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Fibroblast Growth Factor-23 and Frailty in Elderly Community-Dwelling Individuals: The Cardiovascular Health Study

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Abstract

Objectives—Both fibroblast growth factor 23 (FGF-23) and frailty have been previously associated with components of bone mineral metabolism, chronic disease states, and mortality. We sought to evaluate whether FGF-23 is related to frailty and to characterize the nature of their joint association with mortality.

Design—Cross sectional analysis and Cox proportional hazards mortality analysis.

Setting—The Cardiovascular Health Study

Participants—2,977 community dwelling individuals.

Measurements—The predictor was serum FGF-23 concentration (C-terminal ELISA assay) and the outcomes were frailty status (determined by frailty phenotype criteria of weight loss, weakness, exhaustion, slowness, and decreased physical activity) and mortality. Multinomial

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Author Contributions:

Study concept and design: Beben, Ix, and Rifkin

Acquisition, analysis, and interpretation of data: Beben, Ix, Shlipak, Sarnak, Fried, Hoofnagle, Chonchol, Kestenbaum, de Boer, and Rifkin

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logistic regression was used to assess the cross-sectional association of FGF-23 with frailty and prefrailty, adjusting for demographics, cardiovascular disease and risk factors, and kidney markers. Proportional hazards regression was used to assess the association of FGF-23 and frailty with all-cause mortality.

Results—The mean age was 78 years (SD 4.7), 40% were male, 83% were Caucasian and mean eGFR was 64 ± 17 ml/min/1.73m^2. The median FGF-23 value was 70.3 RU/mL [IQR 53.4–99.2]; 52% were prefrail and 13% were frail. After multivariate adjustment, each doubling in FGF-23 concentration was associated with 38% (95% CI 17–62%) higher odds of frailty vs. nonfrailty and 16% (3–30%) higher odds of prefrailty. FGF-23 (HR 1.16; 95% CI 1.10–1.23) and frailty (HR 1.82; 1.57–2.12) were independently associated with mortality, but neither association was meaningfully attenuated when adjusted for the other.

Conclusion—In a large cohort of older adults, higher FGF-23 was independently associated with prevalent frailty and pre-frailty. FGF-23 and frailty were independent and additive risk factors for mortality. FGF-23 may be a marker for functional outcomes.

Keywords

FGF-23; frailty; mortality

INTRODUCTION

Fibroblast growth factor 23 (FGF-23) is a hormone secreted by osteoblasts and osteocytes that is involved in phosphate homeostasis and has been associated with risk of cardiovascular disease (CVD)[1] and mortality.[2] High FGF-23 levels result in lower 1,25-$(OH)_2$ vitamin D levels[3] and deleterious cardiovascular effects[4] that may contribute to frailty, a highly prevalent geriatric syndrome that is associated with disability and multiple adverse health outcomes.[5] Various definitions of frailty have been proposed, including the commonly used frailty phenotype, which was developed by Fried et al. using data from the Cardiovascular Health Study (CHS).[6] This definition is based on 5 criteria: weight loss, weakness, exhaustion, slowness, and low physical activity. Frailty, as defined by the presence of at least 3 of these criteria, has been shown to predict incident falls, disability by activities of daily living (ADL) criteria, hospitalization, and mortality over 7 years of follow-up.[6] Prefrailty, as defined by the presence of 1 or 2 of these criteria, has been shown to predict these outcomes to a lesser degree, while also predicting the future development of frailty.[6] In prior work, chronic kidney disease (CKD), CVD, low 25-OH vitamin D, and high parathyroid hormone (PTH) levels have all been associated with the frailty syndrome.[7–12] However, the mechanisms underlying this clinical phenotype and its associations with the bone-kidney endocrine axis are incompletely understood. In general, it is felt to result from a combination of factors that lead to the development of sarcopenia, osteopenia, anorexia, and multisystem dysregulation.[13] The end result is decreased physiologic reserve and increased vulnerability to stressors and functional decline. An improved understanding of the markers and mechanisms of frailty may provide an opportunity for its early detection and for interventions that may prevent its negative outcomes.

One of these markers of frailty may be serum FGF-23, whose levels generally rise in the setting of CKD, and its major functions are the promotion of renal phosphate excretion and lowering of 1,25-$(OH)_2$ vitamin D levels. Additionally, FGF-23 down-regulates PTH secretion[14] and has direct activity on cardiac myocytes leading to left ventricular hypertrophy in experimental models.[4] In fact, the functions of FGF-23 may be even more diverse as its receptors are expressed not only in the kidney, parathyroid gland, bone, and heart, but also in the brain, thymus, and spleen.[15]

We were interested in whether FGF-23, an integral member of the bone-kidney endocrine axis, has a relationship with frailty in community dwelling elderly persons. In previous studies, both FGF-23[2] and frailty[6] have been independently associated with multiple adverse outcomes and mortality. However, to our knowledge, the relationship between FGF-23 and frailty has not been explored. Thus, we undertook a cross sectional analysis within the CHS to evaluate this association. Based on the prior finding that FGF-23 is associated with CVD and mortality independent of CVD risk factors and CKD,[2] we hypothesized that, in a parallel fashion, higher levels of FGF-23 would be associated with a greater prevalence of frailty.

Additionally, to our knowledge, the joint associations of FGF-23 and frailty with mortality have not been characterized. We therefore set out to assess whether the relationships of FGF-23 and frailty with mortality are independent. Based on FGF-23's association with multiple chronic disease states that contribute to mortality risk, we hypothesized that some of the association of frailty with mortality would be attenuated when adjusted for FGF-23 concentrations.

METHODS

Participants

CHS was designed to investigate CVD risk factors in a large community dwelling cohort of elderly adults. Its design and protocols have been previously described in detail.[16,17] In brief, CHS is an observational prospective cohort study that enrolled men and women age 65 years and older at inception from Medicare eligibility lists. Subjects were non-institutionalized, could give informed consent without a proxy, and were not expected to relocate within 3 years. Those who were wheelchair bound, on hospice, or were receiving radiation or chemotherapy for cancer were excluded. Initially, 5,201 participants were enrolled between 1989 and 1990 from four communities in Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. Subsequently, an additional 687 African Americans were enrolled between 1992 and 1993 from three of these sites. The subjects were examined in-person yearly and had telephone interviews twice yearly until 1999. They subsequently continued to have further follow-up every other year via telephone and via a 2005–2006 in-person visit. Informed consent was obtained from all subjects and the CHS was approved by the institutional review boards at each site.

We conducted our analysis from the 1996–1997 visit of CHS, which was the timepoint of FGF-23 and urine albumin/creatinine ratios (ACR) measurements, as well as anthropometric, physical function, and questionnaire data used to ascertain frailty status. Of

the 3,406 subjects who participated, we excluded individuals who were missing FGF-23 measurements (n=69), subcomponents of the frailty index (n=200), and covariate data (n=160). This resulted in a final sample of 2,977 subjects. In comparison with the included participants, those who were excluded were older (79.1 vs. 77.9 years), had a lower GFR (60.7 vs. 63.7 mL/min/1.73 m^2), and a higher CRP (6.1 vs 4.6 mg/L). However, they did not significantly differ in gender or race. For mortality data, patients were followed for a median of 10.5 years [IQR: 5.9–13.9] after the 1996–1997 visit.

Main Measurements

FGF-23—FGF-23 measurements were performed on 8 hour fasting ethylenediamine tetraacetic acid (EDTA) plasma specimens. These were stored at −70°C until they were thawed in 2010 and a C-terminal ELISA kit (Immutopics, San Clemente, California) was used to measure FGF-23. Intra-assay and inter-assay coefficients of variation ranged from 7.4% and 10.6%.[2]

Outcome

The presence of frailty was defined in accordance with Fried's definition of the frailty phenotype.[6] Five components of frailty were considered: 1. weight loss (unintentional weight loss of ≥10 lbs. or ≥5% loss of body weight in one year), 2. weakness (lowest quintile of grip strength by gender and BMI), 3. exhaustion (based on self-report in the Center for Epidemiologic Studies Depression (CESD) questionnaire), 4. slowness (slowest quintile of 15 foot walk time by gender and height), and 5. low physical activity (lowest quintile of kilocalorie expenditure by gender calculated from questionnaire data). Frailty was defined as the presence of 3 or more of these criteria, prefrailty was defined as the presence of 1 or 2 of these criteria, and nonfrailty was defined as the absence of any of these criteria.

Covariates

Data about potential confounders were obtained at the 1996–1997 study visit and included age, gender, race; prior diagnoses of heart failure (HF), myocardial infarction (MI), stroke, claudication, hypertension (seated systolic blood pressure ≥140, diastolic blood pressure ≥ 90, or the use of antihypertensive medications), diabetes (fasting glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic medications), body mass index (BMI), smoking status (current, former, or never), C-reactive protein (CRP); eGFR (calculated with the CKD-EPI Creatinine-Cystatin C 2012 equation),[18] and ACR. Calcium, phosphorus, intact PTH, and 25-OH vitamin D were measured in a randomly selected subcohort of 1000 individuals. From this subcohort, the 812 individuals who also had all the requisite FGF-23, frailty, and covariate data were used as the study population for sensitivity analyses including bone mineral metabolism markers.

Cystatin C was measured using a BN II nephelometer (Siemens, Munich, Germany).[19] Creatinine was measured using a Kodak Ektachem 700 Analyzer (Kodak, Rochester, New York) and was adjusted for drift.[17] A random morning urine sample was used for urine albumin and creatinine measurements. Urine albumin was determined by rate nephelometry and creatinine was measured with a Kodak Ektachem 700 Analyzer.

Serum calcium and phosphate were measured on a DxC Synchron automated clinical chemistry analyzer (Beckman-Coulter, Brea, CA) by indirect potentiometry and a timed-rate colorimetric reaction method, respectively. Serum 25-hydroxyvitamin D was measured by liquid-liquid extraction and liquid chromatography-tandem mass spectrometry at the University of Washington Department of Laboratory Medicine.[20–22] Serum intact parathyroid hormone was measured by a two-site immunoassay on an Access2 automated clinical immunoassay (Beckman-Coulter).

Statistical Analysis

We initially categorized FGF-23 levels into quartiles to examine the distribution of covariates across the FGF-23 categories using Chi squared and ANOVA testing, as appropriate. We graphically examined the relationship of FGF-23 with frailty by quartiles and determined it to be approximately linear. Thus, we evaluated FGF-23 as a continuous predictor, on a log-base 2 scale (i.e., per doubling) in our analysis. The three standard frailty categories (nonfrail, prefrail, and frail) were retained for the outcome. In order to determine whether FGF-23 was independently associated with prevalent frailty, we used multinomial logistic regression with nonfrailty as the referent and prefrailty and frailty as the alternative outcomes, adjusted for (a) demographic indicators: age, race, and gender; (b) prevalent cardiovascular disease and risk factors: HF, MI, stroke, claudication, BMI, hypertension, diabetes, smoking status, and CRP; and (c) kidney health: eGFR and ACR. These covariates were included in our analysis on the basis of biological plausibility and known associations with FGF-23, bone mineral metabolism pathways, and frailty.[7,12,23–25]

These multivariate analyses were repeated using individual components of the frailty phenotype (weight loss, weakness, exhaustion, slowness, and low physical activity) as the outcome in order to determine whether the association between FGF-23 and frailty differed in relation to these components. The potential mediating or confounding effects of calcium, phosphorus, intact PTH, and 25-OH vitamin D were evaluated in a sensitivity analysis to assess their individual and joint effects on the associations of interest.

Because prior work has shown that CKD modified the association of FGF-23 and outcomes,[2] we tested for this interaction. For this purpose, CKD was defined as an eGFR less than 60 mL/min/1.73m^2 or an ACR greater than or equal to 30 mcg/mg. Additionally, because of the previously described finding of elevated FGF-23 in postmenopausal women not taking estrogen therapy, we tested for a gender interaction.[26] Finally, since frailty was previously shown to be significantly more prevalent in the black population in the CHS cohort, we tested for an interaction between black race and FGF-23.[24]

In order to determine whether the associations of FGF-23 and frailty with mortality were influenced by one another, we examined these associations using adjusted Cox proportional hazards models. Again, FGF-23 was treated as a continuous variable on a log base 2 scale and three categories of frailty were retained for this analysis. We constructed three proportional hazards models, in which the predictors were either 1) FGF-23 individually, 2) frailty individually, or 3) FGF-23 and frailty combined. In all three models, the outcome was mortality. All three models were adjusted for age, gender, race, CHF, MI, stroke, claudication, BMI, hypertension, diabetes, smoking status, CRP, eGFR, and ACR. The

hazard ratios from these three models were then compared to characterize the nature of the joint association between the two predictors, FGF-23 and frailty, with the outcome, mortality.

SAS 9.4 was used to carry out all statistical analyses (SAS Institute Inc., Cary, NC, USA). P-values < 0.05 were considered statistically significant for all analyses including interaction terms.

RESULTS

Among the 2977 participants, the mean age was 78 ± 4.7 years; 60% were women, 83% were Caucasian and 16% were African American. The mean eGFR was 64 ± 17 mL/min/1.73 m^2 and the median urinary ACR was 8.8 mg/g [IQR: 4.7–20.1]. The median FGF-23 value was 70.3 RU/mL [interquartile range (IQR) 53.4–99.2]. Three hundred seventy-three (13%) were frail, 1549 (52%) were prefrail, and 1055 (35%) were non-frail.

We examined baseline characteristics across FGF-23 quartiles (Table 1). Compared to the lower quartiles, those in the highest FGF-23 quartile were older, more frequently female, and non-black. Additionally, they had higher rates of hypertension, diabetes, current smoking, prevalent CHF, MI, and claudication, but not stroke. Estimated GFR was lower and both CRP and urinary ACR were higher in the highest FGF-23 quartile. The proportion of frail and pre-frail subjects increased across increasing FGF-23 quartiles (Figure 1).

In a multinomial logistic regression adjusted for age, gender, and race we found that each doubling of FGF-23 level was associated with 80% higher odds of frailty vs. nonfrailty and 35% higher odds of prefrailty. Further adjustment for CVD risk factors and kidney markers attenuated this association by about half, but did not extinguish the relationship. After full multivariate adjustment, each doubling of FGF-23 level was associated with 38% higher odds of frailty vs. nonfrailty and 16% higher odds of prefrailty (Table 2A). Results were similar in those with and without CKD, by gender, and race (p interactions all > 0.07).

When the analyses were repeated using each of the individual components of frailty as individual outcomes, a doubling of FGF-23 was associated with a 25% higher odds of weight loss, 22% higher odds of slowness, and 19% higher odds of exhaustion (Table 3). Associations were weaker and not statistically significant for weakness measured by grip strength and physical activity. Spearman correlation coefficients between the components used to calculate frailty criteria (walking time, grip strength, weight change, and kcal expenditure) ranged from −0.27 to 0.21.

A sensitivity analysis performed among a random subset of 812 subjects who had phosphorus, calcium, PTH, and vitamin D measurements available demonstrated these measurements did not meaningfully alter the association between FGF-23 and frailty either individually or in aggregate (Table 2B).

An examination of mortality data was performed to investigate the joint associations of FGF-23 and frailty with all-cause mortality. During a median follow-up time of 10.5 years after the 1996–1997 visit, 2019 subjects died (68%). After multivariate adjustment, the

presence of frailty or prefrailty and a doubling of FGF-23 were all associated with increased hazard of death. However, the point estimates for the model containing FGF-23 and frailty together were nearly identical as in the models that evaluated FGF-23 and frailty individually (Table 4).

DISCUSSION

In this analysis, we demonstrated that higher FGF-23 levels are independently associated with frailty and prefrailty in older community-living individuals. This association was independent of demographics, cardiovascular disease and its risk factors, and kidney status as measured by eGFR and albuminuria. Higher FGF-23 and frailty were each associated with mortality, but adjustment for FGF-23 had little influence on the association of frailty with mortality, and similarly, adjustment for frailty had little influence on the association of FGF-23 with mortality.

Mechanisms behind the association of FGF-23 with frailty are currently speculative, but may involve vitamin D regulation and klotho, a transmembrane protein that serves as a cofactor for FGF-23's interaction with its receptors.[15] In addition to being associated with high phosphate levels, FGF-23 levels may also increase in response to end-organ resistance to FGF-23, which may, in turn, be a consequence of low klotho activity. Prior work in rodents has shown that defects in klotho are associated with high FGF-23 levels and accelerated aging through several putative mechanisms.[27,28] FGF-23 has also been found to be independently associated with higher levels of inflammatory markers, including IL-6 and CRP, in the elderly[29] and in patients with CKD.[30] It is unclear whether higher levels of FGF-23 cause an inflammatory response or whether inflammation stimulates release of FGF-23. Alternatively, it is also possible that FGF-23 is simply a marker for abnormal phosphate metabolism in CKD[31] and perhaps other chronic disease states that are associated with both inflammation and poor outcomes.

When analyzing the associations of FGF-23 with the individual components of the frailty phenotype, the associations were stronger for weight loss, self-reported exhaustion, and slow walking speed. Weakness, as measured by low grip strength, and low physical activity were not significantly associated with FGF-23. The lack of an association with low physical activity may be explained by the multiple potential reasons that people have for being sedentary. However, the lack of an association between FGF-23 and low grip strength was surprising, especially in the context of the presence of an association with slow walking speed. Low 25-OH vitamin D levels have been previously associated with sarcopenia and both low proximal and distal strength. However, a prior meta-analysis showed that that vitamin D deficient adults had improved proximal muscle strength, but not grip strength, after vitamin D supplementation.[32] Thus, it is possible that FGF-23, through its inhibition of vitamin D activation may have more of an effect on the proximal muscles and walking speed than on distal muscles and grip strength.

Other components of the bone-kidney endocrine axis, including phosphorus, calcium, intact PTH, and 25-OH vitamin D did not meaningfully attenuate the association between FGF-23 and prevalent frailty. Of these, PTH and 25-OH vitamin D have also been previously

associated with frailty, but, it appears that FGF-23's association with frailty is independent of their effect. We did not have measurements of 1,25-$(OH)_2$ vitamin D or klotho available to explore the possibility that these factors may mediate the effects of FGF-23. This important question requires future study.

FGF-23 and frailty were each associated with mortality independent of one another. This finding makes it unlikely that frailty is the dominant factor in a causal pathway between FGF-23 and mortality. Other factors including more rapid progression of kidney disease, heart failure, or CVD may explain this association. Similarly, our findings also suggest that alterations in FGF-23 are not the dominant factor linking frailty with mortality.

The main strength of our study was the availability of a large cohort of community dwelling elderly persons with long and complete follow-up, who had concurrently measured FGF-23 levels, frailty components, and extensive covariate data. This study is limited by its observational cross sectional design in regards to the association of FGF23 with frailty, in which mechanistic or causal effects cannot be determined and residual confounding may persist. The possibility of reverse causality must also be considered since it is possible that being frail, sedentary, or sarcopenic may change the biology of the bone-kidney endocrine axis in ways that raise FGF-23. Almost all participants were Caucasian or African American, potentially limiting the generalizability of these findings to other races. An additional strength of our study was the availability of phosphorus, calcium, intact PTH, and 25-OH vitamin D measurements, however these were only available in a subset, and other potential confounders or mediators, including 1,25-$(OH)_2$ vitamin D and klotho were not available.

In summary, we demonstrate for the first time a strong and independent association of FGF-23 concentration with frailty in community-living older persons. Both FGF-23 and frailty are associated with mortality, but these associations are independent of one another. Further research is needed to elucidate the mechanisms linking FGF-23 and frailty. Insights to these pathways could make it easier to more accurately interpret the effects of vitamin D levels and PTH on frailty, and may also provide important insights on the effects of vitamin D supplementation. Additionally, FGF-23 may serve as an early marker of frailty risk that may be used to institute early interventions such as moderate exercise[33] that may serve to prevent the adverse health outcomes of elderly patients at risk for frailty and its associated deleterious outcomes.

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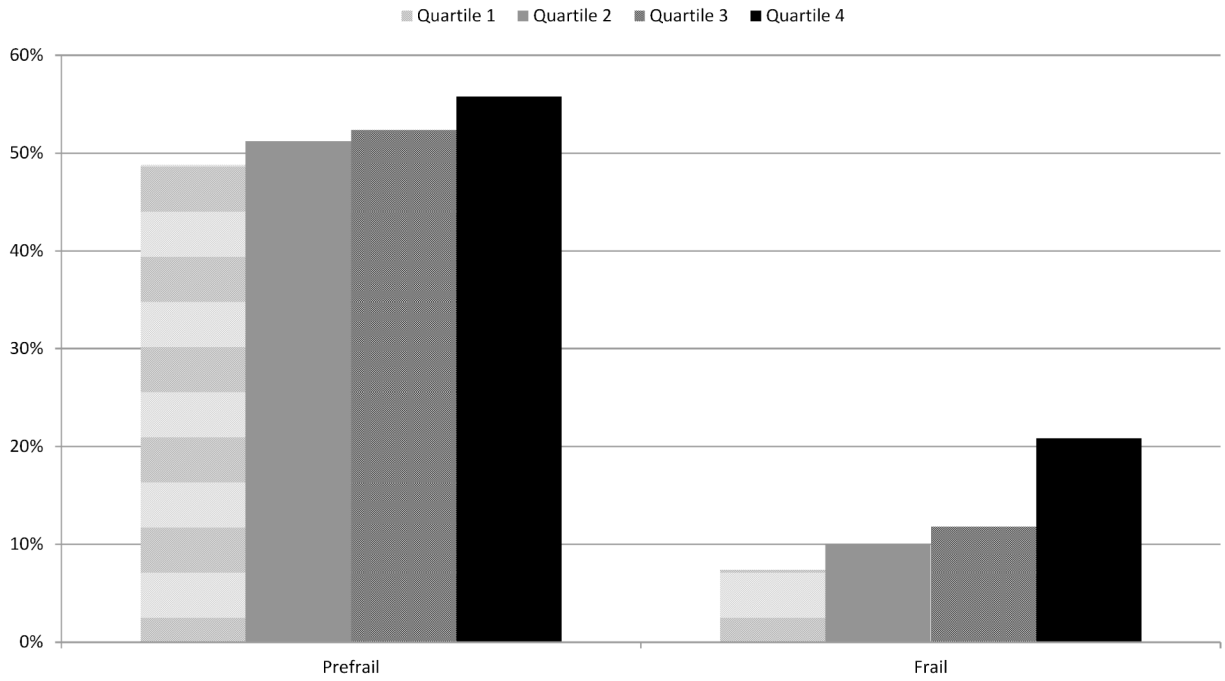

Figure 1. Distribution of Frailty by FGF-23 Quartiles

The prevalence of prefrailty and frailty is given as a percentage of the total number of subjects per FGF-23 Quartile. Total n = 744, 744, 745, and 744 per each FGF-23 quartile, respectively.

Table 1

Baseline Characteristics by FGF-23 Quartiles

	FGF-23 Quartiles			
	1	**2**	**3**	**4**
Number	744	744	745	744
FGF-23 Range (RU/mL)	20.3–53.4	53.4–70.3	70.3–99.3	99.3–14,200
Age	77.4 ± 4.5	77.4 ± 4.5	78.1 ± 4.5	78.8 ± 5.1
Male	344 (46%)	329 (44%)	274 (37%)	255 (34%)
Black	165 (22%)	111 (15%)	89 (12%)	104 (14%)
Hypertension	490 (66%)	514 (69%)	529 (71%)	602 (81%)
Diabetes	78 (10%)	92 (12%)	107 (14%)	154 (21%)
Current Smoker	36 (5%)	40 (5%)	75 (10%)	74 (10%)
Former Smoker	335 (45%)	328 (44%)	338 (45%)	333 (45%)
Never Smoker	373 (50%)	376 (51%)	332 (45%)	337 (45%)
BMI (kg/m^2)	26.3 ± 4.2	26.6 ± 4.1	27.3 ± 4.6	27.5 ± 5.2
CRP (mg/L)	1.8 (0.9–3.9)	2.1 (1.0–4.6)	2.8 (1.3–5.6)	3.1 (1.5–6.6)
History of CHF	22 (3%)	41 (6%)	54 (7%)	146 (20%)
History of MI	53 (7%)	56 (8%)	86 (12%)	125 (17%)
History of Stroke	36 (5%)	45 (6%)	36 (5%)	54 (7%)
History of Claudication	14 (2%)	15 (2%)	25 (3%)	40 (5%)
eGFR ($mL/min/1.73\ m^2$)	73 ± 14	67 ± 14	62 ± 14	53 ± 18
Urinary ACR (mg/g)	6.8 (4.3–14.3)	8.3 (4.5–17.2)	8.4 (4.8–18.5)	13.2 (5.9–50.1)
Serum Albumin (g/L)	3.85 ± 0.30	3.85 ± 0.30	3.82 ± 0.29	3.82 ± 0.30

Values are given as: mean ± SD, n (%), or median (IQR). All p values for comparison between the groups were <0.0001 with the exception of CRP (0.0008), history of stroke (0.1), history of claudication (0.002), and serum albumin (0.07).

Table 2

A. Odds of Frailty and Prefrailty per Doubling of FGF-23 Level

	Prefrail vs. Nonfrail	Frail vs. Nonfrail
Unadjusted	1.39 (1.25–1.54)	1.89 (1.65–2.17)
Age, race, and gender adjusted	1.35 (1.21–1.50)	1.80 (1.57–2.08)
Add CVD and its risk factors	1.21 (1.08–1.36)	1.50 (1.28–1.74)
Add kidney markers	1.16 (1.03–1.30)	1.38 (1.17–1.62)

B. Effect of Bone Mineral Metabolism Markers on the Odds of Frailty and Prefrailty per Doubling of FGF-23 Level

	Prefrail vs. Nonfrail	Frail vs. Nonfrail
Previous Model	1.28 (1.00–1.64)	1.46 (1.05–2.04)
Add Bone Markers	1.31 (1.02–1.68)	1.45 (1.03–2.05)

Results are given as odds ratio (95% confidence intervals).

A. Demonstrates the association of FGF-23 with frailty in unadjusted and adjusted models. CVD and its risk factors include: prevalent congestive heart failure, stroke, myocardial infarction, claudication; smoking; diabetes; hypertension; body mass index; and serum C-reactive protein. Kidney markers includes estimated glomerular filtration rate by the CKD-EPI Creatinine-Cystatin C 2012 equation and urinary albumin to creatinine ratio.

B. Demonstrates the effect of adding bone mineral metabolism markers (calcium, phosphate, PTH, and 25-OH vitamin D) to the previously fully adjusted model (demographics, CVD, and kidney function) in a randomly selected subcohort for whom all these values were available (n=812).

Table 3

Odds of Individual Components of Frailty per Doubling of FGF-23

	Odds Ratio	Percent
Weight Loss	1.25 (1.03–1.50)	5.7%
Weakness	1.08 (0.97–1.20)	28.4%
Exhaustion	1.19 (1.07–1.34)	22.2%
Slowness	1.22 (1.09–1.36)	28.4%
Low Physical Activity	1.09 (0.98–1.22)	28.7%

Results are given as odds ratio (95% confidence interval). The percentage of subjects who met criteria for each individual component of frailty is also given (total n =2977).

Table 4

Individual and Joint Contributions of Frailty and FGF-23 to Mortality

	Individually	Combined
Prefrailty	1.33 (1.20–1.47)	1.32 (1.19–1.46)
Frailty	1.88 (1.62–2.19)	1.82 (1.57–2.12)
FGF23	1.18 (1.12–1.25)	1.16 (1.10–1.23)

Results are given as hazard ratio (95% confidence interval). Results are derived from Cox proportional hazards models inlcuding frailty and FGF-23 individually (left column) and together (right colum). FGF-23 was treated as a continuous variable and frailty was treated as a categorical variable: nonfrailty, prefrailty, and frailty.