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Fibroblast Growth Factor 23 is Associated with Subclinical Cerebrovascular Damage: the Northern Manhattan Study (NOMAS)

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Abstract

Background and Purpose—Elevated fibroblast growth factor 23 (FGF23) regulates phosphate homeostasis and is linked with mortality, cardiovascular events, and stroke. However, the role of FGF23 as a risk factor for subclinical cerebrovascular damage (SCVD) is unclear.

Methods—We used multivariable linear and logistic regression to evaluate associations between FGF23, continuously and by quartiles, with white matter hyperintensity volume (WMHV), expressed as percent intracranial volume (%ICV), and subclinical brain infarction (SBI) in a community-based stroke-free sample.

Results—There were 1,170 stroke-free Northern Manhattan Study participants with FGF23 levels and quantitative MRI data on WMHV and SBI. Participants with FGF23 levels in the top quartile (range=85 to 1425 RU/mL) had greater WMHV (β=0.19 %ICV, 95% CI=0.04 to 0.33 %ICV, p=0.01) compared to those in the lowest quartile (range=15 to 49 RU/mL), adjusted for demographics, vascular risk factors, and estimated glomerular filtration rate (eGFR). These findings remained significant in those without evidence of chronic kidney disease (eGFR < 60 ml/min/1.73m^2). Elevated FGF23 was not associated with SBI overall after adjusting for demographic factors and eGFR, but sex modified the effect of FGF23 on odds of SBI (p for interaction=0.03). FGF23 was associated with significantly greater odds of SBI only in men (OR=1.7, 95% CI=1.1 to 2.7, p=0.03) after full adjustment.

Conclusions—These cross-sectional community-based data from a diverse urban sample show an association between elevated FGF23 and small vessel disease, and MRI-defined brain infarction in men, independent of CKD. Data on elevated FGF23 and subclinical cerebrovascular damage progression are needed.

Keywords

Leukoaraiosis; fibroblast growth factor 23; cohort studies; Magnetic Resonance Imaging (MRI)

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate homeostasis, and when elevated increases cardiovascular disease and stroke risk and mortality. [1-7] However, most studies of FGF23 have focused on those with CKD. Less data are available from the general population, especially with respect to stroke. We previously reported elevated FGF23 increased stroke risk independent of CKD in the race/ethnically diverse community-based Northern Manhattan Study (NOMAS) [7]. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study reported an association between FGF23 and cardioembolic stroke [8]. We also reported that FGF23 was positively associated with carotid plaque presence and area, but FGF23's role in subclinical cerebrovascular damage (SCVD), especially cerebral small vessel disease, is still unknown [9].

Our previous finding that elevated FGF23 was associated with hemorrhagic stroke risk in the NOMAS sample suggested that FGF23 may be a risk factor for cerebral small vessel disease, but we did not find an association with incident lacunar stroke. White matter hyperintensities (WMH) and subclinical brain infarctions (SBI) seen on brain MRI are subclinical markers of cerebral small vessel disease that have been associated with traditional vascular risk factors and increased stroke risk [10-14]. Both WMH and SBI are common, and identifying novel risk factors for these lesions is a priority [15-17]. We carried out the current study to test the hypothesis that elevated FGF23 is associated with a greater burden of SCVD.

METHODS

Cohort

The NOMAS included 3,298 participants at baseline who were identified through random digit dialing using dual-frame sampling to identify published and non-published numbers.[18] People were eligible if they were never diagnosed with stroke, were >40 years of age, and were residents of Northern Manhattan for >3 months in a household with a telephone. Participants were recruited for in-person assessments (overall response rate of 68%) and underwent complete neurological examinations between 1993 and 2001.

Baseline Evaluation

Trained bilingual research assistants and study physicians collected demographic, medical, and laboratory data at enrollment using standardized data collection techniques and risk factor questions based on the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Study definitions for race/ethnicity, diabetes, cardiac disease and other risk factors have been previously described.[19] Subjects were contacted annually via telephone after enrollment to gather information regarding illnesses, hospitalizations, vital status, and cardiovascular events. Race-ethnicity was based on self-identification. Smoking status was categorized as never (reference), past, or current. Body mass index (BMI) was calculated as kg/m^2. Hypertension was defined as blood pressures ≥ 140/90 mm Hg (based on the average of two measurements with a mercury sphygmomanometer), a self-reported history of hypertension, or antihypertensive medication use. Diabetes mellitus was defined by self-reported history, use of hypoglycemic medications, or fasting blood sugar ≥126 mg/dL. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL or use of lipid-lowering medication.

MRI sub-study

Between 2003 and 2008, NOMAS participants were recruited for MRI sequentially during annual telephone follow-up if they met the following criteria: 1) still clinically stroke-free; 2) >50 years of age; and 3) no contraindications to MRI. To reach the planned sample size (N=1300), an additional 199 stroke-free household members of the original NOMAS participants, meeting the above criteria, were added to the prospective cohort from 2006-2008. The Institutional Review Board approved the study and all participants provided written informed consent.

Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Columbia University Medical Center. Quantification of WMH has been previously described.[18] Briefly, we removed non-brain elements manually using operator-guided tracing of the dura matter within the cranial vault, including the middle cranial fossa but above the posterior fossa and cerebellum, to define the total intracranial volume (TIV). Segmentation of WMH required the identification of brain matter, removal of image intensity non-uniformities, and modeling of Gaussian probability functions to determine the segmentation threshold. A single Gaussian distribution was then fitted to image data and a segmentation threshold for WMH volume (WMHV) was determined *a priori* as 3.5 standard deviations (SDs) in pixel intensity above the mean of the fitted distribution of brain parenchyma, with morphometric erosion of two exterior image pixels to remove the effects of partial volume cerebrospinal fluid pixels on WMH determination. We used a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation) [18]. All analyses were performed blind to participant identifying or risk factor data.

Determination of the presence or absence of subclinical brain infarcts (SBIs) has been previously published [16]. A superimposed image of the subtraction, Fluid Attenuated Inversion Recovery (FLAIR), and T2-weighted images at three times magnified view was used to assist in the interpretation of lesion characteristics. Vessels were indicated via signal void, best seen on T2-weighted images. Other imaging characteristics required for interpretation included CSF density on the subtraction image, and if stroke was in the basal ganglia area, distinct separation from the circle of Willis and perivascular spaces. Infarcts were counted for total number, and characterized by location (cortical, subcortical, and specific region) and size (small: <1 cm or large: >1cm). Two raters were used to determine the presence of infarcts, and agreement among them has been generally good (previously published kappa values: 0.73 to 0.90) [20].

Statistical Analysis

Known risk factors for SCVD and potential confounders of the association between FGF23 and MRI markers of SCVD were selected as covariates for multivariable analysis. We defined estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula as: GFR 186.3 X (serum Cr) – 1.154 × age – 0.203 × (0.742 if female) × (1.21 if African American) [21].We used multivariable linear and logistic regression to evaluate associations between FGF23, continuously (natural log transformed) and by quartiles, with WMHV, expressed as percent intracranial volume (%ICV), and subclinical brain infarction (SBI). First we examined the unadjusted association between FGF23 and both WMHV and SBI (Model 1). Next we fit sequential models adjusting for age, sex, race/ethnicity, and eGFR (Model 2), then smoking, BMI, hypertension, diabetes mellitus, and hypercholesterolemia (Model 3). We also conducted several sensitivity analyses: 1) further adjusting for phosphate and parathyroid hormone levels, 2) excluding those with evidence of CKD, and 3) excluding those with evidence of primary hyperparathyroidism. We tested for effect modifiers by including interaction terms for each covariate in the full model, and did stratified analyses for significant interactions. Analyses were conducted using SAS (version 9.4, SAS Institute, NC).

RESULTS

There were 1,170 stroke-free NOMAS participants with FGF23 levels and quantitative MRI data on WMHV and SBI (table 1). From the original cohort 1,150 had strokes or died prior to MRI, 1,057 did not participate in the sub-study (578 refused, 329 ineligible or other, and 150 lost to follow-up). There were minor differences comparing MRI sub-study participants in the study sample to those lacking blood markers (Supplementary Table I).

We found a positive association between FGF23 and WMHV. Each unit increase in natural log-transformed FGF23 was associated with significantly greater WMHV, with sociodemographic factors and eGFR explaining a substantial proportion of the variance. Still, the association remained statistically significant in models 2 and 3 (table 2). Dividing FGF23 levels into quartiles, we found a linear increase in WMHV across FGF23 quartiles (p for trend=0.02) even after adjusting for sociodemographic and vascular risk factors as well as eGFR, but most of the effect was driven by people in the upper FGF23 quartile (table 2). Also, eGFR was not significantly associated with WMHV with FGF23 in the model. To further minimize potential confounding by prevalent chronic kidney disease (CKD), we restricted the sample to participants without evidence of CKD, defined as estimated eGFR ≥60 mL/min/1.73 m^2. The association between natural log-transformed FGF23 and WMHV remained similar in the fully adjusted model (beta=0.11, 95% CI=0.01 to 0.21, p=0.03) and modeling WMHV adjusting for ICV (instead of as a proportion of ICV, data not shown). Associations remained significant in other sensitivity analyses (Supplementary Table II).

In an unadjusted model, each unit increase in natural log-transformed FGF23 was associated with greater odds of having SBI (table 2), but the effect was attenuated after adjusting for sociodemographic factors and eGFR (p=0.08), and vascular risk factors (p=0.21). The trend for increasing odds of SBI across quartiles of FGF23, and comparing the top quartile of FG23 to the lowest, showed a significant association with SBI only in the unadjusted model, with a trend toward significance after adjusting for sociodemographics and eGFR (p=0.06).

We found that sex modified the association between FGF23 and the odds of having SBI (p for interaction=0.03). Stratified by sex and adjusting for demographics, eGFR, and vascular risk factors, we found that FGF23 was associated with significantly greater odds of SBI in men (OR=1.7, 95% CI=1.1 to 2.7, p=0.03) but not women (OR=0.9, 95% CI=0.6 to 1.4, p=0.62). Sex was not an effect modifier of the association between FGF23 and WMHV, and race/ethnicity was not an effect modifier of the association between FGF23 and either marker of SCVD.

DISCUSSION

In this cross-sectional community-based study from a race/ethnically diverse urban sample, we found that participants with greater FGF23 levels had a greater burden of white matter lesions after accounting for demographics, vascular risk factors, and renal function. While FGF23 was not associated with MRI-defined subclinical infarction overall, greater FGF23 was associated with a greater odds of SBI among men.

Although FGF23 has been studied in carotid and coronary artery atherosclerosis, we are aware of no prior studies of FGF23 and small arterial disease. Community based studies of the role of FGF23 in atherosclerosis have shown mixed and controversial results despite some histopathological studies demonstrating FGF23's presence within atheromas of the carotid and coronary arteries [3, 22-25]. Elevated FGF23 has been associated with large vessel disease in CKD patients not on dialysis as well as in this community-based NOMAS cohort, but links with large vessel disease have not been reported in other community-based studies [9, 26]. Elevated FGF23 has been implicated indirectly in damage to peripheral arteries through its association with ankle-brachial index in the Cardiovascular Health Study.[22]

We were unable to find previous studies showing a link between FGF23 and small vessel disease other than through its association with chronic kidney disease. Our previous finding that elevated FGF23 is associated with incident hemorrhagic stroke suggests a role for rupture of both medium sized and small vessels, especially given the high prevalence of hypertension in the NOMAS sample. Moreover, we have previously demonstrated an association of kidney function with WMHV in NOMAS, but the association of eGFR with WMHV was not significant with FGF23 in the model.[7, 27] These data suggest that elevated FGF23 may be a key driving factor underlying the association between CKD and white matter disease. With the caveat that our observational data are cross-sectional, the combination of our previous finding that elevated FGF23 is associated with carotid plaque presence, and now, more severe white matter disease, suggest that FGF23 may be a risk factor for arterial disease across small to large calibers.

Subclinical MRI-defined infarcts and WMHV are markers of subclinical cerebrovascular damage that increase the risk of clinical stroke, but known risk factors do not fully explain the presence of these lesions, and the identification of novel potentially-modifiable risk factors is important [13-16]. Minimal attenuation of the estimated association between FGF23 and both WMHV and SBI after adjusting for traditional vascular risk factors suggests little variance is explained by such exposures and, in the case of WMHV, may be due to more direct effects of the hormone. Until recently, FGF23 has been thought to be predominantly pathologic only in CKD patients, but the associations of FGF23 with WMHV, and SBI in men, and with clinical stroke events suggest that the hormone is a potential target for intervention in a broader population of people [1, 7].

Our finding that FGF23 was associated with SBI presence in men but not in women does not have an obvious explanation. In a study of dialysis patients, male sex was associated with higher levels of FGF23. [28] The Heart and Soul study reported that post-menopausal women not on hormone replacement therapy have greater FGF23 levels than men, or women on hormone replacement therapy. [29] This may help explain the high proportion of women compared to men with FGF23 levels in the upper quartile in NOMAS. Estrogens act indirectly on PTH and reduced phosphate levels and FGF23 in both in-vivo and in-vitro studies.[30] In a cross-sectional analysis of the National Health and Nutrition Examination Survey post-menopausal women had greater phosphate levels independent of PTH, dietary intake, and eGFR[31]. Higher phosphate levels in post-menopausal women could increase FGF23, but phosphate levels did not differ by sex in this sample (data not shown). Even though most women were post-menopausal at the time FGF23 was measured in NOMAS, a

lag in SCVD and SBI development in women compared to men might be expected and is one plausible explanation for sex differences.

This study has several limitations. Our FGF23 and MRI data are cross-sectional and no causal conclusions can be made about the temporal relationship between FGF23 and SBI or WMHV. In addition, the MRI sub-sample was somewhat healthier than the 3,298 participants enrolled into NOMAS at baseline. However, this would be likely to minimize any association and bias our study towards the null. [16] Also, not all lesions labeled as SBI or WMH are due to vascular damage. For example, perivascular spaces can be misclassified as SBI, and WMH can be caused by any process that results in interstitial water. Further, some vascular lesions are below the resolution of our protocol and scanner, and could have gone undetected, limiting our ability to detect associations.[32-34] While WMHV often represents small vessel disease there may be nonvascular and genetic causes. [35] Strengths of our study include its population-based design, the race/ethnically diverse urban sample, and the quantitative measurements of markers of subclinical vascular brain injury.

CONCLUSIONS

Our study shows a cross-sectional association between elevated FGF23 and cerebral small vessel disease, and with MRI-defined infarction in men. These findings were independent of exposure to key sociodemographic and potentially modifiable vascular risk factors in a stroke-free and race-ethnically diverse urban community-based sample. However, prospective data examining elevated FGF23 and incident SCVD are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample Characteristics

	Total (n=1,170)		FGF23 quartiles 1-3 (n=878)		FGF23 quartile 4 (n=292)	
			Range (15.4-84.5)		Range (84.9-1424.6)	
	N	%	N	%	N	%
Sex						
Women	701	59.9	487	55.5	214	73.3
Men	469	40.1	391	44.5	78	26.7
Race/ethnicity						
White	170	14.5	126	14.4	44	15.1
Black	196	16.8	133	15.1	63	21.6
Hispanic	779	66.6	599	68.2	180	61.6
Other	25	2.1	20	2.3	5	1.7
Smoking						
Never	561	47.9	423	48.2	138	47.3
Former	504	43.1	384	43.7	120	41.1
Current	105	9.0	71	8.1	34	11.6
Hypertension						
Yes	842	72.0	611	69.6	231	79.1
No	328	28.0	267	30.4	61	20.9
Diabetes mellitus						
Yes	269	23.0	185	21.1	84	28.8
No	901	77.0	693	78.9	208	71.2
Hypercholesterolemia						
Yes	459	39.2	321	36.6	138	47.3
No	711	60.8	557	63.4	154	52.7
SBI*						
Yes	166	14.7	116	13.7	50	17.9
No	960	85.3	730	86.3	230	82.1
	Mean	SD	Mean	SD	Mean	SD
Age	70	9	69	9	73	9
BMI	29	5	28	5	29	6
FGF23	88.8	119.2	56.0	14.2	187.6	208.4
PO4	3.0	0.5	3.0	0.4	3.1	0.5
PTH	56.9	26.3	54.2	21.3	64.9	36.4
eGFR	77.4	20.3	80.5	18.8	68.3	21.9
WMHV, 1/TCV %	0.7	0.8	0.6	0.7	0.9	1.0

*44 with missing data.

Table 2

Association of FGF23 with WMHV and SBI

	FGF23 level	Model 1		Model 2		Model 3	
		Beta (95% CI)	**P**	**Beta (95% CI)**	**P**	**Beta (95% CI)**	**P**
	per unit lnFGF23	**0.32 (0.23, 0.41)**	**<.0001**	**0.16 (0.07, 0.25)**	**0.0004**	**0.15 (0.06, 0.23)**	**0.002**
WHMV, 1/TCV%*	Quartile 1	Reference		Reference		Reference	
	Quartile 2	0.13 (−0.02, 0.28)	0.10	0.03 (−0.11, 0.16)	0.69	0.01 (−0.12, 0.15)	0.86
	Quartile 3	0.23 (0.07, 0.38)	0.004	0.02 (−0.12, 0.16)	0.79	0.01 (−0.13, 0.15)	0.88
	Quartile 4	0.50 (0.35, 0.66)	<.0001	0.21 (0.06, 0.35)	0.005	0.19 (0.04, 0.33)	0.01
		p for trend <.0001		p for trend =0.01		p for trend =0.02	

		OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
	per unit lnFGF23	**1.33 (1.02, 1.74)**	**0.03**	**1.30 (0.97, 1.76)**	**0.08**	**1.22 (0.90, 1.65)**	**0.21**
SBI	Quartile 1	Reference		Reference		Reference	
	Quartile 2	1.10 (0.67, 1.83)	0.70	1.04 (0.62, 1.75)	0.88	0.98 (0.58, 1.67)	0.95
	Quartile 3	1.55 (0.96, 2.50)	0.07	1.43 (0.86, 2.38)	0.17	1.35 (0.80, 2.26)	0.26
	Quartile 4	1.65 (1.03, 2.66)	0.04	1.53 (0.90, 2.60)	0.11	1.39 (0.81, 2.39)	0.23
		p for trend = 0.02		p for trend = 0.06		p for trend = 0.13	

Model 1: unadjusted

Model 2: adjusted for age, sex, race/ethnicity, eGFR

Model 3: adjusted covariates in model 2 plus smoking, BMI, hypertension, diabetes mellitus, and hypercholesterolemia.

* log-transformed