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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.
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 ($\beta = 6.71$ [95% CI 4.35–9.01] g per doubling of FGF23). 32% ($n = 624$) had CKD (eGFR <60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio >30 mg/g). Associations were stronger among participants with CKD (p interaction = 0.006): LVM $\beta = 9.71$ [95% CI 5.86–13.56] g per doubling of FGF23 compared to those without CKD ($\beta = 3.44$ [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.

1. 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 [2–4] 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].

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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.

2. Methods

2.1. 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 5888 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 3337 participants among whom 2255 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.

2.2. Study variables

The primary independent variable was plasma FGF23 concentrations. Fasting (8-h) 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 $\geq$126 mg/dl; use of antihypertensive medications; systolic blood pressure (SBP); smoking, defined as current, former, or never; and C-reactive protein (CRP) [20]. Sex, weight, height, and study visit site were also included. Cystatin C was measured using a BNII nephelometer (Dade Behring, Deerfield, IL) and was chosen as the primary measure of kidney function [21]. Estimated GFR (eGFR) was calculated with Cystatin C using an equation derived from a pooling of cohorts that used iothalamate clearance as the criterion standard ($eGFR = 76.7 \times 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/1.73 m^2 or by the presence of urine ACR $>$30 mg/g [22].

2.3. 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).