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Association of fibroblast growth factor-23 with arterial stiffness in the Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background. Serum fibroblast growth factor-23 (FGF-23) is associated with cardiovascular disease (CVD), yet the mechanisms remain uncertain. Our objective was to determine whether higher FGF-23 concentrations are associated with arterial stiffness.

Methods. In this cross-sectional study, serum FGF-23 concentrations were measured in 5977 participants without known CVD in the Multi-Ethnic Study of Atherosclerosis. The primary outcomes of interest were large (LAE) and small artery elasticity (SAE), pulse pressure and ankle-brachial index (ABI) > 1.30. LAE and SAE were measured by pulse contour analysis of the radial artery. Pulse pressure was measured with an automated sphygmomanometer using the average of two
resting blood pressure measurements. ABI was calculated as the ratio of the ankle and brachial systolic blood pressures.

**Results.** Serum FGF-23 concentrations were not significantly associated with LAE [relative difference (RD) per doubling: 0%; 95% confidence interval (CI): −2–1%], SAE (RD per doubling: 0%; 95% CI: −3–2%), pulse pressure (β per doubling: 0.44; 95% CI: −0.31–1.19), or a high ABI (odds ratio per doubling: 1.14; 95% CI: 0.84–1.55). Findings were similar irrespective of chronic kidney disease status.

**Conclusions.** Higher serum FGF-23 concentrations are not associated with arterial stiffness, as measured by pulse pressure, LAE, SAE or high ABI, in a community-based population without CVD.

**Keywords:** ABI, arterial elasticity, arterial stiffness, FGF-23, pulse pressure

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**INTRODUCTION**

Fibroblast growth factor-23 (FGF-23) is a circulating osteocyte-derived hormone that plays a key role in regulating serum phosphorous metabolism. FGF-23 responds to increased serum phosphorous concentrations by promoting phosphorous excretion and by inhibiting 1-α-hydroxylase in the renal proximal tubule [1, 2]. Markedly elevated serum concentrations of FGF-23 are often seen in patients with advanced chronic kidney disease (CKD) [3], likely as a compensatory response to the hyperphosphatemia prevalent in this population.

Previous studies have shown an association of FGF-23 concentrations with left ventricular mass and left ventricular hypertrophy, even after adjustment for kidney function, and this finding appears to be causal in animal studies [4, 5]. Additionally, multiple studies have demonstrated an association of FGF-23 with mortality in patients with end-stage renal disease, advanced CKD [6, 7] and coronary artery disease [8]. A recent study demonstrated that FGF-23 is independently associated with mortality and incident heart failure in a community-based elderly population, and this association is most pronounced in patients with CKD [9].

While these findings linking higher FGF-23 with poor cardiovascular outcomes are very strong, particularly in patients with CKD, the mechanisms remain unclear. One possible contributor is direct cardiotoxicity of FGF-23, as high FGF-23 has been shown, experimentally, to promote left ventricular hypertrophy [5]. Nonetheless, the role of FGF-23 in ventricular remodeling has not been definitively delineated, as another group found that neutralizing antibodies to FGF-23 did not have any effect on cardiac hypertrophy in rats with CKD [10]. Aberrant calcium and phosphorous homeostasis has consistently been linked with arterial calcification and stiffness. Because FGF-23 is integral in regulating phosphorous and vitamin D metabolism, it may also induce arterial calcification and stiffness. However, there is considerable controversy because some [11, 12], but not all, prior studies have observed associations of FGF-23 with arterial calcification [13]. Moreover, FGF-23 typically requires its co-receptor, Klotho, to bind to target tissues and exert its biological effects. Most studies show no expression of Klotho in human vascular cells [13, 14], although one recent study has suggested that its expression may be induced by vitamin D receptor activators in human aortic smooth muscle cells [15].

In addition, FGF-23 concentrations are strongly related to kidney function, and arterial stiffness has strong associations with estimated glomerular filtration rate (eGFR) in both cross-sectional and longitudinal studies. Multiple community-based studies have demonstrated associations between measures of increased arterial stiffness [such as lower large artery elasticity (LAE) and small artery elasticity (SAE) [16–18], higher pulse pressure [16, 19] and high ankle-brachial index (ABI) [20–23]] with increased cardiovascular morbidity and mortality, as well as incident hypertension, coronary heart disease, stroke, heart failure and kidney function decline.

The objective of this study was to determine whether there is an independent association between FGF-23 and arterial stiffness, as measured by LAE, SAE, pulse pressure and high ABI.

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**MATERIALS AND METHODS**

**Participants**

The study was a cross-sectional analysis from the baseline examination of the Multi-Ethnic Study of Atherosclerosis (MESA), conducted in 2000–2002 [24]. Briefly, MESA was designed to understand subclinical cardiovascular disease (CVD) and its progression in a multi-ethnic cohort. The study recruited 6814 men and women aged 45–84 years who were free of clinically apparent CVD from six cities in the USA: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. Participants identified themselves as white, black, Hispanic or Chinese.

We measured FGF-23 in stored baseline fasting serum samples for all MESA participants with available samples (n = 6552; 96.2%). For these analyses, we excluded persons who lacked measurements of serum (n = 20) or urine phosphorous (n = 52), serum (n = 5) or urine creatinine (n = 3), small and large artery elasticities (n = 448), ABI (n = 45) or systolic and diastolic blood pressures (n = 2). After exclusions, the total sample size was 5977 persons.

**Primary predictor variable**

**FGF-23.** Serum intact FGF-23 was measured using a commercially available immunoassay that measures the full-length peptide by recognizing both mid-molecule and distal epitopes (Kainos Laboratories, Japan), with a lower limit of detection of 3 pg/mL. Notably, a recent study showed poor agreement between the commercially available assays and found the Kainos assay to have the most reproducible performance characteristics [25]. Standardized high- and low-value FGF-23 controls were used within each run to monitor quality control. The coefficient of variation for high and low control samples were 6.7 and 12.4%, respectively. Serum and urine phosphorous were measured using the timed-rate colorimetry reaction on a Beckman Coulter DxC automated analyzer. Urine
samples were acidified prior to measurement to reduce calcium-phosphorous precipitation.

**Primary outcome variables**

**SAE and LAE.** The methods for measuring LAE and SAE were as previously described [16, 17]. Radial artery pulse waveforms were measured with the HDI PulseWave CR-2000 Research Cardiovascular Profiling Instrument (Hypertension Diagnostics, Inc., Eagan, Minnesota). With the patient supine, the pulse pressure sensor was placed on the supported wrist of the dominant arm, and a blood pressure cuff was placed on the contralateral arm over the brachial artery. Measurements were taken for 30 s.

Arterial capacitive (C1) and oscillatory (C2) indices were obtained using a third-order, six-element Windkessel model that was derived from the diastolic pulse contour, as previously described [17]. The pressure at the radial artery at time (t) at the beginning of diastole was modeled as a decaying exponential function plus a sinusoidal function dampened by a decaying exponential. Systemic vascular resistance (SVR) was calculated as mean arterial pressure divided by cardiac output (CO), and CO was estimated using heart rate, ejection time and body surface area. Estimates combining information from the waveform and SVR variables were used to determine C1 and C2. The terms LAE and SAE were used to describe C1 and C2, respectively, as recommended by Hypertension Diagnostics, Inc. and as done in previous studies [16, 17]. One previous MESA study described the reproducibility of these elasticity measures and found the between-measure correlations for LAE and SAE to be 0.74 and 0.84, respectively [26].

**Pulse pressure.** Seated, resting blood pressure was measured three times in each participant using an automated oscillometric sphygmomanometer, and the average of the last two measurements was used in the analyses. Pulse pressure was calculated as the difference between the systolic and diastolic blood pressures.

**ABI.** ABI was measured as previously described [27]. Briefly, the systolic blood pressure (SBP) measurements in the bilateral brachial, dorsalis pedis and posterior tibial arteries were obtained in the supine position using a hand-held Doppler instrument with a 5-mHz probe. The higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator was the highest pressure (dorsalis pedis or posterior tibial) from that leg. The leg cuff was inflated to a maximum of 300 mmHg, and if a pulse was still detected at this level, the ABI was classified as ‘incompressible.’ For each participant, the higher of the two leg-specific ABI measurements was used. ABI was categorized as low (<0.9), normal (0.9–1.3) or high (>1.3 or ‘incompressible’). High ABI was considered to be a marker of increased arterial stiffness, as it has been strongly linked to medial arterial calcification [28] and has been associated with mortality [20]. Low ABI was considered to be a marker of atherosclerosis.

**Other measurements.** Age, gender, race/ethnicity, medical history and smoking history were obtained using standardized questionnaires. Smoking history was categorized as ever versus never. Diabetes was defined as a fasting glucose of ≥126 mg/dL or use of hypoglycemic medications. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Total and high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were measured from venous samples using standard methods. Urine albumin and creatinine were measured in a single morning urine sample by nephelometry and the rate Jaffé equation, respectively, and eGFR was calculated from the serum creatinine and cystatin C concentrations using the Chronic Kidney Disease Epidemiology Collaboration combined creatinine-cystatin C equation [29].

**Statistical methods.** Serum FGF-23 concentrations were log-transformed and analyzed as a continuous linear variable and also categorized by quintiles. Baseline characteristics of the MESA participants were compared by FGF-23 quintile, and differences in these characteristics across quintiles were evaluated using ANOVA or the Kruskal–Wallis test for continuous variables, and the χ² test for categorical variables, as appropriate. In addition, because the range of FGF-23 concentrations is lower in the general population than in persons with CKD, the highest decile of FGF-23 concentrations was also evaluated as a potential cut point.

The associations of FGF-23 concentrations and the ABI categories were evaluated using multimonial logistic regression, with the intermediate ABI category serving as the reference group. LAE, SAE and pulse pressure were analyzed as continuous variables using linear regression. In these models, LAE and SAE were log-transformed due to their skewed distributions. To improve interpretation of FGF-23’s associations with LAE and SAE, the β coefficients were back-transformed to represent a relative difference (RD) in LAE or SAE. For example, an RD of −5% for LAE signifies that a higher increment of FGF-23 is associated with 5% lower LAE.

The initial models were adjusted for demographics (age, gender, race and clinic site), and the fully adjusted models were adjusted for demographics, diabetes (DM), smoking status, BMI, SBP, total cholesterol, HDL cholesterol, eGFR, serum calcium, intact parathyroid hormone (PTH), serum phosphorus, 25-hydroxy (25-OH) vitamin D, antihypertensive medication use and statin use. However, SBP was left out of the fully adjusted models for the pulse pressure and ABI analyses, as SBP is used in the calculations for both outcomes. In addition, all models were repeated after stratification by CKD status, and interaction testing between FGF-23 and CKD status was performed.

All statistical analyses were conducted with S-Plus (version 8.0, Tibco, Seattle, WA, USA) and SPSS statistical software (version 15.0.1.1, SPSS, Inc., Chicago, IL, USA).

**RESULTS**

The mean age of the 5977 study participants was 62 ± 10 years, and 53% were female. Thirty-eight percent were white, 13% were Chinese, 27% were black and 22% were Hispanic. The mean serum FGF-23 concentration was 40 ± 18 pg/mL.
(median, 38 pg/mL; interquartile range, 30–46 pg/mL); mean eGFR was 84 ± 17 mL/min per 1.73 m², and 490 participants (8%) had eGFR < 60 mL/min per 1.73 m². Compared with participants with lower FGF-23 concentrations, those in the highest quintile were older, more likely to be white, to have hypertension, diabetes and to use statins (Table 1). Other notable differences for the highest FGF-23 quintile were higher SBP, triglycerides, 25-OH vitamin D, serum phosphorous concentrations, urine albumin-to-creatinine ratio (ACR) and lower eGFR.

In both the continuous and categorical analyses, no significant association was observed between FGF-23 concentrations and either LAE or SAE (Table 2). Threshold analyses, comparing participants with FGF-23 > 57 pg/mL (top decile) to the rest of the cohort, also revealed no significant association of FGF-23 with either LAE or SAE. The fully adjusted analyses were repeated without adjusting for SBP, and the results were generally similar (data not shown).

In the demographically adjusted continuous models for pulse pressure, there was a significant association between higher FGF-23 concentrations and larger pulse pressure, but this association was substantially attenuated in the fully adjusted model. In the categorical models, the highest quintile of FGF-23 had a significantly higher pulse pressure compared with the lowest quintile (referent group) in the demographically adjusted analysis, but this association was also substantially attenuated in the fully adjusted model. The highest decile of FGF-23 was associated with a large pulse pressure difference, and while this association was attenuated in the fully adjusted model, it remained statistically significant.

In the analyses of the association of FGF-23 with ABI, no significant association was apparent between FGF-23 and either high or low ABI in any of the models (Table 3). In subgroup analyses of MESA participants with CKD (n = 905), defined by either eGFR < 60 mL/min/1.73 m² or ACR > 30 mg/g, the findings were generally similar (Supplementary data Table S1 and S2). The median values [with interquartile ranges] for eGFR, ACR and FGF-23 in this group were 54 [47, 57] mL/min/1.73 m², 9.0 [4.3, 31.3] mg/g and 47.2 [38.1, 58.6] pg/mL, respectively. Additionally, no significant interaction was observed between FGF-23 and CKD status (P interactions all >0.05; Table 4).

| Table 1. Characteristics of study participants by quintiles of FGF-23: the MESA |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Range                          | FGF-23 quintiles (pg/mL) | P-value    |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| N                              | 1201            | 1182            | 1203            | 1208            | 1183            |
| Demographics                   |                 |                 |                 |                 |                 |
| Age (y)                        |                 |                 |                 |                 |                 |
| Male                           | 60 (10)         | 62 (10)         | 62 (10)         | 62 (10)         | 64 (10)         | <0.001          |
| Race/ethnicity                 |                 |                 |                 |                 |                 |
| White                          | 378 (32%)       | 433 (37%)       | 447 (37%)       | 506 (42%)       | 530 (45%)       | <0.001          |
| Chinese                        | 140 (12%)       | 152 (13%)       | 169 (14%)       | 137 (11%)       | 154 (13%)       |                 |
| Black                          | 355 (30%)       | 305 (26%)       | 332 (28%)       | 297 (25%)       | 299 (25%)       |                 |
| Hispanic                       | 328 (27%)       | 292 (25%)       | 255 (21%)       | 268 (22%)       | 200 (17%)       |                 |
| Medical history                |                 |                 |                 |                 |                 |
| Hypertension                   | 477 (40%)       | 475 (40%)       | 501 (42%)       | 551 (46%)       | 625 (53%)       | <0.001          |
| Antihypertensive meds          | 366 (30%)       | 372 (32%)       | 403 (34%)       | 466 (39%)       | 571 (48%)       | <0.001          |
| Diabetes                       | 145 (12%)       | 158 (13%)       | 134 (11%)       | 127 (11%)       | 179 (15%)       | 0.281           |
| Smoking status                 |                 |                 |                 |                 |                 |
| Never                          | 589 (49%)       | 603 (51%)       | 612 (51%)       | 601 (50%)       | 643 (54%)       | <0.001          |
| Former                         | 400 (33%)       | 421 (36%)       | 435 (36%)       | 462 (38%)       | 440 (37%)       |                 |
| Current                        | 207 (17%)       | 157 (13%)       | 155 (13%)       | 140 (12%)       | 98 (8%)         |                 |
| Statin use                     | 149 (12%)       | 167 (14%)       | 159 (13%)       | 191 (16%)       | 209 (18%)       | 0.002           |
| Measurements                   |                 |                 |                 |                 |                 |
| BMI (kg/m²)                    | 27.7 (5.4)      | 27.8 (5.2)      | 27.9 (5.3)      | 28.8 (5.3)      | 28.9 (5.7)      | <0.001          |
| SBP (mmHg)                     | 125 (22)        | 125 (21)        | 125 (21)        | 127 (21)        | 128 (22)        | <0.001          |
| Total cholesterol (mg/dL)      | 193 (34)        | 194 (35)        | 193 (34)        | 195 (36)        | 195 (37)        | 0.101           |
| HDL cholesterol (mg/dL)        | 54 (15)         | 51 (14)         | 51 (14)         | 49 (14)         | 50 (14)         | <0.001          |
| Triglycerides (mg/dL)          | 105 [73, 152]   | 107 [77,158]    | 107 [74,156]    | 118 [84,171]    | 122 [84,177]    | <0.001          |
| Serum calcium (mg/dL)          | 9.61 (0.38)     | 9.62 (0.37)     | 9.63 (0.38)     | 9.68 (0.39)     | 9.71 (0.44)     | <0.001          |
| eGFR (mL/min/1.73 m²)          | 90 (15)         | 87 (16)         | 85 (16)         | 82 (16)         | 76 (19)         | <0.001          |
| 25-OH vitamin D (mg/L)         | 23 (11)         | 25 (11)         | 25 (11)         | 25 (11)         | 28 (12)         | <0.001          |
| Serum phosphorous (mg/dL)      | 3.61 (0.49)     | 3.65 (0.51)     | 3.64 (0.50)     | 3.68 (0.51)     | 3.75 (0.57)     | <0.001          |
| eGFR < 60 mL/min/1.73 m²        | 39 (3%)         | 48 (4%)         | 72 (6%)         | 113 (9%)        | 218 (19%)       | <0.001          |
| ACR ≥ 10 mg/g                  | 86 (7%)         | 86 (7%)         | 102 (9%)        | 104 (9%)        | 163 (14%)       | <0.001          |

Data are n (%) for categorical variables, mean (SD) or median [range] for continuous variables, as appropriate.

BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; ACR, urine albumin-to-creatinine ratio; eGFR, estimated GFR.
DISCUSSION

In this study, we explored whether higher FGF-23 concentrations were associated with markers of arterial stiffness. We chose a cohort without prevalent CVD to understand the potential associations with incident CVD risk and minimize reverse causality.

Smaller prior studies have evaluated the association of FGF-23 with arterial stiffness measures. In a cohort of 142...
patients with CKD, Desjardins et al. found no association between FGF-23 and pulse wave velocity (PWV) [12]. Similarly, in a study of 200 patients with CKD stage III–IV, Ford et al. also found no association between FGF-23 and PWV in their fully adjusted model [30]. Though different measures of arterial stiffness were used, and though we evaluated a community-living cohort predominantly without CKD, the results of these studies are consistent with those of the present study. In contrast, Mirزا et al. analyzed a community-based cohort of 967 persons aged 70 and found that higher serum FGF-23 concentrations were associated with arterial stiffness, as measured by pulse wave analysis, and this association was stronger in patients with impaired renal function (eGFR < 60 mL/min/1.73 m²) [31]. Notably, this study analyzed an older population from a single community in Sweden and used a measure of arterial stiffness (reflection index) not used in our study, potentially explaining the difference in our findings. Given the larger size and demographic diversity of MESA and the multiple measures of arterial stiffness used in our study, our analysis strongly suggests that there is minimal, if any, association between FGF-23 and arterial stiffness in the general adult population in the USA.

In our fully adjusted threshold model, the highest decile of FGF-23 was associated with larger pulse pressure. Although this finding was statistically significant, the strength of the association was relatively weak. Given the null findings when we evaluated continuous and categorical models and the large sample size of this study, we conclude that there is not a robust association between FGF-23 and pulse pressure.

In our subgroup analysis of participants with CKD, we did not find associations between FGF-23 concentrations and any of the measures of arterial stiffness, although power was lower for this analysis (n = 905). This finding is interesting given that the association of FGF-23 concentrations with all-cause mortality and incident heart failure is stronger in patients with CKD [9, 32]. Thus, while the presence of CKD has been found to augment the risk of CVD outcomes in patients with higher FGF-23 concentrations, we found that it did not appear to modify the association of FGF-23 with arterial stiffness.

A recent experimental study found that protein levels of Klotho, the obligate co-receptor for FGF-23 in kidney and parathyroid tissues, were undetectable in arteries harvested from mice, and FGF-23 treatment did not affect arterial function in ex vivo studies of murine mesenteric arteries [14]. Similarly, Scialla et al. recently found no association between serum FGF-23 concentrations and either coronary artery or thoracic aorta calcification in patients with mild-to-moderate CKD [13]. The same study also demonstrated that in vitro exposure of human vascular smooth muscle cells to FGF-23 did not have any effect on phosphate-induced calcification, and these cells do not express mRNA for FGF-23 or Klotho. It should be noted, however, that FGF-23 may have indirect effects on the vessel wall, as its effects on the myocardium were found to be Klotho-independent [5]. Further, a recent study found that higher FGF-23 concentrations were associated with an increased risk of major cardiovascular events in an older community-based population, and this association was attenuated, yet still significant, after adjusting for measures of arterial stiffness [33]. These findings, combined with the results of our current study, suggest that the association of FGF-23 with risk of CVD outcomes is unlikely to be mediated through a pathway inducing arterial stiffness.

The strengths of our study include its large sample size, its inclusion of multiple different ethnicities and its evaluation of multiple measures of arterial stiffness. The study also has important limitations. The first is the lack of PWV data in the MESA cohort, which is one of the more widely used measures of arterial stiffness. However, the measures used in our study are also widely regarded as surrogate measures of arterial stiffness. Prior studies in MESA and other studies have demonstrated that these measures are strongly associated with incident CVD and kidney outcomes [16–23]. Additionally, our study focused on persons without CVD and has a limited representation of persons with CKD. We still found a wide range of FGF-23 concentrations in our cohort, so we should have been able to detect meaningful associations in our analysis. Yet we acknowledge that this range is relatively low compared with values seen in CKD populations. Further, this study is cross-sectional, and as such, does not assess longitudinal outcomes. We do not exclude the possibility that baseline FGF-23 concentrations may influence changes in arterial stiffness over time.

In summary, higher FGF-23 concentrations are known to be strongly associated with poor cardiovascular outcomes, especially in the setting of advanced CKD. We provide insights that this effect is unlikely to be mediated through increased arterial stiffness.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

Ix has received honoraria from Shire Pharmaceuticals and Keryx Biopharmaceuticals. All of the other authors have declared that they have no other relevant financial interest.

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