Title

Fibroblast growth factor 23, the ankle-brachial index, and incident peripheral artery disease in the Cardiovascular Health Study

Journal

Atherosclerosis, 233(1)

ISSN

0021-9150

Authors

Garimella, Pranav S
Ix, Joachim H
Katz, Ronit
et al.

Publication Date

2014-03-01

DOI

10.1016/j.atherosclerosis.2013.12.015

Peer reviewed

Published in final edited form as:
Atherosclerosis. 2014 March ; 233(1): 91–96. doi:10.1016/j.atherosclerosis.2013.12.015.

Fibroblast Growth Factor 23, the Ankle-Brachial Index, and Incident Peripheral Artery Disease in the Cardiovascular Health Study

Pranav S. Garimella[1], **Joachim H. Ix**[2], **Ronit Katz**[3], **Michel B. Chonchol**[4], **Bryan R. Kestenbaum**[3], **Ian H. de Boer**[3], **David S. Siscovick**[3], **Shani Shastri**[5], **Jade S. Hiramoto**[6], **Michael G. Shlipak**[6], and **Mark J. Sarnak**[1]

[1]Tufts Medical Center, Boston

[2]Universty of California, San Diego

[3]University of Washington, Seattle

[4]University of Colorado, Denver

[5]University of Texas Southwestern Medical Center, Dallas

[6]University of California, San Francisco

Abstract

Background—Fibroblast growth factor 23 (FGF23) has emerged as a novel risk factor for mortality and cardiovascular events. Its association with the ankle-brachial index (ABI) and clinical peripheral artery disease (PAD) is less known.

Methods—Using data (N=3,143) from the Cardiovascular Health Study (CHS), a cohort of community dwelling adults > 65 years of age, we analyzed the cross sectional association of FGF23 with ABI and its association with incident clinical PAD events during 9.8 years of follow up using multinomial logistic regression and Cox proportional hazards models respectively.

Results—The prevalence of cardiovascular disease (CVD) and traditional risk factors like diabetes, coronary artery disease, and heart failure increased across higher quartiles of FGF23. Compared to those with ABI of 1.1–1.4, FGF23 at baseline was associated with prevalent PAD (ABI<0.9) although this association was attenuated after adjusting for CVD risk factors, and kidney function (OR 0.91, 95% CI 0.76–1.08). FGF23 was not associated with high ABI (>1.4) (OR 1.06, 95% CI 0.75–1.51). Higher FGF23 was associated with incidence of PAD events in unadjusted, demographic adjusted, and CVD risk factor adjusted models (HR 2.26, 95% CI 1.28–3.98; highest versus lowest quartile). The addition of estimated glomerular filtration and urine albumin to creatinine ratio to the model however, attenuated these findings (HR 1.46, 95% CI, 0.79–2.70).

Conclusions—In community dwelling older adults, FGF23 was not associated with baseline low or high ABI or incident PAD events after adjusting for confounding variables. These results

Corresponding Author: Mark J. Sarnak, MD, MS, Division of Nephrology, Tufts Medical Center, 800 Washington St, Box 391, Boston, MA 02111, msarnak@tuftsmedicalcenter.org.

suggest that FGF23 may primarily be associated with adverse cardiovascular outcomes through non atherosclerotic mechanisms.

Keywords

Fibroblast growth factor; peripheral artery disease; ankle-brachial index; chronic kidney disease; cardiovascular disease

INTRODUCTION

Older adults and persons with chronic kidney disease (CKD) have a higher prevalence and risk of peripheral artery disease (PAD) than younger persons and those without kidney disease. [1,2] A low ankle-brachial index (ABI <0.9) has high sensitivity and moderately high specificity for atherosclerotic PAD.[3] However, high ABI (> 1.40 or incompressible) values are not normal and are observed commonly in persons with CKD, diabetes, and older age.[4] This is thought to be due to non compressible lower limb arteries as a consequence of medial arterial calcification (MAC).[5] Medial arterial calcification and an elevated ABI have both been shown to be associated with increased cardiovascular mortality and morbidity. [6–8] In CKD a number of unique risk factors like hyperphosphatemia, abnormal parathyroid hormone (PTH levels, and lower 25-(OH) vitamin D levels may increase the risk of calcification and be associated with cardiovascular disease (CVD) events.

Fibroblast growth factor 23 (FGF23) is a novel osteocyte derived hormone that regulates phosphorus homeostasis and the activation of $1,25(OH)_2$ vitamin D (also known as calcitriol).[9] High serum FGF 23 has been associated with cardiovascular morbidity and mortality, especially in patients with CKD. [10–12] We have previously demonstrated that FGF23 levels are elevated at very modest decrements in kidney function[13] and that individuals with either low ABI or high ABI have lower mean glomerular filtration rate (eGFR) than those with “normal” ABI levels. [4] Data are conflicting regarding the role of FGF23 with vascular and coronary calcifications.[14–18,19,20,21] To our knowledge, no prior study has evaluated the relationship of FGF23 with the ABI, and only one has studied the relationship of FGF23 with incident lower limb amputation in advanced CKD. [22] We evaluated the association of FGF23 with ABI and incident PAD in the Cardiovascular Health Study. We hypothesized that FGF23 would be associated both with abnormally high and low ABI measurements in addition to incident PAD events during longitudinal follow-up.

METHODS

Participants

The Cardiovascular Health Study (CHS) is an observational study of risk factors for cardiovascular disease among 5888 men and women 65 years or older living in 4 communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pa). The majority of the 5201 participants who were enrolled in 1989–1990 were white. In 1992–1993, an additional 687 African Americans were enrolled. For both enrollment periods, random samples of Medicare eligibility lists were used to recruit participants. All gave informed consent for participation, and study methods were approved by local institutional review boards. A detailed description of the recruitment and examination methods has been published elsewhere.[23] The enrollment examination included medical history, physical examination, laboratory testing, and assessment for the presence of cardiovascular disease. Participants were seen for yearly study visits until 1998–1999 and interviewed by telephone every 6 months. Using yearly participant-reports and Medicare hospitalization records, discharge summaries have been

requested for all hospitalizations and full medical records have been reviewed for all adjudicated outcomes. (A full list of the principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.)

Exposure Variable

FGF23—Fasting (8-h) ethylenediamine tetraacetic acid specimens collected at the 1996–97 study visit were stored at −70°C until 2010, when they were thawed and measured for FGF23 using a C-terminal ELISA kit (Immutopics, San Clemente, California).[24] Our estimates of the intra-assay and inter-assay coefficients of variation were 7.4% and 10.6%, respectively.

Outcomes

Cross Sectional Analysis

ABI: The protocol used to measure ABI at the time of the 1998–1999 visit has been described previously.[25] Briefly, after at least 5 min rest and with the subject in a supine position, standard mercury sphygmomanometers and a Doppler stethoscope (8 MHz, Huntleigh Technology, Inc., Luton, United Kingdom) determined the right brachial artery and right and left leg posterior tibial artery systolic blood pressures. Duplicate measurements were obtained and averaged. When a blood pressure could not be measured in the right arm, the left arm was used. The ratio of the systolic blood pressure in the leg to the arm defined the leg-specific ABI. The lower of the leg-specific ABIs was used as the patient-specific ABI for this analysis. When arterial flow was not abolished with the leg blood pressure cuff inflated to > 300 mmHg, the artery was deemed incompressible. From the original 3406 participants at the year 9 visit, we excluded those with the following missing values; FGF23 (69), UACR (92), creatinine (1) and ABI (812) to reach our analysis sample of 2432 participants.

Longitudinal Analysis

Incident PAD: Participants with PAD at baseline (defined as either an ABI less than 0.90 at the baseline examination or both exertional leg pain relieved by rest and a physician's diagnosis of PAD), were excluded (n=101, 3%). During follow-up, potential PAD outcomes were initially identified by any of the following methods: 1) report of a PAD diagnosis by the participant at a clinic visit or during a telephone call; 2) a PAD diagnosis found during review of medical records for another event; 3) active surveillance of CMS records for the ICD-9 codes 400.2 (atherosclerosis of the native arteries of the extremities) and 443.9 (peripheral vascular disease, unspecified). After potential PAD outcomes were identified by these methods, medical records were reviewed, and a final decision was adjudicated by the Morbidity Subgroups of the CHS Clinical Events Subcommittee. This analysis includes events that occurred through June 30 2010. From the original 3406 participants at the year 9 visit, we excluded those with the following missing values; FGF23 (69), UACR (92), creatinine (1) and also those with prevalent PAD (101) reaching our final sample of 3,143 participants. Of note, we included participants in the longitudinal analysis even if they did not have baseline ABI as long as they did not carry a 'clinical' diagnosis of PAD. Therefore, the number of participants was higher for the longitudinal analysis than the cross sectional analysis.

Covariates: Age, sex, and race/ethnicity were determined by self report. After a 5-min rest, seated blood pressure was determined in duplicate using standard mercury sphygmomanometers (Hawksley & Sons Ltd., Sussex, United Kingdom)[26] and results were averaged. Prevalent hypertension was defined by a seated systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or treatment for hypertension. Prevalent diabetes

was defined by use of hypoglycemic agents or insulin, or fasting glucose level >126 mg/dl. Smoking history was determined by questionnaire and categorized as current, past, or never. Methods of assessing prevalent cardiovascular disease including coronary heart disease (CHD) and heart failure (HF) in CHS have been described previously.[27–29] Height (cm) and weight (kg) were recorded without shoes and with the patient wearing light clothes, and body mass index was calculated (kg/m^2). The Olympus Demand System (Olympus, Lake Success, New York) determined serum total and high-density lipoprotein (HDL) cholesterol and triglyceride concentrations; low-density lipoprotein cholesterol concentrations were calculated using the Friedewald equation.[30] Cystatin C concentrations were measured using a BN II nephelometer (Dade Behring Inc., Deerfield, Illinois) as described elsewhere.[31] Estimated glomerular filtration rate (eGFR) was calculated using the equation: $\mathrm{eGFR}=76.7\ \mathrm{X}\,\mathrm{cystatin\ C}\,(\mathrm{mg}/1)^{-1.19}$.[32] We defined CKD as either eGFR <60 ml/min/1.73 m2 or ACR >30 mg/g.[33]

Statistical analysis

Cross Sectional Analysis—We categorized participants into quartiles based on levels of FGF23 and compared characteristics using Chi-square tests for categorical variables and t-tests for continuous variables. We then constructed natural piecewise cubic spline functions with ABI as the dependent variable and with pre-specified knots placed at the quartiles of FGF23 to assess the functional form of the association of continuous ABI and FGF23, adjusting for age, sex, and race. Given its right skewed distribution, FGF23 levels were log base 2 transformed, which facilitated interpretation of hazard ratios “per doubling” of FGF23 concentrations. Multinomial logistic regression, with ABI of 1.10–1.40 as the reference group, was then used to compare the cross-sectional association of FGF23 with ABI categories in the following nested models 1. adjusted for age, gender, and race; 2. additionally adjusted for smoking, diabetes mellitus, hypertension, serum total cholesterol, C-reactive protein (CRP), and serum albumin; 3. additionally adjusted for prevalent CVD (defined as coronary artery disease [CAD], myocardial infarction [MI], and stroke), and heart failure [HF], and 4. additionally adjusted for albumin-creatinine ratio (ACR) and eGFR.

Longitudinal Analyses—In 3,143 persons without clinical PAD, we evaluated the association between FGF23 with incident PAD events using Cox proportional hazards regression models. We initially evaluated FGF23 as a continuous variable and in companion analyses we also assessed associations by FGF23 quartiles allowing the lowest quartile to serve as the reference category. Sequential models were adjusted as described in cross-sectional analysis above. We also evaluated an FGF23*CKD interaction term in the final adjusted model based on previous studies showing that associations of FGF23 with CVD outcomes were significantly stronger among individuals with CKD.[34] S-Plus (release 8.0, Insightful Inc, Seattle, WA) and SPSS statistical software (release 15.0, SPSS Inc, Chicago, IL) were used for the analyses. A p-value <0.05 was considered statistically significant for all analyses including interaction terms.

We performed a sensitivity analysis by further adjusting for serum calcium, phosphorus and vitamin D in a sub-cohort of 1,308 CHS participants who had them measured.

RESULTS

Baseline characteristics

Among 2,432 participants included in the cross-sectional analysis, the mean age was 77 ±4 years, with 60% being women and 15% African Americans. Median (IQR) FGF23 level was 68.48 RU/ml (52.76–93.39). In comparison to participants with FGF23 concentrations in the

lowest quartile, those with higher levels were older, more frequently women, and white (Table 1). Participants with higher FGF23 concentrations also had a higher prevalence of diabetes, CVD, CRP, serum cystatin C, and urine ACR, but lower eGFR. Participants with an ABI < 0.9 at baseline comprised 18% of the cohort with the prevalence increasing in the higher FGF-23 quartiles ($p< 0.01$). Three percent of participants had ABI values > 1.4 or incompressible at baseline.

Cross sectional association of ABI with FGF23

In cross-sectional analysis, higher serum FGF23 levels were associated with ABI < 0.9 (Figure 1, Table 2), however the strength and significance was attenuated after adjusting for CVD risk factors, eGFR and ACR (Table 2). Prevalent CVD, HF, and kidney function measures were responsible for most of the attenuating effects. There was no statistically significant association between FGF23 levels and high ABI across the sequence of models.

Longitudinal Association of FGF with Incident PAD

There were 114 incident PAD events during a median follow up of 9.8 years. The crude rates for PAD events were 0.28, 0.29, 0.45, and 0.80 per 100 person-years in the respective higher FGF23 quartiles. The risk of incident PAD increased with higher levels of FGF23, and participants in the highest quartile of FGF23 had 2.3 times the risk of incident PAD in comparison with the lowest quartile, after adjusting for demographics, CVD risk factors, prevalent CVD and HF (Table 3). The addition of eGFR and ACR, however, significantly attenuated this association (HR 1.46 [95% CI, 0.79– 2.70]) and rendered it no longer statistically significant. The annualized rate of incident PAD events was higher (0.74%/year versus 0.33%. year) in those with CKD compared to those without CKD. We found no interaction between FGF23 and kidney function defined by the presence of CKD (eGFR<60 ml/min/1.73m^2 or ACR>30 mg/gm) or using continuous eGFR and ACR measures (p for all interactions >0.75).

There were 59 PAD events among 1,308 participants included in the sensitivity analysis. The addition of calcium, phosphorus and vitamin D to the fully adjusted model did not alter the associations between FGF23 (continuous or quartiles) and clinical PAD events. Compared to the lowest quartile of FGF23, the HR and 95% CI for the second, third and fourth quartiles were 0.72 (0.30– 1.77), 1.30 (0.59–2.88) and 1.43 (0.61–3.34) respectively. In continuous analysis each two-fold increase in FGF23 was not associated with increased risk of PAD events (HR 1.09, 95% CI 0.80–1.49).

DISCUSSION

To our knowledge, this is the first study to evaluate the association between FGF23 levels with ABI and incident PAD. In this study of community dwelling older adults, elevated levels of FGF23 were not significantly associated with either low or high ABI after adjusting for prevalent CVD and measures of kidney function. FGF23 was associated with increased risk of incident PAD in models adjusted for demographics, CVD risk factors and prevalent CVD, however this was attenuated after adjustment for measures of kidney function. Although CKD was associated with a higher risk of PAD events, it did not modify the relationship between FGF23 and PAD events.

The results of our study showed no association between FGF23 with either high or low ABI in cross sectional analyses. Although there are no prior studies of which we are aware which have evaluated this relationship, prior studies have evaluated the association of FGF23 with other measures of atherosclerosis. In particular, Mirza and colleagues in a cross sectional study of 967 adults over the age of 70 years noted that higher FGF23 levels were associated

with impaired vasoreactivity in individuals with eGFR > 60 ml/min/1.73m^2, and with increased arterial stiffness in those with eGFR < 60ml/min/1.73m^2.[35] In a subgroup of these individuals who underwent whole body magnetic resonance angiography, those with higher FGF23 levels had increased odds of both overall atherosclerosis as well as stenosis.[36] This relationship was not modified by kidney function although the magnitude of the association was greater in those with eGFR < 60ml/min/1.73m^2. The latter study did not, however, evaluate lower extremity PAD, nor did adjust for level of ACR which is a potentially important confounding variable. More recently, Scialla et al. evaluated the role of FGF23 on coronary artery calcification (CAC) in persons with CKD using data from the Chronic Renal Insufficiency Cohort (CRIC).[21] In this study, the investigators found no association between FGF23 and CAC, after adjusting for underlying CVD, while elevated serum phosphate was associated with greater CAC. They also demonstrated a procalcific effect of phosphate on vascular smooth muscle *in vitro*, and hypothesize that FGF23 and phosphate may differentially effect the cardiovascular system, with FGF23 acting on the heart and phosphorus on the arteries.[21]

We noted that FGF23 was associated with incident PAD after adjustment for demographic factors, CVD risk factors and prevalent CVD, but not after adjustment for eGFR and ACR. These data are consistent with prior data from CHS, where higher FGF23 levels were not associated with incident myocardial infarction (MI) ($p>0.05$),[34] although they were associated with incident HF and mortality.[34] While the presence of CKD significantly strengthened the association between FGF23 and CVD events (p for interaction <0.006), it did not modify the relationship between FGF23 and MI, which is consistent with our results if MI and low ABI are considered as more direct markers of atherosclerotic burden. Similarly, among 833 persons with stable coronary artery disease in the Heart and Soul Study, FGF23 was not associated in incident MI although it was associated with mortality.[12] Recent data has demonstrated that FGF23 directly induces increased LV mass and LV hypertrophy in animal models.[37] Using data also from the CHS, our group has recently shown that higher FGF23 levels were associated with LVH and LV mass index and the strength of these associations was greater in persons with CKD.[38] Given stronger associations with HF and mortality risk than MI or PAD, it may be that associations with death and HF are principally driven by FGF23's association with cardiac dysfunction and hypertrophy.[37,39,12,34,38] In combination these results suggest that FGF23 may mark risk for adverse outcomes principally through non-atherosclerotic pathways.

We acknowledge however that our results are not consistent with findings from the Homocysteine in Kidney and End Stage Renal Disease (HOST) Study, where participants in the highest quartile of FGF23 had significantly higher risk of amputation and MI. [22] The differences in results may be due to the differences in study populations. Participants in HOST had a median eGFR of 18 ml/min/1.73m^2 in comparison to 73 ml/min/1.73m^2 in CHS, they were also younger (69 versus 77 years) and were recruited as part of a controlled trial while CHS was a community dwelling population. In addition smoking, one of the strongest independent risk factors for atherosclerotic PAD was more prevalent in HOST study (range 10–27% across quartiles) as compared to CHS (range 5–9%).

Our study has a number of limitations. First, measures of FGF23 and ABI were non-concurrent for the cross sectional analysis, although there was only 1 year difference in the timing. Second, our results cannot be extrapolated to persons with advanced kidney disease, since the mean eGFR of CHS participants was 73 ml/min/1.73m^2. Third, we could not adjust for serum phosphorus levels as this was not measured in all participants at the year 9 visit, and we could not account for other measures of mineral metabolism such as activated vitamin D and klotho, which may be intermediaries between FGF23 and vascular outcomes. However, in our sensitivity analysis, our results did not change after adjusting for calcium,

phosphorus and vitamin D levels in a sub-cohort of the population. Fourth the relatively low number of PAD events and individuals with high ABI measurements may have led to reduced statistical power to appreciate any differences, and therefore may have given false negative results. Finally, because FGF-23 may be associated with development and progression of CKD,[40–43] we cannot rule out the possibility that kidney function is not only a confounding variable but also a mediating variable. In the latter case, adjustment for kidney function may hinder the ability to detect a relationship between FGF-23 with PAD. Given extensive data which show cross sectional relationships of FGF-23 with both albuminuria[44,45] and eGFR,[9,46,47] we have adjusted for kidney function in our primary analyses.

Despite these limitations our study also has a number of strengths. First, this is the first study to evaluate the association between FGF23 and both ABI as well as PAD events in a large community living population of older adults. Second, the CHS cohort has a long duration of follow up with accurate ascertainment of risk factors as well as adjudication of PAD events done by a panel of experts. The inclusion of both genders, black and white race, and recruitment from 4 sites across the US increase the generalizability of our results to community living elders.

Conclusions

In community living older adults, FGF23 levels were not independently associated with either high or low baseline values of ABI. FGF23 was associated with incident PAD in analyses adjusting for demographic factors, CVD risk factors and prevalent cardiovascular disease, however, eGFR and ACR significantly attenuated this relationship. These results suggest that FGF23 may primarily be associated with adverse health outcomes through non atherosclerotic mechanisms.

Acknowledgments

This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). Additional support was provided R01HL094555 from the NIA and AHA grant 0575021N. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

References

1. O’Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. Circulation. 2004; 109(3):320–323. [PubMed: 14732743]
2. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey. Circulation. 2004; 110:738–743. [PubMed: 15262830]
3. Lijmer JG, Hunink MG, van den Dungen JJ, Loonstra J, Smit AJ. ROC analysis of noninvasive tests for peripheral arterial disease. Ultrasound Med Biol. 1996; 22(4):391–398. [PubMed: 8795165]
4. Ix JH, Katz R, De Boer IH, et al. Association of chronic kidney disease with the spectrum of ankle brachial index the CHS (Cardiovascular Health Study). J Am Coll Cardiol. Sep 22; 2009 54(13): 1176–1184. [PubMed: 19761940]
5. Leskinen Y, Salenius JP, Lehtimaki T, Huhtala H, Saha H. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirements for diagnostics. American journal of kidney diseases: the official journal of the National Kidney Foundation. Sep; 2002 40(3):472–479. [PubMed: 12200797]

6. Adragao T, Pires A, Branco P, et al. Ankle--brachial index, vascular calcifications and mortality in dialysis patients. Nephrol Dial Transplant. May 6.2010
7. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. Sep; 2003 18(9):1731–1740. [PubMed: 12937218]
8. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation. Jan 24; 2006 113(3):388–393. [PubMed: 16432070]
9. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. Journal of the American Society of Nephrology: JASN. Jul; 2005 16(7):2205–2215. [PubMed: 15917335]
10. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. The New England journal of medicine. Aug 7; 2008 359(6): 584–592. [PubMed: 18687639]
11. Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. Jun 15; 2011 305(23):2432–2439. [PubMed: 21673295]
12. Parker BD, Schurgers LJ, Brandenburg VM, et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Annals of internal medicine. May 18; 2010 152(10):640–648. [PubMed: 20479029]
13. Ix JH, Shlipak MG, Wassel CL, Whooley MA. Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. Mar; 2010 25(3):993–997.
14. Jean G, Terrat JC, Vanel T, et al. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. Sep; 2009 24(9):2792–2796.
15. Moldovan D, Moldovan I, Rusu C, Kacso I, Patiu IM, Gherman-Caprioara M. FGF-23, vascular calcification, and cardiovascular diseases in chronic hemodialysis patients. Int Urol Nephrol. Apr 3.2013
16. Desjardins L, Liabeuf S, Renard C, et al. FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. Jul; 2012 23(7):2017–2025. [PubMed: 22109743]
17. Inaba M, Okuno S, Imanishi Y, et al. Role of fibroblast growth factor-23 in peripheral vascular calcification in non-diabetic and diabetic hemodialysis patients. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. Oct; 2006 17(10):1506–1513. [PubMed: 16896512]
18. Schoppet M, Hofbauer LC, Brinskelle-Schmal N, et al. Serum level of the phosphaturic factor FGF23 is associated with abdominal aortic calcification in men: the STRAMBO study. J Clin Endocrinol Metab. Apr; 2012 97(4):E575–583. [PubMed: 22319041]
19. Khan AM, Chirinos JA, Litt H, Yang W, Rosas SE. FGF-23 and the progression of coronary arterial calcification in patients new to dialysis. Clin J Am Soc Nephrol. Dec; 2012 7(12):2017–2022. [PubMed: 22997345]
20. Srivaths PR, Goldstein SL, Silverstein DM, Krishnamurthy R, Brewer ED. Elevated FGF 23 and phosphorus are associated with coronary calcification in hemodialysis patients. Pediatr Nephrol. Jun; 2011 26(6):945–951. [PubMed: 21359960]
21. Scialla JJ, Lau WL, Reilly MP, et al. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. Kidney Int. Jun; 2013 83(6):1159–1168. [PubMed: 23389416]

22. Kendrick J, Cheung AK, Kaufman JS, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. Journal of the American Society of Nephrology: JASN. Oct; 2011 22(10):1913–1922. [PubMed: 21903574]
23. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. Feb; 1991 1(3):263–276. [PubMed: 1669507]
24. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. The New England journal of medicine. Apr 24; 2003 348(17): 1656–1663. [PubMed: 12711740]
25. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol. Mar; 1999 19(3):538–545. [PubMed: 10073955]
26. Tell GS, Rutan GH, Kronmal RA, et al. Correlates of blood pressure in community-dwelling older adults. The Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. Hypertension. Jan; 1994 23(1):59–67. [PubMed: 8282331]
27. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. Ann Epidemiol. Jul; 1995 5(4):270–277. [PubMed: 8520708]
28. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol. Jul; 1995 5(4):278–285. [PubMed: 8520709]
29. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. Ann Epidemiol. Sep; 1993 3(5):504–507. [PubMed: 8167827]
30. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. Jun; 1972 18(6):499–502. [PubMed: 4337382]
31. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. Scandinavian journal of clinical and laboratory investigation. Feb; 1999 59(1):1–8. [PubMed: 10206092]
32. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. American journal of kidney diseases: the official journal of the National Kidney Foundation. Mar; 2008 51(3):395–406. [PubMed: 18295055]
33. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney International Supplements. 2012; 2:337–414.
34. Ix JH, Katz R, Kestenbaum BR, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). J Am Coll Cardiol. Jul 17; 2012 60(3):200–207. [PubMed: 22703926]
35. Mirza MA, Larsson A, Lind L, Larsson TE. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. Atherosclerosis. Aug; 2009 205(2):385–390. [PubMed: 19181315]
36. Mirza MA, Hansen T, Johansson L, et al. Relationship between circulating FGF23 and total body atherosclerosis in the community. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. Oct; 2009 24(10): 3125–3131.
37. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. Nov; 2011 121(11):4393–4408. [PubMed: 21985788]
38. Jovanovich A, Ix JH, Gottdiener J, et al. Fibroblast growth factor 23, left ventricular mass, and left ventricular hypertrophy in community-dwelling older adults. Atherosclerosis. Nov; 2013 231(1): 114–119. [PubMed: 24125420]
39. Gutierrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. May 19; 2009 119(19):2545–2552. [PubMed: 19414634]
40. Fliser D, Kollerits B, Neyer U, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. Journal of the American Society of Nephrology: JASN. Sep; 2007 18(9):2600–2608. [PubMed: 17656479]

41. Titan SM, Zatz R, Graciolli FG, et al. FGF-23 as a predictor of renal outcome in diabetic nephropathy. Clin J Am Soc Nephrol. Feb; 6(2):241–247. [PubMed: 20966122]

42. Clinical management of primary hypertension in adults. National Clinical Guideline Centre; UK: 2011. Hypertension: Evidence Update March 2013: A summary of selected new evidence relevant to NICE clinical guideline 127.

43. Semba RD, Fink JC, Sun K, et al. Serum fibroblast growth factor-23 and risk of incident chronic kidney disease in older community-dwelling women. Clin J Am Soc Nephrol. Jan; 2012 7(1):85–91. [PubMed: 22076875]

44. Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. Clin J Am Soc Nephrol. May; 2012 7(5):727–734. [PubMed: 22383747]

45. Vervloet MG, van Zuilen AD, Heijboer AC, et al. Fibroblast growth factor 23 is associated with proteinuria and smoking in chronic kidney disease: an analysis of the MASTERPLAN cohort. BMC Nephrol. 2012; 13:20. [PubMed: 22530966]

46. Larsson T, Nisbeth U, Ljunggren O, Juppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int. Dec; 2003 64(6):2272–2279. [PubMed: 14633152]

47. Marsell R, Grundberg E, Krajisnik T, et al. Fibroblast growth factor-23 is associated with parathyroid hormone and renal function in a population-based cohort of elderly men. Eur J Endocrinol. Jan; 2008 158(1):125–129. [PubMed: 18166826]

Highlights

- FGF 23 is associated with CVD events
- We examined the association of FGF23 with ABI and incident PAD in older adults
- FGF23 levels were not associated with either low or high ABI values at baseline
- FGF23 levels were not associated with incident PAD events after adjusting for kidney function
- The adverse CVD ascribed to FGF23 may occur through non atherosclerotic mechanisms

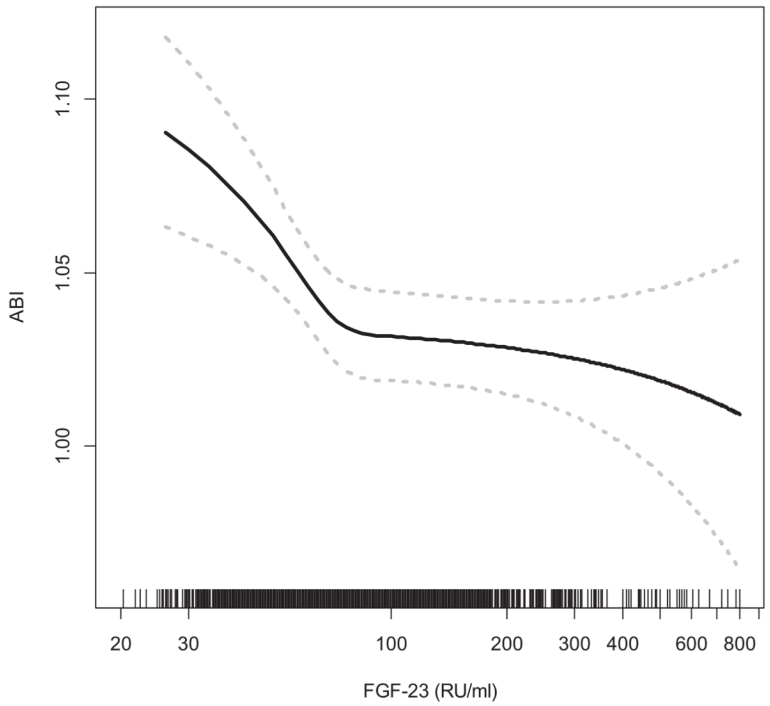

Figure 1.
Spline of ABI (y-axis) by FGF23 (x-axis) adjusted for age, gender and race.
Abbreviations: FGF23- Fibroblast growth factor 23, ABI- ankle-brachial index

Table 1

Baseline participant characteristics stratified by FGF23 level

Characteristic		FGF23 levels				
	All participants	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Range		20.26 – 53.62	53.63 – 70.84	70.85 – 100.38	100.39 – 3715.86	p for linearity
N	2432	657	645	624	506	
Mean age	77 (4)	77 (4)	77 (4)	78 (4)	78 (4)	<0.001
Female	1447 (60%)	341 (52%)	371 (58%)	390 (63%)	345 (68%)	<0.001
Blacks	382 (16%)	147 (22%)	97 (15%)	74 (12%)	64 (13%)	<0.001
Current smoker	173 (7%)	35 (5%)	32 (5%)	62 (10%)	44 (9%)	0.001
Diabetes	324 (13%)	62 (9%)	86 (13%)	84 (14%)	92 (18%)	<0.001
CVD	654 (27%)	143 (22%)	156 (24%)	165 (26%)	190 (38%)	<0.001
HF	163 (7%)	15 (2%)	30 (5%)	36 (6%)	82 (16%)	<0.001
Stroke	113 (5%)	29 (4%)	39 (6%)	21 (3%)	21 (5%)	0.629
SBP (mm Hg)	136 (20)	136 (21)	136 (19)	136 (21)	136 (21)	0.941
DBP(mm Hg)	70 (11)	71 (10)	70 (11)	70 (11)	68 (11)	<0.001
Medication use						
ASA	17 (0.7%)	5 (0.8%)	1 (0.2%)	3 (0.5%)	8 (1.6%)	0.111
Beta blocker	372 (15%)	65 (10%)	95 (15%)	105 (17%)	107 (21%)	<0.001
Statin	245 (10%)	47 (7%)	58 (9%)	80 (13%)	60 (12%)	0.001
ACE-I	350 (14%)	68 (10%)	84 (13%)	84 (14%)	114 (23%)	<0.001
Lab measures						
Total cholesterol (mg/dL)	202 (39)	199 (37)	203 (38)	202 (41)	203 (40)	0.077
Serum albumin (mg/dL)	3.83 (0.29)	3.85 (0.30)	3.85 (0.29)	3.82 (0.29)	3.82 (0.29)	0.024
C-reactive protein* (mg/L)	2.30 [1.06, 5.04]	1.76 [0.88, 3.89]	2.24 [0.99, 4.55]	2.75 [1.25, 5.51]	3.02 [1.46, 6.77]	<0.001
eGFR ml/min/1.73 m^2	73 (19)	81 (19)	75 (17)	70 (16)	61 (19)	<0.001
Serum cystatin C mg/l	1.11 (0.33)	0.99 (0.19)	1.06 (0.22)	1.13 (0.24)	1.33 (0.50)	<0.001
Urine ACR* (mg/gm)	8.00 [4.46, 17.34]	6.70 [4.09, 13.92]	8.26 [4.42, 16.39]	7.56 [4.47,16.49]	10.67 [5.12, 32.58]	<0.001
Baseline ABI value						
• < 0.90	18%	15%	16%	20%	24%	<0.001

Atherosclerosis. Author manuscript; available in PMC 2015 March 01.

Characteristic		FGF23 levels				
	All participants	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
• 0.90–1.09	42%	44%	41%	43%	38%	0.120
• 1.10–1.40	37%	39%	41%	35%	34%	0.028
• >1.40	3%	3%	2%	2%	3%	0.734

Abbreviations: FGF23- Fibroblast growth factor 23, CVD-cardiovascular disease, HF-heart failure, SBP-systolic blood pressure, DBP-diastolic blood pressure, ASA-aspirin, ACE-I- angiotensin converting enzyme inhibitor, eGFR-estimated glomerular filtration rate, ACR- albumin-creatinine ratio, ABI- ankle brachial index

Data are presented as number (percentages) or mean (SD), *median [IQR]

Table 2

Association of FGF23 levels with ABI categories

FGF 23 levels	Baseline ABI value			
	< 0.90	0.90–1.09	1.10–1.40 (reference)	> 1.40
N (%)	447 (18)	1017 (42)	908 (37)	60 (3)
Continuous FGF23 (per doubling)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted	1.30 (1.13, 1.48) p<0.001	1.00 (0.89, 1.12) p=0.944	1.00	1.19 (0.87, 1.62) p=0.267
Model 1*	1.28 (1.11, 1.47) p=0.001	0.95 (0.84, 1.07) p=0.409	1.00	1.22 (0.84, 1.07) p=0.215
Model 2**	1.14 (0.98, 1.34) p=0.095	0.92 (0.80, 1.04) p=0.183	1.00	1.14 (0.83, 1.58) p=0.423
Model 3†	1.07 (0.91, 1.26) p=0.409	0.90 (0.79, 1.02) p=0.097	1.00	1.13 (0.81, 1.57) p=0.461
Model 4‡	0.91 (0.76, 1.08) p=0.280	0.88 (0.77, 1.01) p=0.064	1.00	1.06 (0.75, 1.51) p=0.730

*Age, gender and race

**Further adjusted for smoking, diabetes, hypertension, total Cholesterol, C-reactive protein and serum albumin.

†Further adjusted for prevalent cardiovascular disease and prevalent heart failure

‡Further adjusted for eGFR and albuminuria

Table 3

Association of FGF23 with incident PAD events

	FGF23 Quartiles				Linear model	
	1	2	3	4	Per Doubling of FGF23	p-value§
FGF23 Range (RU/mL)	**< 53.63**	**53.63–70.84**	**70.85–100.38**	**> 100.38**		
Annual event rate (# events/# at risk)	0.28%(21/808)	0.29%(21/804)	0.45%(30/780)	0.80%(42/751)		
Unadjusted; HR (95% CI)	1.00 (ref)	1.05 (0.57, 1.95)	1.61 (0.91, 2.85)	2.99 (1.75, 5.11)	1.54 (1.29, 1.83)	<0.001
Model 1*; HR (95% CI)	1.00 (ref)	1.12 (0.60, 2.09)	1.75 (0.98, 3.11)	3.26 (1.89, 5.64)	1.56 (131, 1.86)	<0.001
Model 2**; HR (95% CI)	1.00 (ref)	1.01 (0.54, 1.89)	1.39 (0.78, 2.49)	2.37 (1.36, 4.13)	1.38 (1.13, 1.67)	0.001
Model 3†; HR (95% CI)	1.00 (ref)	1.01 (0.54, 1.89)	1.38 (0.77, 2.46)	2.26 (1.28, 3.98)	1.35 (1.10, 1.64)	0.003
Model 4‡; HR (95% CI)	1.00 (ref)	0.89 (0.48, 1.67)	1.12 (0.62, 2.02)	1.46 (0.79, 2.70)	1.12 (0.89, 1.41)	0.331

Abbreviations: FGF23=Fibroblast growth factor-23; SD standard deviation; HR=hazard ratio; Cl=confidence interval.

§P-value for the linear Cox model.

*adjusted for age, gender and race

**further adjusted for diabetes, hypertension, total cholesterol, CRP and albumin

†further adjusted for prevalent CVD and HF

‡further adjusted for eGFR and ACR