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

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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 ($N = 3143$) 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 per doubling 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 suggest that FGF23 may primarily be associated with adverse cardiovascular outcomes through non atherosclerotic mechanisms.

1. 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.

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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 FGF23 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 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.

2. Methods

2.1. 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, 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).

2.2. 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.

2.3. Outcomes

2.3.1. 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.

2.3.2. 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 3143 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 mmHg, diastolic blood pressure >90 mmHg, 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: $eGFR = 76.7 \times \text{cystatin C (mg/l)}^{-1.19}$ [32]. We defined CKD as either eGFR <60 ml/min/1.73 m^2 or ACR >30 mg/g [33].

2.4. Statistical analysis

2.4.1. 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