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Fibroblast Growth Factor 23 is Associated with Carotid Plaque Presence and Area: the Northern Manhattan Study

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Abstract

OBJECTIVE—Elevated fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate homeostasis, has been associated with mortality, cardiovascular events, and stroke, and to arterial calcification in chronic kidney disease (CKD), but its role in atherosclerosis is unclear and population-based studies are lacking. We hypothesized that elevated FGF23 would associate with carotid plaque presence, area, and echogenicity in the race/ethnically diverse community-based Northern Manhattan Study (NOMAS) sample.

APPROACH AND RESULTS—There were 1,512 stroke-free NOMAS participants with FGF23 and 2D carotid ultrasound data (mean age 68±9 years; 61% women; 62% Hispanic, 18% black, 18% white). We used multivariable linear and logistic regression to evaluate FGF23, continuously and by quintiles, as a correlate of carotid plaque, plaque area (cubic root transformed), and echogenicity adjusting for sociodemographic and vascular risk factors. Participants with FGF23 levels in the top quintile were more likely to have carotid plaque (OR=1.49 95% CI=1.02-2.19, p=0.04) and larger plaque area (beta=0.32 mm^2, 95% CI=0.10-0.53 mm^2, p=0.004) than those in the lowest quintile, adjusting for eGFR, demographics, and vascular risk factors. Linear regression models also showed that log transformed FGF23 (LnFGF23) associated with greater odds of plaque presence (OR=1.26 per LnFGF23, 95% CI=1.01-1.58, p=0.04), and plaque area (beta=0.19 mm^2 per LnFGF23, 95% CI=0.07-0.31 mm^2, p=0.002).

CONCLUSIONS—Higher FGF23 associated with greater likelihood and burden of carotid atherosclerosis independent of CKD. Atherosclerosis may be a mechanism through which FGF23 increases cardiovascular events and stroke.

Keywords

Risk Factors for Stroke; Epidemiology; Atherosclerosis Risk Factors

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Elevated fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate homeostasis, is a novel risk factor associated with cardiovascular events, stroke, and mortality in chronic kidney disease (CKD) [1, 2]. Despite reported associations between elevated FGF23 levels and cardiovascular disease in CKD, and increasingly in the general population, the underlying mechanisms remain unclear [3-7]. A potential etiology is suggested by cross-sectional studies showing that elevated FGF23 is associated with greater carotid plaque across CKD stages, but data on the association with carotid plaque in the general population are lacking [6, 8-10].

Carotid plaque is a significant risk factor for cerebrovascular and cardiovascular disease [11, 12]. Given previous findings that elevated FGF23 is a risk factor for incident stroke[13, 14], an association with carotid plaque would provide one possible mechanism. In light of previous pathological and in vitro studies we hypothesized that elevations of plasma FGF23 would associate with greater carotid plaque prevalence and plaque burden[10, 15]. In addition, given the possible role of FGF23 in arterial calcification, we also hypothesized that elevated FGF23 would be associated with greater plaque echogenicity. We tested these

hypotheses in the race/ethnically diverse community-based Northern Manhattan Study sample because race/ethnic differences in the impact of carotid plaque on stroke risk have been reported, but their causes are not clear, and little is known about the role of FGF23 [16, 17].

MATERIAL AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

There were 1,512 stroke-free NOMAS participants with FGF23 levels and 2D carotid ultrasound data available. There were minor differences between NOMAS participants in the study sample and those not included (Supplementary Table 1). The characteristics of the sample are shown in Table 1. Carotid plaque was present in 57% of the study group, which is similar to the prevalence in the overall NOMAS sample (mean total plaque area 12±18 mm^2) [18].

Examining FGF23 (mean=74.6 ± 102.8, RU/mL) as a continuous variable, we found that each unit increase in natural log-transformed FGF23 levels was associated with significantly greater odds of having carotid plaque and with greater total carotid plaque area (TCPA) after adjusting for eGFR and sociodemographic and vascular risk factors (Table 2, model 3). When we adjusted for serum phosphate and parathyroid hormone levels, the associations were attenuated and were non-significant for plaque presence, but remained significant for total plaque area (beta=0.17 mm^2, 95% CI=0.06-0.30 mm^2, p=0.006) per unit increase in natural log-transformed FGF23 levels.

We also looked for a dose effect by dividing FGF23 into quintiles. Compared to the lowest quintile of FGF23, there was a significant positive linear trend across increasing quintiles of FGF23 for its association with plaque presence (p for trend=0.01) and TCPA (p for trend=0.0007), adjusting for demographic and vascular risk factors (Table 2). However, only participants with FGF23 values in the top quintile were significantly more likely to have carotid plaque, or greater TCPA, than those in the lowest quintile, adjusting for sociodemographic and vascular risk factors.

Restricting our analysis to participants without evidence of CKD (eGFR>59 mL/min/1.73 m^2), participants with FGF23 levels in the top quintile had greater TCPA (p=0.02 for the top quintile vs. the lowest quintile; p for trend=0.009), but the association with carotid plaque presence no longer reached significance (p=0.13 for the top quintile vs. the lowest quintile; p for trend=0.05). The association between FGF23 and carotid plaque presence and area did not differ by race/ethnicity.

To assess the association of elevated FGF23 with plaque echogenicity, we examined FGF23 in relation to GSM maximum values. First, we examined potential dose effects by analyzing the top four quintiles (Q2, Q3, Q4, Q5) of FGF23 compared to the bottom quintile (Q1) as correlates of GSM. We found a threshold effect for Q5. We then compared participants with FGF23 levels in Q5 to those below and found those in Q5 to have significantly greater GSM

adjusting for age, sex, race/ethnicity, and eGFR (beta=2.6, 95% CI=0.7 to 4.6, P=0.008). Adjusting further for vascular risk factors, the positive association remained but no longer reached significance (beta=1.9, 95% CI=−0.1 to 3.8,P=0.06). In a sensitivity analysis, when limited to participants with eGFR>=60 and FGF23<400, all the associations with plaque area remained similar and significant.

In a sensitivity analyses excluding participants with probable primary hyperparathyroidism (n=4), those with FGF23 levels in the top quintile had greater odds of having carotid plaque (OR=1.48 CI=1.01-2.18; p=0.04) and had greater plaque areas (beta=0.31 CI=0.09-0.52; p=0.004) than those with FGF23 levels in the lowest quintile. None of the sociodemographic or vascular risk factors were found to be effect modifiers of the associations between FGF23 and the markers of carotid atherosclerosis.

DISCUSSION

While cross-sectional and observational, these are the first population-based data that we are aware of to support FGF23 as a possible risk factor for large vessel atherosclerosis. In this stroke-free community-based sample of Latino, black, and white people living in the same community, participants with elevated FGF23 levels were more likely to have carotid plaque and greater TCPA, after adjusting for estimated kidney function, sociodemographic and vascular risk factors. The association between FGF23 and TCPA remained significant even in those without evidence of CKD.

The role of elevated FGF23 in atherosclerosis is controversial. The Cardiovascular Health Study found that FGF23 was not associated with ankle brachial index, a measure of peripheral artery disease, or with related events after controlling for vascular risk factors and kidney function [19]. Conversely, elevated FGF23 has been associated with impaired radial and brachial vasoreactivity in a community population, suggesting a link with disease of medium-sized arteries [20].

A recent histopathological analysis of calcified carotid plaques from patients who underwent carotid endarterectomy found that FGF23 was present in 48 of 53 resected plaques even though only 28 patients had detectable serum C-terminal FGF23.They also found that 45 of 48 plaques stained positive for intracellular FGF23. FGF23 was not found in healthy segments of the vessel, suggesting FGF23 is produced locally in plaques and selectively in diseased arteries To our knowledge no studies have evaluated associations of serum and local FGF23 production and in our study all patients had detectable FGF23.

Mechanisms through which elevated FGF23 may cause atherosclerosis are unclear. To date there has been mixed clinical evidence to support elevated FGF23 as a risk factor for arterial calcification, including in the aorta, coronary artery, and carotid across CKD stages [8, 21, 22]. The community-based Multi-Ethnic Study of Atherosclerosis did not find FGF23 levels to be associated with atherosclerosis. [23] However, there is recent evidence that elevated FGF23 plays a role in fat mass and pathological lipid metabolism that might help explain how FGF23 might have an impact on atherosclerosis since FGF23 null mice have both cardiovascular calcifications due to dysregulated parathyroid hormone, Vitamin D, and

calcium metabolism in addition to abnormal lipids. [24, 25] In model 3, LDL was significantly associated with echogenicity, and therefore a potential meditator along with smoking, blood pressure and treatment for diabetes mellitus (data not shown). Lipid-lowering medication was not a significant contributor.

Further study is also needed to investigate the role of other factors such as phosphorus intake. Because FGF23 tightly regulates serum phosphate, it is not surprising that we found no significant correlation between levels of the two markers. In vitro studies suggest that isolated FGF23 overexpression does not potentiate vascular calcification [6]. However, in vitro elevated serum phosphate can increase expression of genes that predispose to calcification [26]. Other in vitro evidence has demonstrated that FGF23 potentiates arterial smooth muscle calcification when local phosphate levels increase [15, 27]. Calcified tissue increases echogenicity, and calcified plaque has been associated with a greater risk of vascular events in this cohort [28]. In the current study, FGF23 was associated with greater echogenicity after adjusting for demographics and eGFR, but this was no longer significant after adjusting for vascular risk factors. Also, there was no association between FG23 and echogenicity when we restricted the analysis to those with plaque. Therefore, we are unable to link FGF23 to calcified plaque.

Elevated FGF23 has been linked to an increased risk of stroke and a number of mechanism could underlie this association [29]. We recently reported that elevated FGF23 was associated with an increased risk of incident hemorrhagic stroke in NOMAS [13]. While the underlying etiologies of the intracerebral hemorrhages in our sample were unknown, the high prevalence of hypertension in NOMAS suggests that most were due to microvascular disease, perhaps due to rupture of vessels previously damaged by arteriolosclerosis. While the etiologies of small and large vessel disease do not overlap entirely, it is possible that inflammation is a common underlying process. Inflammation is known to potentiate atherosclerosis [30]. We have previously shown that markers of inflammation are associated with carotid atherosclerosis and white matter lesions, a marker of cerebral small vessel disease, in NOMAS [31-33]. Recently, other studies have shown that FGF23 is associated with elevation of inflammatory markers, and we plan future studies with NOMAS to explore these relationships [5, 34].

Several limitations are noteworthy. Our data are cross-sectional and no causal conclusions can be made about the temporal relationship between elevated FGF23 and carotid plaque formation. Half of participants had FGF23 and carotid ultrasound on the same day, so we are unable to account for potential changes in FGF23 over time, however longitudinal studies of FGF23 levels demonstrate that they are stable [35]. In order to account for changes in time, we adjusted for the time difference between FGF23 and carotid ultrasound. Strengths of our study include the race/ethnically diverse urban population-based prospective design, and the stroke-free status of participants at the time of the carotid and FGF23 measurements. We also adjusted for important confounders, including co-morbid vascular risk factors and kidney function.

Our study provides cross-sectional evidence of a relationship between elevated FGF23 and carotid plaque presence, as well as greater plaque burden, after adjusting for estimated

kidney function. Further, those with elevated FGF23 but without evidence of CKD also had greater carotid plaque burden. These associations suggest FGF23 may be a risk factor for large vessel atherosclerosis. If prospective observational and clinical studies further implicate FGF23 in atherosclerotic plaque formation and progression, this hormone could become a target for therapeutic interventions designed to lower it for prevention of large vessel disease [36].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FGF23	Fibroblast Growth Factor 23
CKD	Chronic Kidney Disease
NOMAS	Northern Manhattan Study
TCPA	Total Carotid Plaque Area
eGFR	Estimated Glomerular Filtration Rate

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Significance

The hormone FGF23 is a novel risk factor for stroke and cardiovascular outcomes. These are the first population-based data demonstrating that elevated FGF23 is associated with the likelihood and burden of carotid atherosclerosis independent of CKD. Carotid atherosclerosis is an important potentially modifiable stroke risk factor and may be a mechanism through which FGF23 increases cardiovascular events and stroke.

Table 1

Characteristics of Analytic Sample (Total and by the Quintiles of FGF23)

Characteristic	Total (n=1,512)	FGF23 Quintiles 1-4 Range 6.6-80.3 RU/mL (n=1,210)	FGF23 Quintile 5 Range 80.5-1340 RU/mL (n=302)
Demographics			
Age, mean ± SD, yrs	68.9 ± 9.0	68.5 ± 8.9)	70.6 ± 9.2
Male, n (%)	587 (38.8)	419 (40.6)	96 (31.8)
Race/Ethnicity, n (%)			
Hispanic	932 (61.6)	741 (61.2)	191 (63.2)
Black	276 (18.3)	219 (18.1)	57 (18.9)
White	269 (17.8)	219 (18.1)	50 (16.6)
Other	35 (2.3)	31 (2.6)	4 (1.3)
CV Risk Factors			
Smoking, n (%)			
Current	239 (15.8)	183 (15.1)	56 (18.5)
Former	546 (36.1)	430 (35.5)	116 (38.4)
Never	727 (48.1)	597 (49.3)	130 (43.0)
Moderate alcohol drinking, n (%)	611 (40.4)	510 (42.1)	101 (33.4)
Anti-hypertension medication use, n (%)	626 (42.1)	475 (39.3)	161 (53.3)
Anti-diabetes medication use, n (%)	194 (12.8)	142 (11.7)	52 (17.2)
Lipid-lowering medication use, n (%)	262 (17.3)	193 (16.0)	69 (22.8)
BMI, mean ± SD, kg/m^2	28.2 ± 5.0	27.9 ± 4.8	29.4 ± 5.8
SBP, mean ± SD, mmHg	141 ± 20.1	140.5 ± 19.9	142.8 ± 21.2
DBP, mean ± SD, mmHg	83.1 ± 10.9	83.1 ± 10.8	82.8 ± 11.3
BS, mean ± SD, mg/dL	101.4 ± 41.2	101.1 ± 41.1	102.6 ± 41.6
LDL-C*, mean ± SD, mg/dL	128.3 ± 34.8	129.1 ± 33.9	125.3 ± 38.2
HDL-C†, mean ± SD, mg/dL	46.7 ± 14.3	46.7 ± 14.2	46.8 ± 14.9
Biomarkers			
FGF23, mean ± SD, RU/ml	74.6 ± 102.8	50.3 ± 13.6	172.0 ± 201.1

Characteristic	Total (n=1,512)	FGF23 Quintiles 1-4 Range 6.6-80.3 RU/mL (n=1,210)	FGF23 Quintile 5 Range 80.5-1340 RU/mL (n=302)
Phosphate, mean ± SD, mg/dl	3.0 ± 0.5	3.0 ± 0.5	3.1 ± 0.5
PTH, mean ± SD, pg/ml	55.7 ± 24.8	53.9 ± 22.5	63.1 ± 31.5
eGFR, mean ± SD, ml/min/1.73 m^2	82.8 ± 20.7	84.4 ± 20	76.2 ± 22.1
Carotid Plaque Measures			
Plaque presence, n (%)	862 (57.0)	668 (55.2)	194 (64.2)
TCPA[‡], mean ± SD, mm^2	11.7 ± 18.8	10.8 ± 17.8	15.4 ± 22.1
Time interval[§], mean ± SD, yrs	2.9 ± 3.4	3.1 ± 3.4	2.4 ± 3

[*] HDL-C: High density lipoprotein cholesterol

[†] LDL-C: Low density lipoprotein cholesterol

[‡] TCPA: Total Carotid Plaque Area (cube root transformed)

[§] Time interval between FGF23 measure and carotid ultrasound examination

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Table 2

Association between FGF23 and Carotid Plaque Presence and TCPA*

	FGF23 level	Model 1		Model 2		Model 3	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Plaque presence	per lnFGF23	1.26 (1.04, 1.52)	0.02	1.26 (1.02, 1.56)	0.03	1.26 (1.01, 1.58)	0.04
	Quintile 1	Reference		Reference		Reference	
	Quintile 2	0.94 (0.68, 1.30)	0.71	0.96 (0.68, 1.35)	0.82	0.94 (0.66, 1.34)	0.73
	Quintile 3	1.14 (0.83, 1.57)	0.42	1.27 (0.89, 1.80)	0.19	1.16 (0.81, 1.67)	0.41
	Quintile 4	1.22 (0.89, 1.69)	0.22	1.33 (0.93, 1.90)	0.12	1.24 (0.86, 1.79)	0.28
	Quintile 5	1.56 (1.13, 2.17)	0.007	1.57 (1.09, 2.26)	0.02	1.49 (1.02, 2.19)	0.04
		p for trend = 0.002		p for trend = 0.003		p for trend = 0.01	

		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
TCPA	per lnFGF23	0.21 (0.08, 0.33)	0.001	0.20 (0.08, 0.32)	0.001	0.19 (0.07, 0.31)	0.002
	Quintile 1	Reference		Reference		Reference	
	Quintile 2	−0.06 (−0.28, 0.16)	0.61	−0.02 (−0.22, 0.19)	0.89	−0.02 (−0.23, 0.17)	0.77
	Quintile 3	0.10 (−0.12, 0.31)	0.39	0.18 (−0.02, 0.39)	0.08	0.12 (−0.08, 0.32)	0.24
	Quintile 4	0.14 (−0.08, 0.36)	0.20	0.22 (0.01, 0.43)	0.04	0.15 (−0.05, 0.36)	0.15
	Quintile 5	0.38 (0.17, 0.60)	0.0006	0.38 (0.17, 0.60)	0.0005	0.32 (0.10, 0.53)	0.004
		p for trend = 0.0001		p for trend <.0001		p for trend = 0.0007	

Model 1: unadjusted

Model 2: adjusted for age, sex, race/ethnicity, eGFR, and time interval between FGF23 and carotid examination.

Model 3: adjusted for age, sex, race/ethnicity, eGFR, and time interval between FGF23 and carotid examination plus vascular risk factors.

*TCPA: Total Carotid Plaque Area (cube root transformed)