR per doubling of FGF23, 1.02; 95%CI 0.86 – 1.22), and these findings were not modified by gender or CKD status. FGF23 levels are not associated with bone loss or fracture risk in older adults with low prevalence of CKD.

Introduction

Fractures result in substantial morbidity, shortened lifespan and increased health care expenditures (1–4). Bone mineral density is an established intermediate measure of bone fragility, and it reliably predicts fracture risk in most clinical scenarios (5). Identification of modifiable factors that contribute to accelerated bone loss and fracture risk in older adults may suggest novel strategies to reduce fracture rates in this high-risk population.

Fibroblast growth factor 23 (FGF23) is an endocrine hormone that regulates serum phosphate levels (6). FGF23 is secreted by osteocytes in response to high phosphate diet and states of impaired phosphate excretion, such as chronic kidney disease (CKD) (6–8). In these settings, elevated FGF23 maintains normal serum phosphate by stimulating urinary phosphate excretion (6). FGF23 also reduces the efficiency of phosphate absorption in the gut by impairing production and accelerating degradation of the active form of vitamin D (9, 10). In primary disorders of FGF23 excess, including tumor induced osteomalacia, the FGF23-induced phosphate leak and calcitriol deficiency cause profound bone loss and lead to bone pain and fractures as the primary clinical presentation (11, 12). Data on the

relationship between FGF23 elevation secondary to early CKD and fracture risk are inconsistent (13–15). Some reports demonstrate an independent association between higher FGF23 levels and greater fracture risk in elderly men, especially among those with decreased estimated glomerular filtration (eGFR) (14, 15). Cross-sectional studies examining the association of FGF23 with bone mineral density have also yielded mixed findings (13, 16, 17), with most reporting no significant relationships (13, 17). However, data on FGF23 and longitudinal trajectories in change in bone mineral density in individuals with and without CKD are not available. We tested the hypothesis that an elevated baseline FGF23 level would be associated with longitudinal bone loss and incident fractures in the Health, Aging, and Body Composition (Health ABC) study, a prospective biracial cohort of community-dwelling well-functioning older adults.

Materials and Methods

Study Population

The Health ABC Study is a prospective cohort study that began in 1997 and enrolled 3075 well-functioning black and white adults aged 70 to 79 years who lived in Memphis, Tennessee, or Pittsburgh, Pennsylvania (18). Individuals were excluded if they reported difficulties performing activities of daily living, walking a quarter of a mile, or climbing 10 steps without resting. Enrolled participants had to be free of life-threatening cancers and plan to remain within the study area for at least 3 years. During the year 1 visit, baseline data were recorded, including demographics, medical and medication history, and physical exam findings. Participants then returned for yearly follow up visits and underwent biannual telephone interviews to update their health status and undergo additional measurements. The institutional review boards of the participating clinical centers (University of Pittsburgh and the University of Tennessee, Memphis) and the coordinating center (University of California, San Francisco) approved the study, and all participants provided written informed consent.

We analyzed data from 2786 of the Health ABC Study participants who had year 2 FGF23 measurements.

Exposure

The primary exposure was year 2 FGF23 level, which was measured with an intact assay (Kainos Laboratories Tokyo, Japan) that exclusively detects the intact hormone because the two epitopes recognized by the ELISA flank the proteolytic cleavage site of FGF23 (19). Samples were shipped on dry ice to Department of Laboratory Medicine at the University of Washington, where they remained at −70°C until analysis. The FGF23 assay has a limit of detection of 3 pg/mL and the coefficient of variation (between-batch) was 6.1–10.7% across the analyses, which spanned two months.

Outcome

The primary outcomes were change in total hip areal BMD over time and incident vertebral and non-vertebral fractures. Total hip areal BMD was measured using dual energy X-ray absorptiometry (QDR 4500A; software version 9.03; Hologic, Bedford, MA, USA). Both

study sites conducted quality-assurance procedures, which were monitored by the coordinating center to ensure scanner reliability and identical scan protocols. A hip phantom was scanned once per week to assess longitudinal performance of the scanners. In the parent study, serial measures of total hip areal BMD were performed at years 1, 3, 5, 8, and 10; participants were asked about fractures every 6 months, and reported fractures were validated by radiology reports. Since for our study FGF23 levels were measured at year 2, we used repeated measures of total hip areal BMD at years 3, 5, 8, and 10 and fracture events that occurred after year 2. The sample BMD analysis consisted of 2234 participants who had at least two serial total hip areal BMD measures.

Assessment of Covariates

Covariates obtained at the year 1 baseline examination included: smoking, alcohol use, and the following comorbid medical conditions (diabetes, hypertension, ischemic heart disease, heart failure, any fracture after age 45). With the exception of measures of kidney function, which were performed at year 1, all laboratory measurements and other covariates (age, sex, race, education, medication use, systolic blood pressure, BMI, dietary intake, functional status, and history of falls within past 12 months) were ascertained at year 2. Serum creatinine was measured on the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). Serum cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C) using a BNII nephelometer (Dade Behring Inc). Urinary albumin and creatinine were measured by immunoturbidimetry and colorimetric enzyme assay, respectively, using a Siemens Dimension Xpand plus HM clinical analyzer. We estimated GFR at year 1 using the 2012 CKD-EPI creatinine and cystatin C equation (20). CKD at year 1 was defined as presence of an eGFR <60 ml/min per 1.73 m^2 or urine albumin to creatinine ratio (UACR) > 30 mg/g. Serum 25-hydroxyvitamin D was measured using a two-step RIA (25-hydroxyvitamin D 125I RIA Kit; DiaSorin, Stillwater, MN). Intact parathyroid hormone (PTH) was measured in EDTA plasma using a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin). Serum calcium and phosphate levels were measured using direct quantitative colorimetric determination (Stanbio Laboratory, Boerne, TX, USA).

Statistical Analysis

We examined participant characteristics by quartiles of FGF23 levels. FGF23 was skewed and was therefore natural log transformed or modeled in quartiles. Linear mixed-effects models were used for longitudinal measurements of total hip areal BMD to estimate the effect of FGF23 on the average annualized percentage change in total hip areal BMD. Adjusted models included terms for age, sex, race, BMI, eGFR, PTH, and the interaction between time and each variable. All models included a random intercept for each subject and a random slope for time as a continuous variable to account for within-subject correlation. We estimated the average crude and adjusted mean percent change in total hip areal BMD annually by FGF23 quartiles in the entire study sample and according to CKD status at baseline. We determined the P value for trend across the quartiles.

Time-to-incident bone fracture according to FGF23 was analyzed. The association between bone fracture and FGF23 was assessed using the proportional subdistribution hazard regression model subject to competing risks of death (21), adjusting for age, sex, black race;

and clinical risk factors for fracture, including comorbidities, functional status, history of falls, fractures; and laboratory values, including eGFR, serum phosphate, calcium, vitamin D, PTH, and year 3 total hip areal BMD. This survival analysis was performed using SAS macro %PSHREG. The hazard ratios (HR) with 95% confidence intervals (CI) for fracture were estimated with the lowest FGF23 quartile as the reference category. We performed sex-specific analyses and tested for effect modification by gender and baseline CKD status by including interaction terms between FGF23 and gender and FGF23 and baseline CKD status in the fully adjusted models. Incidence densities were calculated using the R packages epiR and fsmb. All the statistical analyses were performed by using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.1.3 (2015-03-09; http://cran.r-project.org).

Results

Table 1 presents the participant characteristics for the entire analytic sample and by FGF23 quartiles. The mean ± standard deviation eGFR at the baseline visit was 70.6 ± 16.0 mL/min/1.73 m^2. The median FGF23 level was 46.7 pg/mL (interquartile range [IQR], 36.7–60.2 pg/mL), which is within the reported limit of FGF23 levels in healthy adults, in whom levels ranged from 8.2 to 54.3 pg/mL (22). Thirty four percent of Health ABC participants had FGF23 levels above 54.3 pg/mL. Compared to participants with FGF23 levels in the lowest quartile, participants with higher FGF23 levels had higher BMI and higher total hip areal BMD, were more often diabetic and hypertensive, had greater prevalence of ischemic heart disease and heart failure, and had lower eGFR and higher UACR.

Crude and adjusted mean annualized percent changes in total hip areal BMD according to FGF23 levels in the entire study population are summarized in Table 2. The mean total hip areal BMD declined during follow up. However, there was no difference in total hip areal BMD loss over time according to FGF23 levels (P for lnFGF23 × time interaction in the fully adjusted model = 0.93). Per each doubling in FGF23 levels, the adjusted % change in total hip areal BMD (95%CI) was −0.65 (−1.42; 0.04), and there was no significant trend across quartiles of FGF23 (P for trend in adjusted models = 0.70).

Because baseline CKD status modified the relationship between FGF23 and total hip areal BMD loss (P for lnFGF23 × time × CKD interaction < 0.001, in the model adjusted for demographics, BMI and eGFR), we performed stratified analyses. In participants without CKD, crude and adjusted % change in total hip areal BMD did not vary significantly according to FGF23 levels (P for trend in unadjusted model = 0.18, and P for trend =0.16 in the model adjusted for demographics, BMI and eGFR). In contrast, among those with CKD, the unadjusted % change in total hip areal BMD was greater with higher levels of FGF23 (P for trend =0.02 in unadjusted model, Table 3). However, this trend was attenuated with adjustment for eGFR and PTH (P for trend = 0.30 in the model adjusted for demographics, eGFR, PTH, and BMI, Table 3). In the final multivariable model, PTH, but not eGFR, remained a significant independent predictor of bone loss in the CKD subgroup.

During a median follow-up of 4.95 years, 567 participants (20.9/1000 person-years, 95% CI 19.2 – 22.7) sustained a new fracture. There were no significant differences in FGF23 levels

between participants with and without a fracture (46.4 versus 46.7 pg/ml, P=0.40). FGF23 was not associated with risk of fracture in either crude or adjusted models (Table 4). Per each doubling in FGF23 levels, the adjusted HR (95%CI) for fracture was 1.02 (0.86, 1.22). Compared to participants with FGF23 in the lowest quartile, participants with FGF23 in the highest quartile had an adjusted HR (95%CI) for fracture that was 1.15 (0.87, 1.55). There was no effect modification by gender (P for interaction in the fully-adjusted model = 0.28) or by baseline CKD status (P for interaction in the fully-adjusted model = 0.22). Sex-specific analyses confirmed absence of a significant association between elevated FGF23 and risk of fracture (data not shown).

Discussion

In a prospective biracial cohort of community-dwelling well-functioning older adults with relatively normal levels of FGF23 and other mineral metabolism markers, we showed that there were no differences in FGF23 levels between individuals who fractured and those who did not, and that FGF23 levels were not associated with bone loss or fracture risk during a median follow-up period of 4.95 years. Among participants with CKD, median FGF23 levels were elevated and higher levels were associated with more rapid decline in total hip areal BMD, but this trend was attenuated with adjustment for eGFR and PTH. The results suggest that higher FGF23 levels within the normal range are not associated with greater risk of fracture or bone loss in the general population. Additional studies are needed to determine whether an elevated FGF23 level is associated with bone outcomes in individuals with CKD whose progressive disease course is frequently complicated by abnormal mineral metabolism and FGF23 excess.

Since the initial discovery of a circulating hormone as the causative factor in hereditary hypoposphatemic rickets and tumor-induced osteomalacia (23, 24), a large body of experimental evidence has demonstrated that FGF23 regulates phosphate homeostasis by inducing phosphaturia, inhibiting PTH secretion and decreasing calcitriol levels (9, 10, 25, 26). Human and animal studies have also established that FGF23 levels increase with dietary phosphate loading (19, 27, 28) and as kidney function declines (29–32). In CKD, elevated FGF23 maintains normal serum phosphate levels at the expense of FGF23-mediated suppression of calcitriol, which leads to secondary hyperparathyroidism (33). Furthermore, observational studies consistently suggest that FGF23 excess contributes to risk of cardiovascular disease and mortality both in the CKD and in the general population (32, 34–36).

The data on the association of FGF23 elevation secondary to early stage CKD with bone outcomes are less well-developed. Findings from animal models of hereditary hypophosphatemic rickets implicate FGF23-mediated hypophosphatemia as one mechanism of abnormal bone mineralization (37–39). Of greater relevance to our analyses of normophosphatemic individuals is the evidence in support of phosphate-independent effects of FGF23 on bone metabolism (40–43). These direct actions of FGF23 on bone may include effects on bone cell differentiation, number and activity, and on bone turnover and mineralization (40–43). Therefore, it is reasonable to speculate that secondary elevation in

FGF23 in normophosphatemic patients with early stage CKD may be associated with bone loss and fracture risk.

The few observational studies that examined FGF23 as a predictor of fracture risk in the general population yielded conflicting results (13–15). Two of the cohorts were composed of older men (14, 15), and when BMD was available, it was only examined at one time point (13). While our study is also limited by low prevalence of CKD and FGF23 excess, the Health ABC cohort included men and women, and we were able to perform longitudinal analyses of change in total hip areal BMD. Consistent with a prior report from the Cardiovascular Health Study, we found no association between the FGF23 level and risk of fracture (13). Though our fracture finding was not modified by baseline presence of CKD or by gender, dedicated studies of CKD patients are needed to determine whether an elevated FGF23 level may be associated with fracture risk in the population that has a high prevalence of FGF23 excess.

We found no relationship between FGF23 and total hip bone loss in the entire study. Although in crude and demographics-adjusted models there was a trend toward faster bone loss among individuals with CKD who had the highest FGF23 levels, this relationship was attenuated in models that adjusted for eGFR and PTH. Moreover, an elevated PTH was an independent predictor of bone loss in the multivariable model. Therefore, we conclude that secondary hyperparathyroidism and other CKD-related factors that we did not measure, including microvascular disease, metabolic acidosis and inflammation, contributed to bone loss in the CKD subgroup (44–47).

Our study has several strengths. We analyzed data from a large well-characterized biracial community-based cohort study that prospectively ascertained and formally adjudicated fractures and had repeated assessments of BMD. However, we were limited by single measurements of FGF23 and by low prevalence of severe CKD and FGF23 excess in the study population. Thus, our results are not generalizable to individuals with markedly reduced eGFR and high FGF23 levels. Given that participants who did not have repeated BMD measures may have been too frail to come in for serial study visits and could have been the ones to experience the greatest loss in BMD, by excluding these 552 individuals, our analysis of BMD loss may have underestimated the true change in BMD over time in the study population. Assessments of kidney function were available only at the year 1 visit, whereas FGF23 measurements were done at year 2, and serial BMD measures at year 3 and thereafter were examined. While dyssynchronous assessments of eGFR, FGF23 and BMD may have affected our analyses, the low prevalence of CKD in Health ABC makes it unlikely that eGFR and FGF23 levels changed markedly between visits. Serum creatinine was not measured by a method with calibration traceable to an isotope dilution mass spectrometry (IDMS), but we relied on a validated IDMS-traceable equation for GFR estimation.

In this community-based study population of well-functioning black and white older adults, FGF23 levels were not associated with bone loss or fracture risk. Given our finding in minimally adjusted models of a trend toward faster bone loss among participants with CKD who have the highest FGF23 levels and prior reports of elevated FGF23 predicting fracture

risk in the CKD subgroup (15), dedicated studies of patients with CKD are warranted to determine whether elevated FGF23 is associated with bone outcomes in this population with high prevalence of FGF23 excess.

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Table 1

Participant characteristics according to FGF23 levels

	FGF23 (pg/ml), median (IQR)				
	All **46.7 (36.7 – 60.2)** **N=2786**	**Q1** **30.6 (26.2 – 34.1)** **N=697**	**Q2** **41.7 (39.2 – 44.4)** **N=698**	**Q3** **52.1 (49.3 – 56.2)** **N=698**	**Q4** **73.3 (65.1 – 86.4)** **N=693**
Age (years)	74.7 ± 2.9	74.5 ± 2.9	74.6 ± 2.8	74.8 ± 3.0	74.8 ± 2.8
Female gender, n (%)	1426 (51.2)	387 (55.5)	362 (51.9)	328 (47.0)	349 (50.4)
Black race, n (%)	1106 (39.7)	305 (43.8)	261 (37.4)	260 (37.3)	280 (40.4)
Education <high school, n (%)	667 (24.0)	182 (26.2)	156 (22.5)	160 (22.9)	169 (24.5)
Current smoking, n (%)	267 (9.6)	85 (12.2)	61 (8.7)	60 (8.6)	61 (8.8)
Current alcohol use, n (%)	1390 (50.1)	338 (48.6)	367 (53.0)	356 (51.2)	329 (47.6)
Diabetes, n (%)	403 (14.5)	83 (11.9)	88 (12.6)	104 (14.9)	128 (18.5)
Hypertension, n (%)	1403 (50.4)	305 (43.8)	318 (45.6)	365 (52.3)	415 (59.9)
Ischemic heart disease, n (%)	316 (11.4)	65 (9.3)	62 (8.9)	83 (11.9)	106 (15.3)
Heart failure, n (%)	76 (2.7)	9 (1.3)	11 (1.6)	14 (2.0)	42 (6.1)
Use of hypoglycemic medications, n (%)	362 (13.0)	76 (10.9)	80 (11.5)	92 (13.2)	114 (16.5)
Use of oral steroids, n (%)	74 (2.7)	23 (3.3)	15 (2.2)	15 (2.2)	21 (3.0)
Use of inhaled steroids, n (%)	77 (2.8)	23 (3.3)	21 (3.0)	13 (1.9)	20 (2.9)
Use of loop diuretics, n (%)	206 (7.4)	30 (4.3)	32 (4.6)	44 (6.3)	100 (14.5)
Use of thiazide diuretics, n (%)	545 (19.6)	107 (15.4)	118 (17.0)	139 (19.9)	181 (26.2)
Systolic blood pressure (mmHg)	133.7 ± 20.9	133.3 ± 19.7	133.2 ± 20.4	133.3 ± 20.8	134.9 ± 22.5
BMI (kg/m^2)	27.2 ± 4.8	26.6 ± 4.6	26.8 ± 4.7	27.4 ± 4.7	28.0 ± 5.1
Total hip BMD (gm/cm^2)	0.89 ± 0.17	0.86 ± 0.16	0.88 ± 0.17	0.90 ± 0.17	0.91 ± 0.17
Health ABC performance score (0–4)	2.2 ± 0.5	2.2 ± 0.5	2.3 ± 0.5	2.3 ± 0.5	2.1 ± 0.6
Time spent walking (min/week)	40 (0 – 175)	43 (0 – 178)	45 (0 – 180)	50 (0 – 180)	30 (0 – 140)
Any falls in past 12 months, n (%)	638 (23.6)	167 (24.4)	152 (22.5)	151 (22.1)	168 (25.4)
Any fracture after age 45 years, n (%)	617 (22.2)	159 (22.8)	175 (25.1)	151 (21.6)	132 (19.1)
Dietary calcium intake (mg)	716 (515 – 971)	702 (506 – 944)	719 (516 – 978)	712 (525 – 993)	731 (517 – 1000)
Calcium supplement intake, n (%)	586 (21.1)	150 (21.5)	146 (21.0)	159 (22.8)	131 (19.0)

FGF23 (pg/ml), median (IQR)					
	All **46.7 (36.7 – 60.2)** **N=2786**	**Q1** **30.6 (26.2 – 34.1)** **N=697**	**Q2** **41.7 (39.2 – 44.4)** **N=698**	**Q3** **52.1 (49.3 – 56.2)** **N=698**	**Q4** **73.3 (65.1 – 86.4)** **N=693**
Vitamin D supplement intake, n (%)	289 (10.4)	71 (10.2)	67 (9.6)	95 (13.6)	56 (8.1)
eGFR (ml/min per 1.73 m^2)	70.5 ± 16.3	74.8 ± 14.4	74.8 ± 14.0	69.7 ± 14.5	63.0 ± 18.0
UACR (mg/g)	8.5 (4.6 – 21.2)	7.8 (4.4 – 17.0)	7.4 (4.4 – 17.6)	7.8 (4.1 – 19.6)	10.3 (5.4 – 34.1)
PTH (pg/ml)	33.7 (25.1 – 45.8)	31.7 (23.5 – 41.9)	31.2 (24.0 – 41.4)	34.4 (26.1 – 45.6)	38.5 (27.9 – 56.0)
25-hydroxyvitamin D (ng/ml)	25.8 ± 11.4	23.9 ± 11.7	25.6 ± 10.2	26.7 ± 11.0	27.1 ± 12.4
Phosphate (mg/dl)	3.6 ± 0.5	3.5 ± 0.4	3.5 ± 0.5	3.5 ± 0.5	3.7 ± 0.5
Calcium (mg/dl)	8.9 ± 0.4	8.8 ± 0.4	8.8 ± 0.4	8.9 ± 0.4	9.0 ± 0.5

Abbreviations: BMI, body mass index; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

Values are N (%), means ± standard deviation, or medians (interquartile range).

eGFR and UACR values are from the year 1 visit.

Table 2

FGF23 and mean annualized percent change in total hip areal BMD

	Mean annualized % change in total hip areal BMD	Lower 95% CI	Upper 95% CI	*p* trend
Unadjusted				
FGF23 Quartile 1	−0.69	−0.78	−0.59	0.31
FGF23 Quartile 2	−0.60	−0.69	−0.51	
FGF23 Quartile 3	−0.65	−0.73	−0.56	
FGF23 Quartile 4	−0.69	−0.79	−0.60	
Demographics adjusted				
FGF23 Quartile 1	−0.70	−0.79	−0.61	0.43
FGF23 Quartile 2	−0.62	−0.71	−0.53	
FGF23 Quartile 3	−0.65	−0.74	−0.56	
FGF23 Quartile 4	−0.69	−0.79	−0.60	
Demographics, BMI and eGFR adjusted				
FGF23 Quartile 1	−0.72	−0.81	−0.62	0.99
FGF23 Quartile 2	−0.64	−0.73	−0.55	
FGF23 Quartile 3	−0.64	−0.72	−0.55	
FGF23 Quartile 4	−0.67	−0.76	−0.57	

Demographics: age, sex, black

Table 3

FGF23 and mean annualized percent change in total hip areal BMD in participants with CKD (N=715)

	Mean annualized % change in total hip areal BMD	Lower 95% CI	Upper 95% CI	*p* trend
Unadjusted				
FGF23 Quartile 1	−0.59	−0.81	−0.37	0.02
FGF23 Quartile 2	−0.75	−0.99	−0.51	
FGF23 Quartile 3	−0.63	−0.81	−0.44	
FGF23 Quartile 4	−0.90	−1.06	−0.74	
Demographics adjusted				
FGF23 Quartile 1	−0.59	−0.81	−0.38	0.02
FGF23 Quartile 2	−0.79	−1.03	−0.55	
FGF23 Quartile 3	−0.64	−0.82	−0.45	
FGF23 Quartile 4	−0.91	−1.07	−0.75	
Demographics and eGFR adjusted				
FGF23 Quartile 1	−0.63	−0.84	−0.41	0.10
FGF23 Quartile 2	−0.82	−1.06	−0.58	
FGF23 Quartile 3	−0.62	−0.81	−0.44	
FGF23 Quartile 4	−0.88	−1.04	−0.72	
Demographics and PTH adjusted				
FGF23 Quartile 1	−0.67	−0.89	−0.45	0.16
FGF23 Quartile 2	−0.81	−1.04	−0.57	
FGF23 Quartile 3	−0.63	−0.81	−0.45	
FGF23 Quartile 4	−0.87	−1.03	−0.72	
Demographics, eGFR and PTH adjusted				
FGF23 Quartile 1	−0.68	−0.90	−0.47	0.28
FGF23 Quartile 2	−0.82	−1.06	−0.58	
FGF23 Quartile 3	−0.62	−0.80	−0.44	
FGF23 Quartile 4	−0.85	−1.01	−0.70	
Demographics, eGFR, PTH and BMI adjusted				
FGF23 Quartile 1	−0.70	−0.91	−0.48	0.30
FGF23 Quartile 2	−0.83	−1.07	−0.59	
FGF23 Quartile 3	−0.62	−0.80	−0.44	
FGF23 Quartile 4	−0.86	−1.02	−0.70	

Demographics: age, sex, black

Table 4

FGF23 and risk of fracture accounting for competing risk of death

	FGF23 Median (IQR)	N (Total)	N (Events)	Rate per 1000 person-years	HR (95% CI)			
					Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
Per doubling of FGF23	46.7 (36.7 – 60.2)	2786	567	20.9 (19.2 – 22.7)	0.97 (0.85 – 1.12)	0.95 (0.83 – 1.10)	1.03 (0.88 – 1.21)	1.02 (0.86 – 1.22)
FGF23 Quartiles								
1	30.6 (26.2 – 34.1)	697	150	21.2 (18.0 – 24.9)	Reference	Reference	Reference	Reference
2	41.7 (39.2 – 44.4)	698	140	20.0 (16.9 – 23.6)	0.96 (0.75 – 1.21)	0.94 (0.75 – 1.19)	0.92 (0.71 – 1.20)	0.97 (0.74 – 1.27)
3	52.1 (49.3 – 56.2)	698	139	20.3 (17.0 – 23.9)	0.94 (0.74 – 1.19)	0.93 (0.73 – 1.18)	0.94 (0.73 – 1.23)	0.94 (0.71 – 1.24)
4	73.3 (65.1 – 86.4)	693	138	22.0 (18.5 – 26.0)	0.95 (0.75 – 1.21)	0.95 (0.75 – 1.21)	1.15 (0.88 – 1.49)	1.16 (0.87 – 1.55)

Model 1: demographics adjusted

Model 2: demographics adjusted + clinical risk factors for fracture, including comorbidities and medications, functional status, history of falls, fractures, and baseline total hip areal BMD

Model 3: demographics adjusted + clinical risk factors for fracture, including comorbidities and medications, functional status, history of falls, fractures, baseline total hip areal BMD, + labs, including eGFR, UACR, serum phosphate, calcium, vitamin D, PTH