Fibroblast Growth Factor-23 and Cardiovascular Disease in the General Population

The Multi-Ethnic Study of Atherosclerosis

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Background—Fibroblast growth factor-23 (FGF-23) is a phosphate regulatory hormone that directly stimulates left ventricular hypertrophy in experimental models. The role of FGF-23 in cardiovascular disease development in the general population is unclear. We tested associations of FGF-23 with major subclinical and clinical cardiovascular disease outcomes in a large prospective cohort.

Methods and Results—We evaluated 6547 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) who were initially free of cardiovascular disease. We measured serum FGF-23 using the Kainos immunoassay. The MESA measured left ventricular mass by MRI, coronary calcium by computed tomography, and carotid intima-media thickness by ultrasound. The MESA adjudicated incident heart failure, coronary heart disease, and stroke by medical record review. After adjustment, the highest FGF-23 quartile was associated with an estimated 2.4-g greater left ventricular mass (95% confidence interval, 0.4–4.5 greater) and a 26% greater odds of higher coronary calcium scores (95% confidence interval, 5%–46% greater) compared with the lowest quartile. During 7.5-year follow-up, each 20-pg/mL higher FGF-23 concentration was associated with a 19% greater risk of heart failure (95% confidence interval, 3%–37% greater) and a 14% greater risk of coronary heart disease (95% confidence interval, 1%–28% greater). FGF-23 was not associated with carotid intima-media thickness or stroke.

Conclusions—Higher serum FGF-23 concentrations are associated with subclinical cardiac disease and with new heart failure and coronary disease events, but not with carotid intima-media thickness or stroke. FGF-23 may be a novel cardiovascular risk factor in the general population. (Circ Heart Fail. 2014;7:409-417.)

Key Words: cardiovascular diseases ■ carotid intima-media thickness ■ coronary disease ■ fibroblast growth factor 23 ■ heart failure ■ hypertrophy, left ventricular ■ stroke

Fibroblast growth factor-23 (FGF-23) is a major phosphate regulatory hormone that is produced in bone and acts on the kidneys to enhance urinary phosphate excretion and inhibit synthesis of calcitriol, the biologically active form of vitamin D. Serum FGF-23 concentrations are elevated in rare phosphate-wasting disorders, such as hypophosphatemic rickets and tumor-induced osteomalacia. FGF-23 concentrations also rise substantially in the setting of chronic kidney disease (CKD) presumably to defend against phosphate overload.

The phosphaturic effects of FGF-23 on the kidneys coincide with potentially adverse effects on the myocardium. In isolated cardiac myocytes, FGF-23 mimics the activity of FGF-2, a general FGF, by activating hypertrophic gene programs, promoting cardiomyocyte growth, and stimulating the release of natriuretic peptides. Administration of recombinant FGF-23 substantially increases left ventricular mass in animal models. In humans who have established CKD, higher serum FGF-23 concentrations are associated with left ventricular hypertrophy (LVH) and heart failure events. Moreover, human vascular tissue expresses FGF receptors and klotho,
target for FGF-23 binding. Higher FGF-23 concentrations are also associated with atherosclerosis burden, ischemic cardiovascular events, and all-cause mortality in cohorts of patients with established CKD, individuals with stable coronary disease, and general older adults.

Previous human studies of FGF-23 have assessed ethnically homogenous populations, focused on individuals who have pre-existing cardiovascular and kidney diseases, and used differing methods to measure cardiovascular outcomes. To evaluate FGF-23 as a potential novel cardiovascular risk factor in the general population, we measured serum FGF-23 concentrations in a prospective, multiethnic cohort of 6547 individuals who were initially free of clinical cardiovascular disease. We delineated associations of FGF-23 with left ventricular mass, assessed by cardiac MRI, coronary artery calcification, and carotid intima-media thickness (IMT). We then determined prospective associations of FGF-23 with incident heart failure, coronary heart disease, and stroke events during long-term follow-up.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of cardiovascular disease among 6814 community-living individuals. Between 2000 and 2002, the MESA recruited participants aged 45 to 84 years from study sites in Baltimore, MD; Chicago, IL; St. Paul, MN; Forsyth County, NC; New York, NY; and Los Angeles, CA. By design, the MESA recruited a final population that was 38% white, 28% black, 22% Hispanic, and 12% Asian. The MESA excluded participants who had any previous self-reported diagnosis of cardiovascular disease, defined by myocardial infarction, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, nitroglycerin use, angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator, or any surgery on the heart or arteries. All participants gave informed consent, and institutional review board approval was obtained for each site.

We evaluated 6552 participants (96.2%) who had adequate stored serum for FGF-23 measurements. We excluded 2 subjects who had evidence of severe CKD (estimated glomerular filtration rate [eGFR] <15 mL/min per 1.73 m²) and 3 subjects who had FGF-23 values that were extremely out of range and were considered by the laboratory to represent laboratory error.

Measurement of Serum FGF-23 Concentrations

MESA study personnel collected blood and urine samples in the morning after an overnight fast. The University of Vermont Laboratory for Clinical Biochemistry stored samples using established methods and shipped first use samples on dry ice to the University of Washington. We measured serum FGF-23 concentrations using the Kainos immunoassay, which detects the full-length, biologically intact FGF-23 molecule via midmolecule and distal epitopes. We used standardized high- and low-value FGF-23 controls within each run to monitor quality control. The coefficient of variation for singlicate high and low control samples across 81 plates was 6.7% and 12.4%, respectively.

Measurements of Subclinical Disease

MESA personnel performed cardiac MRI using scanners with 1.5-T magnets. Central readers blinded to other study data read cardiac MRI images using commercial software (MASS 4.2; Leiden, The Netherlands). Left ventricular mass was calculated as the difference between the epicardial and endocardial areas, multiplied by slice thickness and the section gap, and then multiplied by the specific gravity of myocardium. Among 75 subjects who underwent repeat MRI measurements, the intraclass correlation coefficient for left ventricular mass was 0.98. We also assessed left ventricular mass indexed to height, weight, and sex using equations that were developed in previous MESA analyses. The MESA defined LVH by a left ventricular mass index >55.3 g/m² for women or >107.8 g/m² for men, which correspond to sex-specific 95th percentile scores in subjects without diabetes mellitus or hypertension.

Study personnel at each site measured coronary calcium using ECG-gated electron beam computed tomography or multidetector row helical computed tomography. Personnel scanned participants twice in succession over phantoms of known physical calcium concentration. Central readers blinded to other study data averaged results from the 2 scans and calculated coronary calcium scores using the Agatston method. Interobserver and intraobserver agreement for coronary calcium were 0.90 and 0.93, respectively.

Trained examiners performed carotid ultrasound imaging centered on a 10-mm segment of the common carotid arteries ±1 cm below the common carotid bulb. Common carotid IMT was measured centrally by trained readers and defined as the mean of the maximum IMT of the near and far walls of the right and left sides. In replicate readings, the between-reader correlation coefficient was 0.84 to 0.86. Carotid artery plaques were defined as any versus none in the common or internal artery.

Ascertainment of Cardiovascular Events

MESA personnel screened participants for incident events through telephone contacts and scheduled follow-up examinations. Potential events prompted collection of hospitalization records, outpatient reports, and death certificates. Two study physicians blinded to other study data independently reviewed the medical records. For the purposes of this study, we considered incident heart failure events as probable or definite cases of heart failure. The MESA Events Committee defined probable heart failure by a physician diagnosis of heart failure plus medical treatment for heart failure. The Events Committee defined definite heart failure by the above criteria plus either echocardiographic or chest x-ray evidence of heart failure. The committee defined coronary heart disease as myocardial infarction, definite angina, probable angina if followed by coronary artery bypass grafting or percutaneous coronary intervention, resuscitated cardiac arrest, or coronary heart disease death. The committee defined ischemic stroke as a focal neurological deficit lasting >24 hours or stroke symptoms lasting <24 hours with clinically relevant lesion on brain imaging.

Other Study Variables

MESA personnel ascertained medical and personal histories using standardized questionnaires and assessed medication use via the inventory method. Study personnel calculated dietary micronutrient intake using a 127-item Block-style food frequency questionnaire and Nutrition Data System for Research software. The University of Vermont Laboratory for Clinical Biochemistry measured serum creatinine using a modified Jaffé reaction that was indirectly calibrated to Cleveland Clinic laboratory standards, serum cystatin C and C-reactive protein concentrations using a BNII system nephelometer (Siemens), and urine albumin and creatinine from spot morning collections using nephelometry and the rate Jaffé reaction, respectively. We measured serum and urine phosphate from previously frozen samples using timed-rate colorimetry on a Beckman-Coulter DxC chemistry analyzer.

MESA investigators defined diabetes mellitus by the use of a diabetes mellitus medication or a fasting blood glucose level ≥126 mg/dL. MESA personnel calculated metabolic equivalent-minutes per day of moderate or vigorous physical activity from self-reported frequency, duration, and intensity of individual activities. We estimated GFR using serum creatinine and cystatin C concentrations from the 2012 CKD-EPI equation that incorporates both of these markers. We defined CKD by the presence of either eGFR <60 mL/min per 1.73 m² or a urine albumin-to-creatinine ratio ≥30 mg/g. Cardiac biomarkers (NT-proBNP [N-terminal pro-brain natriuretic peptide] and troponin T) were previously measured as part of an MESA ancillary study in a subset 5438 participants.
Statistical Analysis

We tabulated baseline characteristics by FGF-23 quartiles and used Kendall τ statistic to report correlations. We used linear regression to estimate cross-sectional associations of FGF-23 with continuous cardiovascular MRI variables and carotid IMT; however, the linear model provided the best statistical fit to the data. We used a proportional odds model to estimate associations of FGF-23 with previously established categories of coronary calcium that predict cardiovascular events: 0, 1 to 100, 101 to 300, and >300 Agatston units. Coefficients from this polytomous model are interpreted as odds ratios for having a higher coronary calcium score per unit difference in exposure (FGF-23 quartile). We used the Kaplan–Meier method to construct cumulative incidence plots and used proportional hazards models to estimate adjusted hazard ratios for time to each binary event. In race-stratified proportional hazard analyses, there was no evidence of nonproportional hazards. We defined time at risk as elapsed time from the baseline examination until the first occurrence of each event or the data were censored because of death, dropout, or end of follow-up.

We adjusted for potential confounders using 2 nested models that were specified before the analyses. The first model was stratified by gender, race, and baseline cardiovascular disease risk factors. The second model was adjusted for education and physical activity. All analyses were performed with SAS software (version 9.4; SAS Institute).
Results

Description of Serum FGF-23 Concentrations

The median and mean (SD) serum FGF-23 concentration was 37.7 and 40.0 (15.2) pg/mL, respectively; 99.4% of FGF-23 values were <100 pg/mL. Mean serum FGF-23 concentrations were quantitatively similar, although statistically different by race/ethnicity: 41.7 pg/mL in whites, 39.3 pg/mL in blacks, 39.8 pg/mL in Chinese Americans, and 38.1 pg/mL in Hispanics (ANOVA \(P\lt0.001\)). Mean FGF-23 concentrations were on average 1.0 pg/mL higher in men compared with women (\(P=0.01\)), and this sex difference was numerically similar across race/ethnicity groups. Serum FGF-23 concentrations were most robustly associated with eGFR (Table 1; rank correlation [\(r\]=−0.18), and less strongly related to serum phosphate (\(r=+0.06\)), urinary phosphate (\(r=+0.02\)), and dietary phosphate intake (\(r=+0.03\)).

Associations With Subclinical Cardiovascular Disease

Higher serum FGF-23 concentrations were associated with progressively greater left ventricular mass and a greater prevalence of LVH (Table 2). Associations of FGF-23 with left ventricular mass were found to be approximately linear and persisted after adjustment for established LVH risk factors. When analyzed continuously, each 20-pg/mL higher serum FGF-23 concentration was associated with an estimated 1.2-g greater left ventricular mass (95% confidence interval, 0.2–2.2 g greater) after full adjustment for covariates in model 2. Higher serum FGF-23 concentrations were similarly associated with left ventricular mass directly indexed to height, weight, and sex and with the left ventricular mass-to-volume ratio. When analyzed categorically, 

Table 2. Associations of FGF-23 With Subclinical Cardiovascular Disease: Left Ventricular Mass

<table>
<thead>
<tr>
<th>FGF-23, pg/mL</th>
<th>Left Ventricular Mass (n=4832)</th>
<th>Mean Differences in Left Ventricular Mass, g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVH, %</td>
<td>Mean, g (SD)</td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>10.5</td>
<td>139.5 (37.8)</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>8.9</td>
<td>144.6 (38.6)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>9.5</td>
<td>146.7 (39.7)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>11.7</td>
<td>149.9 (41.1)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: stratified by race and adjusted for age, sex, study site, height and weight. Model 2: adds diabetes mellitus, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log[urine albumin-to-creatinine ratio]. Average of maximal on right and left (calculated variable in Multi-Ethnic Study of Atherosclerosis [MESA]). FGF-23 indicates fibroblast growth factor-23; and LVH, left ventricular hypertrophy.

Table 3. Associations of FGF-23 With Subclinical Cardiovascular Disease: CAC

<table>
<thead>
<tr>
<th>FGF-23, pg/mL</th>
<th>Prevalence, %</th>
<th>Median Score*</th>
<th>Odds Ratios for Higher CAC Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>43.1</td>
<td>74.8 (223.4)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>48.2</td>
<td>77.6 (271.9)</td>
<td>1.09 (0.95–1.25)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>49.9</td>
<td>88.1 (283.7)</td>
<td>1.08 (0.94–1.24)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>57.3</td>
<td>106.3 (334.8)</td>
<td>1.32 (1.15–1.52)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>&lt;0.001</td>
<td></td>
<td>0.005</td>
</tr>
</tbody>
</table>

Model 1: stratified by race and adjusted for age, sex, study site, height and weight. Model 2: adds diabetes mellitus, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log[urine albumin-to-creatinine ratio]. Average of maximal on right and left (calculated variable in Multi-Ethnic Study of Atherosclerosis [MESA]). CAC indicates coronary calcium; and FGF-23, fibroblast growth factor-23.

*Median Agatston score among participants who had a nonzero coronary calcium score.
Table 4. Associations of FGF-23 With Subclinical Cardiovascular Disease: Carotid IMT

<table>
<thead>
<tr>
<th>FGF-23, pg/mL</th>
<th>Carotid IMT (n=6470)</th>
<th>Mean Differences in Carotid IMT, μm</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Plaque, %*</td>
<td>Mean, μm (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>37.6</td>
<td>852.1 (181.1)</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>40.3</td>
<td>860.5 (181.7)</td>
<td>-4.06 (−15.21 to 7.09)</td>
<td>0.21 (−10.69 to 11.1)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>40.9</td>
<td>866.0 (197.7)</td>
<td>-4.28 (−15.68 to 7.12)</td>
<td>-1.79 (−13.04 to 9.46)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>46.2</td>
<td>896.7 (210.6)</td>
<td>13.09 (0.89 to 25.28)</td>
<td>11.77 (−0.34 to 23.88)</td>
</tr>
</tbody>
</table>

P for trend

Model 1: stratified by race and age, sex, study site, height and weight. Model 2: adds diabetes mellitus, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log(urine albumin-to-creatinine ratio). Average of maximal on right and left (calculated variable in Multi-Ethnic Study of Atherosclerosis [MESA]). FGF-23 indicates fibroblast growth factor-23. IMT, intima-media thickness.

*Median Agatston score among participants who had a nonzero coronary calcium score.

The overall prevalence of coronary calcium was 49.6%, and the median coronary calcium score among subjects who had a positive score was 86.5 Agatston units. In unadjusted analyses, higher serum FGF-23 concentrations were associated with a greater prevalence and a greater extent of coronary calcification (Table 3). After full adjustment, higher FGF-23 concentrations were associated with significantly greater coronary calcium scores. Carotid IMT values tended to be greatest in the highest FGF-23 quartile; however, associations of FGF-23 with carotid IMT were not statistically significant (Table 4). Associations of FGF-23 concentrations with coronary calcium and IMT measures were generally linear (Figure I in the Data Supplement).

Associations With Incident Cardiovascular Events

Median (intraquartile range) follow-up times for incident heart failure events (n=183), incident coronary heart disease events (n=363), and incident stroke events (n=140) were 8.5 (7.7–8.6), 8.5 (7.6–8.6), and 8.5 (7.7–8.6) years, respectively. Serum FGF-23 concentrations were most strongly associated with incident heart failure (Table 5; Figure 1). Crude heart failure incidence rates were 2-fold greater, comparing the highest to the lowest quartile of FGF-23. After full adjustment, each 20-pg/mL greater FGF-23 concentration was associated with an estimated 19% greater risk of heart failure (hazard ratio, 1.19; 95% confidence interval, 1.03–1.37) and a 14% greater risk of incident coronary heart disease (hazard ratio, 1.14; 95% confidence interval, 1.01–1.28). FGF-23 was not associated with stroke (hazard ratio, 1.04; 95% confidence interval, 0.86–1.27). Associations of FGF-23 with heart failure and coronary disease events were approximately linear (Figure II in the Data Supplement).

Sensitivity Analyses

Associations of FGF-23 with heart failure and coronary disease events were minimally altered by further adjustment for serum and urine phosphate concentrations, dietary phosphate intake, and serum 25-hydroxyvitamin D concentrations (Table 6). Moreover, associations of FGF-23 with cardiovascular events were unaltered by adjustment for cardiovascular medications or for serum concentrations of low-density lipoprotein, high-density lipoprotein, and triglycerides plus statin use. The associations of FGF-23 with coronary heart disease events were qualitatively similar after excluding angina cases from this outcome. Among the 182 heart failure events, 30 were preceded by a coronary heart disease event. Associations of FGF-23 with heart failure were unchanged when analyses were censored for coronary heart disease.

Table 5. Associations of FGF-23 With Incident Cardiovascular Events

<table>
<thead>
<tr>
<th>FGF-23, pg/mL</th>
<th>Rate Per 1000 Person-Years (Events)</th>
<th>Adjusted Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Heart failure (n=183)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>2.1 (26)</td>
<td>Reference</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>2.9 (36)</td>
<td>1.25 (0.75, 2.06)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>3.9 (49)</td>
<td>1.56 (0.96, 2.52)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>5.8 (72)</td>
<td>2.02 (1.27, 3.22)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary heart disease (n=363)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>5.5 (68)</td>
<td>Reference</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>6.3 (78)</td>
<td>1.03 (0.74, 1.44)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>7.2 (89)</td>
<td>1.14 (0.83, 1.58)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>10.4 (128)</td>
<td>1.51 (1.11, 2.05)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke (n=140 events)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30.5</td>
<td>2.8 (35)</td>
<td>Reference</td>
</tr>
<tr>
<td>30.5–37.7</td>
<td>2.1 (27)</td>
<td>0.72 (0.43, 1.2)</td>
</tr>
<tr>
<td>37.7–46.4</td>
<td>2.8 (35)</td>
<td>0.89 (0.56, 1.42)</td>
</tr>
<tr>
<td>46.4–223</td>
<td>3.4 (43)</td>
<td>0.98 (0.62, 1.54)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.821</td>
</tr>
</tbody>
</table>

Model 1: stratified by race and age, sex, study site, height and weight. Model 2: adds diabetes mellitus, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log(urine albumin-to-creatinine ratio). FGF-23 indicates fibroblast growth factor-23.
Subgroup Analyses

The size of associations of FGF-23 with heart failure and coronary heart disease events did not differ materially or statistically by race/ethnicity (Figure 2; P for interaction >0.4). Similarly, associations of FGF-23 with cardiovascular events were numerically and statistically similar by age, sex, serum phosphate concentration, and CKD status. The association of FGF-23 with heart failure and coronary heart disease events was also similar across quartiles of the urinary phosphate-to-creatinine ratio (P for interaction >0.5).

Discussion

In a community-based, multiethnic cohort that was initially free of clinical cardiovascular disease, we found higher serum FGF-23 concentrations to be associated with modest differences in subclinical cardiovascular disease: left ventricular mass and coronary artery calcification, and with clinical cardiovascular events: heart failure and coronary heart disease. We did not observe associations of FGF-23 with carotid IMT or incident stroke. Although power to detect interactions by race/ethnicity may be limited, associations of FGF-23 with cardiovascular events were quantitatively similar in white, black, Chinese, and Hispanic participants.

Experimental evidence supports a possible causal role for FGF-23 in cardiovascular disease development. In isolated rat ventricular myocytes, FGF-23 promotes dose-dependent expansion of myocardial surface area and stimulates the expression of atrial and brain natriuretic peptides. Injection of recombinant FGF-23 into adult mice significantly increases heart weight and left ventricular wall thickness. FGF-23

Table 6. Sensitivity Analyses for Incident Heart Failure and Coronary Heart Disease Events

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>Coronary Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Hazard Ratio</td>
<td>Adjusted Hazard Ratio</td>
</tr>
<tr>
<td></td>
<td>(95% Confidence Interval)</td>
<td>(95% Confidence Interval)</td>
</tr>
<tr>
<td>Association per 20 pg/mL greater FGF-23</td>
<td>1.19 (1.03–1.37)</td>
<td>1.13 (1.01–1.26)</td>
</tr>
<tr>
<td>Additional adjustments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add adjustment for serum phosphate</td>
<td>1.17 (1.01–1.35)</td>
<td>1.12 (1.00–1.25)</td>
</tr>
<tr>
<td>Add adjustment for urine phosphate</td>
<td>1.19 (1.03–1.37)</td>
<td>1.14 (1.02–1.27)</td>
</tr>
<tr>
<td>Add adjustment for dietary phosphate</td>
<td>1.18 (1.01–1.37)</td>
<td>1.12 (0.99–1.25)</td>
</tr>
<tr>
<td>Add adjustment for serum 25-hydroxyvitamin D</td>
<td>1.21 (1.04–1.41)</td>
<td>1.15 (1.02–1.29)</td>
</tr>
<tr>
<td>Modified definitions of events:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclude angina from coronary heart disease events</td>
<td></td>
<td>1.12 (0.96–1.30)</td>
</tr>
<tr>
<td>Censor heart failure analyses for coronary heart disease</td>
<td>1.20 (1.03–1.40)</td>
<td></td>
</tr>
</tbody>
</table>

Model 2: stratified by race and adjusted for age, sex, study site, height, weight, diabetes mellitus, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log(urine albumin-to-creatinine ratio). FGF-23 indicates fibroblast growth factor-23.
also inhibits 1,25-dihydroxyvitamin D, the potent biological form of vitamin D, via effects on CYP27B1 and CYP24A1 enzymes. Experimental disruption of the vitamin D receptor directly modulates the contractile properties of cardiomyocytes, stimulates the renin–angiotensin system, and promotes cardiac hypertrophy. Klotho, a key cofactor for FGF-23 binding, is linked with an advanced aging phenotype in animal models, and some klotho gene polymorphisms are associated with cardiovascular diseases in humans.

Most human studies of FGF-23 have focused on patients with established CKD who tend to have markedly elevated serum FGF-23 concentrations and prevalent cardiovascular diseases. In the Chronic Renal Insufficiency Cohort study, the largest prospective study of CKD to date, higher serum FGF-23 concentrations are associated with prevalent LVH, new-onset LVH during follow-up, and all-cause mortality. Among 1099 late-stage CKD patients from the Homocysteinemia in Kidney and End Stage Renal Disease Trial, higher serum FGF-23 concentrations are associated with a composite outcome of myocardial infarction, amputation, or stroke. However, FGF-23 was not associated with stroke in a subanalysis of individual events.

Emerging data from non-CKD populations also demonstrate associations of FGF-23 with LVH and cardiovascular events. A study of 795 general older Swedish adults reported associations of higher serum FGF-23 concentrations with a greater prevalence of LVH, assessed by echocardiography. A related study using whole-body magnetic resonance angiography in 306 older adults found higher FGF-23 concentrations to be associated with greater total atherosclerosis burden. A cohort study of older US adults (mean age, 78 years) found associations of higher serum FGF-23 concentrations with a composite outcome of myocardial infarction, stroke, or cardiovascular death and separately with heart failure. FGF-23 is also associated with all-cause mortality among stable outpatients who have established coronary artery disease.
In contrast, a nested case–control study of male participants in the Health Professionals Follow-Up Study found no association of FGF-23 with a composite outcome of nonfatal myocardial infarction plus fatal coronary heart disease.1,32

Our study builds on previous work in several ways. First, we assessed associations of FGF-23 with concurrent measurements of subclinical cardiovascular disease among individuals who were free of clinically apparent disease, strengthening inference for a possible role of FGF-23 in disease development. Second, we evaluated separate associations for adjudicated heart failure, coronary disease, and stroke events, which may occur through divergent biological pathways. Third, we adjusted for a set of established cardiovascular risk factors that were measured using uniform procedures, including estimates of kidney function by serum cystatin C, serum creatinine, and urine albumin excretion. Fourth, we demonstrated numerically similar associations with cardiovascular events across 4 major race/ethnicity categories in a large, multietnic study population that specifically oversampled black, Chinese, and Hispanic individuals. Stratified analyses by race/ethnicity are important given known race-specific differences in mineral metabolism and cardiovascular disease development.

Our study has some limitations. We cannot prove causal relationships of FGF-23 with cardiovascular disease outcomes because observed associations may be confounded by other factors that were not measured in this study. FGF-23 represents an individual biomarker within complex pathways of bone and phosphate metabolism. Other factors within these pathways may be linked with both FGF-23 and cardiovascular disease development. Measurements of FGF-23 and subclinical cardiovascular disease were contemporaneous, precluding demonstration of temporal relationships. Heart failure cases in MESA were defined based on the presence of symptomatic disease; however, cases were not subcategorized as to systolic or diastolic dysfunction, because information necessary for this distinction was not uniformly available. In summary, we observed associations of higher serum FGF-23 concentrations with subclinical and clinical cardiovascular disease outcomes in a large, multietnic, community-based cohort study. Our findings suggest that FGF-23 may be a novel risk factor for the development of heart failure and coronary heart disease in the general population. Important next steps include confirmation of these findings in other general, healthy populations, clarification of clinically relevant FGF-23 concentrations in terms of cardiovascular risk, and further exploration of putative mechanisms that may link FGF-23 with cardiovascular disease.

Acknowledgments

We thank the investigators, staff, and participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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Disclosures

Dr Kestenbaum reports receiving consulting fees and grant support from Amgen Inc. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Fibroblast growth factor-23 (FGF-23) is a phosphate regulatory hormone that is associated with ventricular hypertrophy, cardiovascular events, and mortality among people who have chronic kidney disease. In animal models, FGF-23 directly stimulates left ventricular growth. Whether FGF-23 is related to clinical cardiovascular disease in the general population is unknown. We measured serum intact FGF-23 concentrations in 6547 cardiovascular disease–free individuals from the Multi-Ethnic Study of Atherosclerosis (MESA). After adjustment for traditional risk factors, higher FGF-23 concentrations were associated with greater left ventricular mass, measured by cardiac MRI, and greater coronary artery calcification scores, measured by computed tomography. During 7.5-year follow-up, each 20-pg/mL higher serum FGF-23 concentration was associated with an estimated 19% greater adjusted risk of incident heart failure events (95% confidence interval, 3%–37% greater) and a 14% greater adjusted risk of coronary heart disease (95% confidence interval, 1%–28% greater). FGF-23 was not associated with stroke. In summary, higher serum FGF-23 concentrations were associated with subclinical cardiovascular disease, new heart failure events, and new coronary heart disease events. FGF-23 may be a novel cardiovascular risk factor in the general population.
Fibroblast Growth Factor-23 and Cardiovascular Disease in the General Population: The Multi-Ethnic Study of Atherosclerosis


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### Supplemental Table. Associations of FGF-23 with cardiac magnetic resonance imaging data.

<table>
<thead>
<tr>
<th>FGF-23 (pg/mL)</th>
<th>Adjusted Left Ventricular (LV) Mass</th>
<th>Difference in adjusted LV Mass (95% CI)</th>
<th>LV mass to volume ratio</th>
<th>Difference in LV mass to volume ratio (95% CI)</th>
<th>LV end diastolic volume (mL)</th>
<th>Difference in LV end diastolic volume (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent predicted (standard deviation)</td>
<td>Model 1</td>
<td>Model 2</td>
<td>Mean (standard deviation)</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>&lt; 30.5</td>
<td>103.83 (18.55)</td>
<td>reference</td>
<td>reference</td>
<td>103.82 (19.26)</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>30.5 – 37.7</td>
<td>103.63 (18.30)</td>
<td>0.2 (-1.23, 1.62)</td>
<td>0.66 (-0.67, 2)</td>
<td>103.91 (21.00)</td>
<td>-0.16 (-1.67, 1.36)</td>
<td>0.08 (-1.4, 1.56)</td>
</tr>
<tr>
<td>37.7 – 46.4</td>
<td>103.58 (19.02)</td>
<td>0.56 (-0.9, 2.01)</td>
<td>0.98 (-0.38, 2.34)</td>
<td>105.45 (21.19)</td>
<td>1.25 (-0.28, 2.78)</td>
<td>1.21 (-0.28, 2.7)</td>
</tr>
<tr>
<td>46.4 – 223</td>
<td>104.64 (19.46)</td>
<td>1.85 (0.32, 3.37)</td>
<td>1.63 (0.21, 3.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-for-trend</td>
<td></td>
<td>0.018</td>
<td>0.024</td>
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</tr>
</tbody>
</table>

**Note:** P-values are calculated using linear mixed-effects models with adjustment for age, sex, and body mass index.
<table>
<thead>
<tr>
<th>Range</th>
<th>LV stroke volume (mL)</th>
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<th>LV ejection fraction</th>
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<td>reference</td>
<td>69.50 (7.18)</td>
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<td>0.33 (-0.96, 1.61)</td>
<td>68.78 (7.30)</td>
</tr>
<tr>
<td>37.7 – 46.4</td>
<td>86.61 (19.61)</td>
<td>-0.85 (-2.14, 0.44)</td>
<td>-0.59 (-1.87, 0.69)</td>
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P-for-trend

Model 1: Stratified by race and adjusted for age, sex, study site, height and weight.

Model 2: Adds diabetes, systolic blood pressure, any hypertension medication, current smoking, log C-reactive protein concentration, and education level (high school or less, high school to some college, college degree or more), estimated glomerular filtration rate (creatinine/cystatin C) and log(urine albumin to creatinine ratio).
Supplemental Figure 1. Continuous associations of serum FGF-23 concentrations with subclinical cardiovascular disease measures.

Y-axis depicts left ventricular mass (left panel), coronary artery calcium score (middle panel), and carotid intima-media thickness (right panel). X-axis depicts serum FGF-23 concentrations (pg/mL). Plots demonstrate penalized splines, shown as black lines, and raw data, shown as grey circles, for 99.7% of the study data (serum FGF-23 concentrations <120 pg/mL). All models are adjusted for age, race/ethnicity, gender, height, weight, and study site. Coronary calcium data are shown as ln(coronary calcium score + 25).

Supplemental Figure 2. Continuous associations of serum FGF-23 concentrations with incident cardiovascular events.

Y-axis depicts the adjusted log hazard of incident coronary heart disease (left panel), heart failure (middle panel), and stroke events (right panel) during follow-up. X-axis depicts serum FGF-23 concentrations (pg/mL). Plots demonstrate penalized splines, shown as solid black lines, and point wise 95% confidence limits, shown as dashed black lines, for 99.7% of the study data (serum FGF-23 concentrations <120 pg/mL). All models are adjusted for age, race/ethnicity, gender, height, weight, and study site.
Supplemental Figure 1. Continuous associations of serum FGF-23 concentrations with subclinical cardiovascular disease measures.
Supplemental Figure 2. Continuous associations of serum FGF-23 concentrations with incident cardiovascular events.