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Fibroblast Growth Factor 23, Left Ventricular Mass, and Left Ventricular Hypertrophy in Community-Dwelling Older Adults

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Abstract

Objectives—In chronic kidney disease (CKD), high FGF23 concentrations are associated with left ventricular hypertrophy (LVH), cardiovascular events, and death. The associations of FGF23 with left ventricular mass (LVM) and LVH in the general population and the influence of CKD remains uncertain.

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DISCLOSURES
None

Methods—C-terminal plasma FGF23 concentrations were measured, and LVM and LVH evaluated by echocardiogram among 2255 individuals ≥65 years in the Cardiovascular Health Study. Linear regression analysis adjusting for demographics, cardiovascular, and kidney related risk factors examined the associations of FGF23 concentrations with LVM. Analyses were stratified by CKD status and adjusted linear and logistic regression analysis explored the associations of FGF23 with LVM and LVH.

Results—Among the entire cohort, higher FGF23 concentrations were associated with greater LVM in adjusted analyses (β=6.71 [95% CI 4.35–9.01] g per doubling of FGF23). 32% (n=624) had CKD (eGFR <60 mL/min/1.73m^2 and/or urine albumin-to-creatinine ratio >30 mg/g). Associations were stronger among participants with CKD (p interaction = 0.006): LVM β=9.71 [95% CI 5.86–13.56] g per doubling of FGF23 compared to those without CKD (β=3.44 [95% CI 0.77, 6.11] g per doubling of FGF23). While there was no significant interaction between FGF23 and CKD for LVH (p interaction = 0.25), the OR (1.46 95% CI [1.20–1.77]) in the CKD group was statistically significant and of larger magnitude than the OR for in the no CKD group (1.12 [95% CI 0.97–1.48]).

Conclusion—In a large cohort of older community-dwelling adults, higher FGF23 concentrations were associated with greater LVM and LVH with stronger relationships in participants with CKD.

Keywords

Left ventricular mass; left ventricular hypertrophy; chronic kidney disease; fibroblast growth factor 23; older adults; cardiovascular disease

INTRODUCTION

Fibroblast growth factor 23 (FGF23), a hormone secreted by osteocytes, is important in phosphorus and active 1,25-dihydroxyvitamin D (1,25(OH)$_2$D) regulation.[1] It is elevated in chronic kidney disease (CKD) and higher FGF23 concentrations have been associated with more rapid kidney disease progression[2,3,4] as well as increased risk of cardiovascular events[5] and death in CKD.[2,5] Furthermore, in prior studies, including the Cardiovascular Health Study (CHS), high plasma FGF23 concentrations were associated with cardiovascular disease (CVD), heart failure, and all-cause mortality in older adults; associations that were much stronger in participants with CKD.[6,7]

FGF23 has also been associated with left ventricular hypertrophy (LVH) in both CKD and ESRD patient cohorts.[8,9] Associations of FGF23 with LVH in community-dwelling populations are less certain, but the relationship may be stronger in subjects with CKD.[10] In animal studies, there is evidence that FGF23 causes cardiomyocytes to hypertrophy by a direct, klotho-independent mechanism,[11] suggesting that FGF23 independently causes LVH. Together these epidemiological and animal data suggest that while FGF23 plays a compensatory role in patients with CKD by stimulating phosphorus excretion as glomerular filtration rate declines, it may also adversely affect the cardiomyocyte.

To better understand the role of FGF23 in cardiomyocyte hypertrophy in older adults and its relationship with kidney function, we performed a cross-sectional analysis evaluating the association of plasma FGF23 concentrations with echocardiographic data measuring left ventricular mass (LVM) and LVH in a large group of community-dwelling older adults with and without CKD. *A priori*, we hypothesized that higher plasma FGF23 concentrations would be associated with increased LVM and the presence of LVH; and, furthermore, that these associations would be stronger in participants with CKD.

METHODS

Participants

The Cardiovascular Health Study (CHS) is a prospective, longitudinal study of older community-dwelling adults. The study methods have been previously described.[12] Participants were recruited from Medicare eligibility lists at four locations: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. To be eligible, participants were required to be community-dwelling, aged 65 or older, expected to remain in the area for three years after recruitment, not receiving active treatment for cancer, and able to give informed consent without a proxy. The original cohort was recruited in 1989–1990, and a second cohort of 687 black individuals was recruited in 1992–1993, resulting in 5,888 participants, all of whom provided informed consent. FGF23 was measured in plasma samples collected at the 1996–1997-study visit. This visit was selected because it was the first visit at which morning urine samples were collected and measured for albumin-to-creatinine ratios (ACR). FGF23 measurements were performed in 3,337 participants among whom 2,255 had undergone an echocardiogram at the 1994–1995-study visit. Electrocardiograms (ECG) were performed in these study participants at the 1996–1997 study visit concurrent with FGF23 measurements.

Study Variables

The primary independent variable was plasma FGF23 concentrations. Fasting (8-hour) EDTA plasma specimens were stored at −70° Celsius until 2010 until they were thawed and FGF23 measured. FGF23 was measured using a commercially available ELISA kit (Immutopics, San Clemente, CA)[13] that recognizes two epitopes on the C-terminal side of FGF23. Never previously thawed specimens were used. Our estimates of the intra-assay and inter-assay coefficients of variation ranged from 7.4 to 10.6%.

The dependent variables of interest were LVM and LVH measured by echocardiogram as well as LVM estimated by ECG. The design for echocardiographic study of participants in CHS has been published previously.[14] M-mode and 2-dimensional echocardiograms were obtained using a standardized protocol and interpreted at a core laboratory by two trained independent readers who were unaware of the participants' clinical information. LVM was calculated from a necropsy-validated formula.[15] LVH was defined using a LVM cut-point at the 97.5th percentile from the 1994–1995 study visit and compared to a reference population that included participants without congestive heart failure, CVD, hypertension, subclinical disease or diabetes, who were not on medications, and who were not obese.

Twelve-lead resting ECGs were recorded by technicians specifically trained in careful chest electrode placement in order to reduce interindividual variability. The ECGs were recorded using MAC PC-DT ECG acquisition units (Marquette Electronics, Inc., Milwaukee, WI) and stored in the MAC PC units, which were transmitted daily to the Electrocardiographic Reading Center (Department of Public Health Sciences, Bowman-Gray School of Medicine, Winston-Salem, NC) for analysis and classification using the Novacode ECG measurement and classification program.[16,17] Race- and sex specific models with an adjustment for body size were used to estimate LVM from these ECG data.[18,19]

Confounders related to FGF23 and LVM were selected *a priori* as potential covariates. Race was determined by participant self-report and for this analysis was categorized as black or non-black. Cardiovascular and kidney disease risk factors included: diabetes, defined as the use of insulin, oral hypoglycemic agents, or fasting glucose level ≥126 mg/dl; use of antihypertensive medications; systolic blood pressure (SBP); smoking, defined as current, former, or never; and C-reactive protein (CRP).[20] Sex, weight, height, and study visit site were also included. Cystatin C was measured using a BNII nephelometer (Dade Behring,

Deerfield, IL) and was chosen as the primary measure of kidney function.[21] Estimated GFR (eGFR) was calculated with Cystatin C using an equation derived from a pooling of cohorts that used iothalamate clearance as the criterion standard ($eGFR = 76.7*cysC^{-1.19}$).[22] Urine ACR was determined from random morning urine samples; urine albumin was measured by rate nephelometry using the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA), and urine creatinine was measured on a Kodak Ektachem 700 Analyzer (Eastman Kodak Company, Rochester, NY). The urine ACR was calculated in mg/g. CKD was defined as an eGFR <60 mL/min/1.73m^2 or by the presence of urine ACR >30mg/g. [22]

Statistical Analysis

Univariate associations of clinical and demographic variables were compared using the Wilcoxon Rank Sum test for continuous variables and the χ^2 Test of Independence and Fisher's Exact for categorical variables. The relationships of plasma FGF23 concentrations and LVM (measured by echocardiogram and estimated by ECG) were assessed with multiple linear regression analysis, whereas associations with LVH were evaluated using logistic regression analysis. All analyses evaluated FGF23 quartiles with the lowest quartile as the reference category. Due to skewed distributions FGF23 was explored as a continuous predictor variable after log base 2 transformations to facilitate interpretation of the parameter coefficient as "per doubling of FGF23." The initial model for all analyses was adjusted for age, sex, race, study visit site, height, and weight. Height was excluded when examining the relationship with LVH. Model 2 was further adjusted for smoking, diabetes, antihypertensive medication use, SBP, and CRP. Further adjustments included eGFR and urine ACR (Model 3). As we were interested in understanding the proposed relationship in patients with and without CKD we also re-examined the associations of FGF23 with each marker after stratification by CKD status, and tested for multiplicative interactions by CKD status. $P < 0.05$ was considered significant for all analyses including interaction terms. All statistical analyses were performed with SAS software, version 9.13 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics at Baseline

Among the 2,255 study participants with FGF23 and echocardiogram measurements, the mean age was 78 ± 5 years, 36% (n=821) were male, and 17% (n=388) were black. The mean eGFR was 72 ± 20 mL/min/1.73m^2, the median urine ACR was 10.0 (IQR: 5.6 to 20.8) mg/g, and 32% (n=624) had CKD (eGFR < 60mL/min/1.73m^2 or urine ACR > 30mg/g). The median plasma FGF23 concentration was 70 (IQR 53–99) RU/mL, the mean LVM was 150.7 ± 48.5 g, and 14% (n=310) of participants met criteria for LVH. Compared to participants in the lower FGF23 quartiles, those with plasma FGF23 concentrations in the highest quartile were older, more frequently white and female, had a higher BMI, and were more likely to have diabetes, to use antihypertensive medication, to smoke, and have a lower eGFR, and higher urine ACR (Table 1). Echocardiographic characteristics by FGF23 quartile are shown in table 2.

Associations of plasma FGF23 concentrations with LVM and LVH

Higher FGF23 concentrations were associated with LVM throughout the sequence of adjustment models (Table 3). In unadjusted analyses, plasma FGF23 concentrations in the highest quartile had 14.2 g greater LVM compared to the lowest quartile. Furthermore, this statistically significant relationship was only slightly attenuated after the model was fully adjusted, including adjustment for eGFR and urine ACR, (β=13.45 [95% CI 7.56, 19.34]). Similar results were obtained when FGF23 was modeled continuously. In the final adjusted model, each doubling of FGF23 was associated with 6.7 g greater LVM. However, these

associations differed when the participants' CKD status was considered (p for interaction = 0.006).

Among participants with CKD, higher plasma FGF23 concentrations were significantly associated with greater LVM (Table 4). After full adjustment, plasma FGF23 concentrations in the fourth quartile (compared to the first quartile) were associated with an 18.8 g greater LVM, and each doubling of plasma FGF23 concentration was associated with a 9.7 g greater LVM. However, among participants without CKD, the magnitude of the association of plasma FGF23 concentrations and greater LVM was remarkably diminished albeit still significant (β =7.13 [95% CI 0.77, 13.56] g in the fourth quartile; β=3.44 [95% CI 0.77, 6.11] g per doubling of FGF23).

Finally, serum calcium, phosphorus, 25-hydroxyvitamin (25(OH)D), and intact parathyroid hormone (iPTH) measurements were available in a random subset at the 1997–98 study visit among 977 CHS participants. Among this subset LVM measured by 2D-echocardiogram was available in 601 participants. After multivariable adjustment which included serum calcium, phosphorus, 25(OH)D and iPTH, increasing plasma FGF23 concentrations were associated with LVM (β =17.69 [95% CI 5.59, 29.78] g in the fourth quartile; β=6.98 [95% CI 1.65, 12.31] g per doubling of FGF23). Among this subset the association between plasma FGF23 concentrations and LVM was of greater magnitude in those with CKD β=8.22 [95% CI 1.75, 14.69] g per doubling of FGF23 than in those without CKD β=4.98 [95% CI −1.31, 11.27] g per doubling of FGF23 (p for interaction=0.04).

In our study, the FGF23 measurements were made at a study visit approximately 2 years after the echocardiographic measures. Thus, we examined the associations of FGF23 and LVM estimated by ECG, measured at the same study visit as FGF23 (1997–98). Consistent with the results obtained using echocardiographic measurements, the association of FGF23 and LVM was stronger among participants with CKD compared to those without CKD (p for interaction = 0.02; Supplemental Table 1). In fully adjusted models, plasma FGF23 concentrations in the fourth quartile were associated with a 7.32 g greater LVM compared to the first quartile; and each doubling of FGF23 was associated with a 5.48 g greater LVM in those with CKD. Among participants without CKD, for each doubling of plasma FGF23 concentration there was only a slight, albeit a statistically significant, association with LVM (β=1.79 [95% CI 0.15, 3.43] g). Echocardiographic measurement and electrocardiographic estimation of LVM were well correlated ($r = 0.55$, $p < 0.0001$).

Results were similar for the association of FGF23 and LVH by echocardiography (Table 5). While there was not a statistically significant interaction between FGF23 and CKD status for LVH (p interaction = 0.25), given the strong results obtained for LVM, we proceeded with analyses stratified by CKD status. In fully adjusted models, among participants with CKD, those in the fourth quartile of FGF23 had twice the odds of LVH compared to those in the first quartile. In contrast, there was no statistically significant association of FGF23 and LVH among participants without CKD.

DISCUSSION

In this cross-sectional analysis of 2,255 community-dwelling older persons, higher plasma FGF23 concentrations were associated with greater LVM and LVH; associations that were consistently much stronger in participants with CKD. These results are similar to other cohort studies, which also observed stronger associations of FGF23 concentrations with echocardiographic evidence of cardiac hypertrophy such as LVM index (LVMI) and LVH in subjects with CKD.[8,10,11]

In the Swedish PIVUS study,[10] Mirza and colleagues studied the association of FGF23 with LVH, LVMI, and LV geometry in a European cohort of 795 community-living individuals aged 70 years and without heart disease. Higher levels of FGF23 were associated with greater LVMI and LVH in all subjects, but similar to our findings, these associations were stronger in a subset (n=164, 21%) of participants whose eGFR was <60 mL/min/1.73m^2. Thus, our findings add to these existing data by confirming a significant association of higher plasma FGF23 concentrations and greater LVM and LVH. More importantly, we confirm that the association is modified and stronger in participants with CKD, with a much larger population and greater number of participants with CKD. In addition, our findings were reproduced when LVM was estimated by ECG.

Cardiac analyses in klotho heterozygous mice have revealed a left ventricular hypertrophy phenotype in a pattern that is intermediate between klotho-deficient mice and wild-type mice. These experimental results support the concept that FGF23 seems to have a dose-dependent effects on the heart[23]. In fact, direct application of FGF23 on *in vitro* rat and *in vivo* mouse cardiomyocytes resulted in cardiac hypertrophy while blockade of the FGF receptor in 5/6th nephrectomized mice with high levels of circulating FGF23 attenuated cardiac hypertrophy. However, these animal data are as yet unconfirmed and somewhat conflicting. In a recent study by an independent group evaluating 6 weeks of treatment with an FGF23 neutralizing antibody, there was no difference in cardiac mass in treated compared to control rats.[24] Therefore, the mechanism by which FGF23 causes cardiomyocyte hypertrophy has yet to be fully elucidated. In human subjects, regardless of kidney disease status, there is a positive association of FGF23 and echocardiographic markers of cardiac hypertrophy, however, this association is consistently more pronounced in those with CKD as demonstrated in this study and by Mirza.[10] Moreover, these findings may have clinical significance, as has previously been observed, that the association of FGF23 with incident heart failure is much stronger in persons with CKD.[7] These observations suggest that factors unique to kidney disease may be required for FGF23 to induce cardiac hypertrophy in humans. However, the FGF23 efects on the heart still need to be proven experimentally in humans.

One possibility to explain these observations is that the uremic milieu may augment the effects of FGF23 on the myocardium. Higher phosphorus concentrations are associated with myocardial hypertrophy.[25,26] Early in CKD, FGF23 levels rise to increase phosphorus excretion in order to compensate for decreased nephron mass and glomerular filtration rate, however, as CKD progresses both FGF23 and phosphorus increase to greater than normal levels. Another important action of FGF23 in CKD is 1-α-hydroxylase suppression leading to 1,25$(OH)_2$D deficiency, which has been associated with cardiac hypertrophy. The associations of hyperphosphatemia and 1,25$(OH)_2$D deficiency with cardiac hypertrophy may simply be mediated by FGF23, however, it is also possible that higher FGF23 levels combined with hyperphosphatemia and 1,25$(OH)_2$D deficiency could potentiate each molecule's independent effects on the myocardium causing accelerated hypertrophy in CKD when multiple factors are abnormal concurrently. FGF23 may also affect the myocardium through its interaction with the renin-angiotensin-aldosterone system (RAAS). Animal studies demonstrate that 1,25$(OH)_2$D deficiency activates RAAS,[27] therefore, FGF23 may indirectly activate RAAS. Recent evidence suggests that FGF23 may also have a direct impact on RAAS up-regulation through its inhibition of angiotensin 2.[28,29] Taken together, these findings suggest that while elevated serum FGF23 functions as a phosphaturic hormone to maintain serum phosphate levels in patients with CKD, the supraphysiological levels may also be maladaptive and contribute to increased morbidity, and mortality in patients with kidney disease.

Rather than direct effects of FGF23 on the myocardium, another possibility is that high FGF23 may be marking a novel aspect of kidney disease that is not captured by eGFR or urine ACR, and may not be causally related to LVH. Indeed, in a recent study, Dominguez and colleagues demonstrated that FGF23 was more strongly associated with CVD events and death when accompanied by low urine phosphorus excretion, independent of eGFR or PTH levels.[30] These data suggest that some individuals may have relative renal tubular resistance to the phosphaturic actions of FGF23, and that such individuals may be at higher risk for adverse outcomes. Thus, whether high FGF23 levels contribute to new-onset LVH and progression to incident heart failure or whether higher FGF23 levels simply mark aspects of kidney disease not fully captured by eGFR or urine ACR requires future study.

Greater LVM and the presence of LVH are associated with diastolic heart failure,[31,32] an important cause of congestive heart failure in older adults. Our results evaluating echocardiographic and electrocardiographic markers of cardiac function are strengthen by findings from a prior CHS study, in which the association of higher plasma FGF23 concentrations with incident heart failure was also stronger in participants with CKD. [7] Taken together, these data suggest that the FGF23-heart failure relationship may be principally driven by diastolic heart failure, which is associated with significant morbidity and mortality.[33]

Strengths of this study include the large number of diverse participants, the inclusion of a substantial number of participants with CKD, numerous ways in which cardiac hypertrophy was evaluated, the use of both eGFR and urine ACR to define CKD, and the available measures of multiple confounding variables. Despite these and other strengths, our study has important limitations. First, echocardiograms were not performed concurrently with the measurement of plasma FGF23 concentrations, which was obtained two years later. However, Faul and colleagues report that elevated FGF23 concentrations can precede the development of LVH[10] suggesting that in those participants with LVH on echocardiogram, FGF23 levels were likely already elevated. Moreover, our results were similar when we evaluated LVM by ECG obtained concurrently with FGF23 measurements. Second, while our regression models adjusted for many confounding variables, we lacked concurrent measurements of serum $1,25(OH)_2D$ and alkaline phosphatase concentrations. Third, our study was limited to adults aged ≥65 years, therefore, these results may not be generalized to other age groups.

In this cohort of older community-dwelling adults, we conclude that FGF23 is associated with greater LVM measured by both echocardiogram and ECG, independent of eGFR and urine ACR. However, the association of plasma FGF23 concentrations and LVM and LVH is much stronger in older persons with CKD. Thus, potentially causal associations of FGF23, LVH, and heart failure risk may be particularly strong in persons with CKD. Importantly, FGF23 is being considered as a potential target for pharmaceutical intervention to decrease the incidence and progression of LVH. Our data, and that reported by others, consistently suggest that such a strategy may have the most impact in persons with CKD, rather than all individuals with elevated FGF23. Studies are needed to further elucidate the potentially different pathophysiologic effects of FGF23 on the myocardium in CKD and non-CKD populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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HIGHLIGHTS

- The association of FGF23 with left ventricular mass and hypertrophy was studied.
- We compared older adults with and without chronic kidney disease.
- Higher FGF23 is associated with greater left ventricular mass in older adults.
- FGF23 is more strongly related to greater left ventricular mass in kidney disease.
- FGF23 is more strongly related to left ventricular hypertrophy in kidney disease.

Table 1

Baseline Characteristics by Fibroblast Growth Factor 23 Quartile (N = 2255)

	Total	**Quartile 1 ≤51 RU/mL (N = 468)**	**Quartile 2 52–70 RU/mL (N = 640)**	**Quartile 3 71–100 RU/mL (N = 596)**	**Quartile 4 >100 RU/mL (N = 551)**	**P – value for trend**
Age (years)	78 ± 5	77 ± 5	77 ± 4	78 ± 4	79 ± 5	< 0.001
Male	821 (36%)	200 (43%)	259 (40%)	193 (32%)	169 (31%)	< 0.001
Black	388 (17%)	116 (25%)	112 (18%)	78 (13%)	82 (15%)	<0.001
Current smoker	157 (7%)	19 (4%)	28 (4%)	59 (10%)	51 (10%)	0.0001
Diabetes	321 (14%)	51 (11%)	74 (12%)	83 (14%)	113 (21%)	< 0.001
Hypertension	1391 (62%)	258 (55%)	387 (61%)	367 (62%)	379 (69%)	< 0.001
BMI (kg/m^2)	26.7 ± 4.6	26.2 ± 4.1	26.4 ± 4.1	27.1 ± 4.5	27.2 ± 5.4	0.0002
SBP (mmHg)	137 ± 21	137 ± 21	137 ± 20	136 ± 20	136 ± 21	0.79
CRP [mg/L] *	2.71 [1.57, 4.80]	2.25 [1.10, 4.04]	2.44 [1.24, 4.12]	2.68 [1.55, 4.56]	3.45 [1.86,7.07]	<0.001
$eGFR_{cys}$ ($mL/min/1.73m^2$)	72 ± 20	82 ± 17	76 ± 18	70 ± 17	60± 20	< 0.0001
Urine ACR [mg/g] *	10.0 [5.6, 20.8]	8.4 [5.2, 16.3]	9.4 [5.5, 16.1]	9.6 [5.4, 20.2]	14.1 [6.7, 46.5]	<0.001

Data show mean ± SD or N (%) unless otherwise specified.

* Median [IQR].

Abbreviations: BMI, body mass index; SBP systolic blood pressure; CRP, c-reactive protein; $eGFR_{cys}$, estimated glomerular filtration rate by cystatin C; urine ACR, urine albumin to creatinine ratio.

Table 2

Echocardiographic Characteristics by Fibroblast Growth Factor 23 Quartile

	Total	Quartile 1 ≤51 RU/mL (N = 468)	Quartile 2 52–70 RU/mL (N = 640)	Quartile 3 71–100 RU/mL (N = 596)	Quartile 4 >100 RU/mL (N = 551)	P - value
Left ventricular mass (gm)	150.7 ± 48.5	146 ± 45	147.7 ± 48.2	148.9 ± 45.9	160.1 ± 53	<0.001
LVEDD (cm)	4.76 ± 0.60	4.73 ± 0.54	4.75 ± 0.60	4.74 ± 0.58	4.82 ± 0.67	0.05
IVSd (cm)	0.92 ± 0.15	0.90 ± 0.14	0.91 ± 0.15	0.92 ± 0.14	0.95 ± 0.16	<0.001
PWd (cm)	0.89 ± 0.14	0.88 ± 0.13	0.88 ± 0.14	0.89 ± 0.14	0.95 ± 0.16	<0.001

Abbreviations: LVEDD, left ventricle end-diastolic dimension; IVSd, interventricular septal thickness at enddiastole (mm); PWd, posterior wall thickness at end-diastole.

Table 3

Associations of Plasma Fibroblast Growth Factor 23 Concentrations with Left Ventricular Mass by Echocardiogram Independent of eGFR and Urine Albumin-to-Creatinine Ratio (N = 2255)

	FGF23 Quartiles				Per doubling FGF23
Models	**Quartile 1 ≤51 RU/mL**	**Quartile 2 52–70 RU/mL**	**Quartile 3 71–100 RU/mL**	**Quartile 4 >100 RU/mL**	
Unadjusted	0 (REF)	1.73 (−4.03, 7.48)	2.94 (−2.91, 8.78)	14.16* (8.21, 20.11)	6.83* (4.56, 9.11)
Model 1	0 (REF)	1.74 (−3.28, 6.76)	3.96 (−1.19, 9.11)	15.11* (9.81, 20.42)	7.12* (5.08, 9.17)
Model 2	0 (REF)	1.61 (−3.49, 6.71)	3.80 (−1.46, 9.06)	14.65* (9.18, 20.12)	7.19* (5.05, 9.33)
Model 3	0 (REF)	1.62 (−3.52, 6.76)	2.95 (−2.45, 8.35)	13.45* (7.56, 19.34)	6.71* (4.35, 9.07)

Beta coefficients (difference in left ventricular mass, in grams) with 95% confidence intervals.

Model 1 = age, sex, race, clinic site, weight, height

Model 2 = Model 1 + smoking status, diabetes, use of antihypertensive medications, systolic blood pressure, C-reactive protein

Model 3 = Model 2 +estimated glomerular filtration rate, urine albumin to creatinine ratio

* $p < 0.0001$

Table 4

Associations of Plasma Fibroblast Growth Factor 23 Concentrations with Left Ventricular Mass by Echocardiogram Stratified by Chronic Kidney Disease Status

No CKD					
	FGF23 Quartile				**Per doubling of FGF23**
	Quartile 1 ≤51 RU/mL	**Quartile 2 52–70 RU/mL**	**Quartile 3 71–100 RU/mL**	**Quartile 4 >100 RU/mL**	
Unadjusted	0 (REF)	−1.71 (−7.54, 4.11)	0.84 (−5.22, 6.90)	5.93 (−1.05, 12.90)	2.93* (0.06, 5.79)
Model 1	0 (REF)	−0.03 (−5.11, 5.05)	2.92 (−2.44, 8.27)	7.43* (1.22, 13.63)	3.64* (1.09, 6.19)
Model 2	0 (REF)	0.14 (−5.03, 5.30)	3.27 (−2.21, 8.76)	7.16* (0.77, 13.56)	3.44* (0.77, 6.11)
CKD					
	FGF23 Quartile				**Per doubling of FGF23**
	Quartile 1 ≤51 RU/mL	Quartile 2 52–70 RU/mL	Quartile 3 -100 RU/mL	Quartile 4 >100 RU/mL	
Unadjusted	0 (REF)	5.85 (−8.77, 20.48)	0.90 (−13.44, 15.24)	12.00 (−1.63, 25.62)	6.46* (2.43, 10.48)
Model 1	0 (REF)	3.45 (−9.60, 16.50)	2.32 (−10.53, 15.18)	17.21* (4.94, 29.47)	8.47** (4.76, 12.18)
Model 2	0 (REF)	3.69 (−9.57, 16.94)	3.59 (−9.56, 16.74)	18.78* (6.20, 31.35)	9.71** (5.86, 13.56)

Beta coefficients (difference in left ventricular mass, in grams) with 95% confidence intervals; CKD defined as eGFR <60 ml/min/1.73m^2, urine ACR >30 mg/g, or both.

Model 1 = age, sex, race, clinic site, weight, height

Model 2 = Model 1 + smoking status, diabetes, use of antihypertensive medications, systolic blood pressure, C-reactive protein

* $p < 0.05$

** $p < 0.0001$

Table 5

Associations of Plasma Fibroblast Growth Factor 23 Concentrations with Left Ventricular Hypertrophy by Echocardiogram Stratified by Chronic Kidney Disease Status

No CKD					
	Quartile 1 ≤51 RU/mL	**Quartile 2 52–70 RU/mL**	**Quartile 3 71–100 RU/mL**	**Quartile 4 >100 RU/mL**	**Per doubling of FGF23**
Unadjusted	1 (REF)	0.94 (0.60, 1.48)	1.02 (0.64, 1.63)	1.33 (0.80, 2.21)	1.13 (0.92, 1.38)
Model 1	1 (REF)	0.99 (0.62, 1.56)	1.14 (0.71, 1.84)	1.50 (0.89, 2.53)	1.17 (0.95, 1.43)
Model 2	1 (REF)	0.99 (0.63, 1.58)	1.16 (0.72, 1.88)	1.50 (0.91, 2.64)	1.12 (0.97, 1.48)
CKD					
	Quartile 1 ≤51 RU/mL	Quartile 2 52–70 RU/mL	Quartile 3 71–100 RU/mL	Quartile 4 >100 RU/mL	**Per doubling of FGF23**
Unadjusted	1 (REF)	0.81 (0.41, 1.62)	0.77 (0.39, 1.51)	1.51 (0.82, 2.79)	1.32* (1.11, 1.57)
Model 1	1 (REF)	0.87 (0.43, 1.79)	0.91 (0.45, 1.86)	1.90 (0.99, 3.65)	1.39* (1.16, 1.68)
Model 2	1 (REF)	0.89 (0.43, 1.85)	0.93 (0.45, 1.91)	2.03* (1.04, 3.96)	1.46* (1.20, 1.77)

Odds ratios with 95% confidence intervals; CKD defined as eGFR <60 ml/min/1.73m^2, urine ACR >30 mg/g, or both.

Model 1 = age, sex, race, clinic site, weight

Model 2 = Model 1 + smoking status, diabetes, use of antihypertensive medications, systolic blood pressure, C-reactive protein

* $p < 0.05$