ARIC Manuscript Proposal #2206

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum fibroblast growth factor 23, phosphorus, and risk of incident hypertension: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): FGF23, Phos, & Hypertension

2. Writing Group: Amber Fyfe-Johnson, Alvaro Alonso, Elizabeth Selvin, Sunil Agarwal, James Pankow, Julie Bower, Pamela Lutsey. Other interested investigators welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AFJ_ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Data analysis to begin immediately. Anticipated draft completion Fall 2013.

4. Rationale:

According to the National Health and Nutrition Examination Survey (NHANES), 77.9 million Americans 20 years of age or older currently have hypertension[1]. In the

same survey, the age-adjusted prevalence of hypertension was estimated to be 75% for women and 65% for men aged 65 an over[2,3]. Hypertension frequently underlies cardiovascular disease; evidence suggests that hypertension is present in 69% of adults with incident myocardial infarction, 77% with incident stroke, and 74% diagnosed with incident heart failure[1,3].

Fibroblast growth factors (FGFs) are a family of proteins involved in numerous biological activities throughout the body[4]. FGF23 is principally involved in the regulation of energy and mineral metabolism. FGF23 is produced by osteocytes and osteoblasts, and participates in calciophosphoregulation and bone homeostasis[4,5]. The components of the bone and renal systems are highly interrelated; as kidney function declines disruption of mineral homeostasis occurs. Therefore calcium[6], phosphorus[7], magnesium[8], and vitamin D imbalance[9,10] are all involved in the development of chronic kidney disease – mineral bone disease (CKD-MBD)[11]. Cardiovascular disease is a leading cause of mortality among those with CKD[12–15]. Furthermore, in both the general population[16–18] and those with CKD[18–20], positive associations have been found between FGF23 and cardiovascular morbidity and mortality. It is increasingly believed that the cardiovascular pathologies associated with CKD may be due, in part, to disturbances in mineral regulation[4,21,22].

Development of hypertension with aging occurs in conjunction with, (i) the inability of the renal system to maintain mineral homeostasis, and (ii) changes in cardiac and vascular structure[23]. A rise in serum phosphorus precedes FGF23 elevation, and though limited, existing literature is suggestive of a positive association between elevated serum phosphorus and incident hypertension[24]. Prior work has shown elevated serum phosphorus to be associated with vascular calcification[25]; structural and functional vascular alterations have been associated with risk of incident hypertension[26,27]. A positive association has also been found between FGF23 and atherosclerosis[18], though it is unclear whether it acts independently of phosphorus[28,29]. Additionally, high circulating FGF23 has been associated with endothelial dysfunction and arterial wall stiffness[30–32], and inflammation[33,34] - factors which may contribute to the increased peripheral resistance typical of essential hypertension. Lastly, it is also possible that FGF23 is an early indicator of impaired kidney function; volume overload as a consequence of poor renal function may be a precursor to incident hypertension[35].

To date, the association between FGF23 and hypertension has not been examined; information on serum phosphorus in relation to hypertension risk is sparse. Therefore, we aim to explore the association between FGF23, serum phosphorus, and incident hypertension in the ARIC cohort.

5. Main Hypothesis:

- Elevated serum FGF23 will be positively associated with risk of incident hypertension.
- Elevated serum phosphorus will be positively associated with risk of incident hypertension.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary

of data analysis, and any anticipated methodological limitations or challenges if present).

Study Design

Prospective cohort from ARIC visit 2, when serum FGF23 and phosphorus were measured, to the development of incident hypertension.

Inclusion/Exclusion

Participants with prevalent hypertension (diagnosed or undiagnosed according to ARIC criteria) will be excluded at baseline. Additionally, individuals who are neither African American nor white, and African Americans from the MN and MD centers will be excluded at baseline.

Variables

Exposures: Serum FGF23, serum phosphorus.

Outcome:

- *Primary*: Incident hypertension based on measured blood pressure (SBP≥140 mmHg and/or DBP≥90 mmHg) and/or antihypertensive medication use at ARIC visits 3 and 4.
- *Secondary*: Incident self-reported hypertension based on ARIC annual follow-up phone calls.

Potential effect modifiers and/or mediators: Race, sex, diabetes, and eGFR (modeled as ≥90, 60-89, and 15-59 ml/min/1.73 m^2; derived using the CKD-EPI 2012 equation which incorporates both creatinine and cystatin C[36].

Other confounders: Age, sex, ARIC field center, education, physical activity, smoking status, alcohol intake, BMI, diabetes, prevalent CVD (CHD/HF/stroke), LDL-C, HDL-C, triglycerides, and lipid lowering medication.

Data analysis

Baseline characteristics of participants will be described using means and proportions stratified by levels of the exposures. Cox proportional hazards regression will be used to explore the relationship between serum FGF23, serum phosphorus, and risk of incident hypertension. Cubic splines may also be used to visually depict the associations, and aid in selecting the most appropriate representation. The exposures will likely be modeled categorically. Incident hypertension will be modeled as a dichotomous variable.

Our first model will adjust for age, sex, and race/ARIC field center. Model 2 will additionally adjust for education, physical activity, smoking status, BMI, and prevalent CVD. Model 3 will further adjust for: (i) eGFR alone, and (ii) eGFR, diabetes, CHD, and lipid lowering medication use. Finally, when FGF23 is modeled as the exposure we will also adjust for serum phosphorus.

Sensitivity analyses will explore: (i) the impact of modeling eGFR using alternate approaches (continuously and derived from different equations), (ii) excluding

individuals with prehypertension to verify the robustness of the association, and (iii) excluding individuals with prevalent CVD to evaluate the robustness of the association. Initial analysis will include only objectively measured hypertension at study visits; a secondary analysis will include self-reported hypertension obtained though study visits and annual follow-up telephone calls. Cross-product terms will be used to evaluate whether race, sex, diabetes, and kidney function modify the relationship between (i) serum FGF23, and (ii) serum phosphorus and risk of incident hypertension. Stratified results will be presented, as appropriate. Mediation will be considered present if beta coefficients are altered by 10% or more upon inclusion of diabetes or eGFR in the statistical models.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#1893: Serum magnesium, phosphorus, calcium and risk of incident heart failure: The Atherosclerosis Risk in Communities Study. *Pamela L. Lutsey, Aaron R. Folsom, Alvaro Alonso, Laura Loehr, Brad Astor, Joe Coresh.*

#2108: Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and total mortality: The Atherosclerosis Risk in Communities Study (ARIC). *Pamela L*

Lutsey, Jim Pankow, Alvaro Alonso, Joe Coresh, Elizabeth Selvin, Erin Michos, Sunil Agarwal, Laura Loehr, John Eckfeldt.

#2133 : Cardiac Biomarkers and Risk of Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study. *Julie K. Bower, Jonathan Rubin, Mariana Lazo, Kunihiro Matsushita; Ron Hoogeveen; Christie Ballantyne; Elizabeth Selvin.*

#2184: Parathyroid hormone and CVD. *Aaron Folsom, Elizabeth Selvin, Erin Michos, Alvaro Alonso, Jeff Misialek, John Eckfeldt, Josef Coresh, Jim Pankow, Pamela Lutsey.*

#2019: 25-hydroxyvitamin D levels and incident stroke: Twenty-year follow-up in a biethnic cohort. *Erin D. Michos, Pamela L. Lutsey, Thomas Mosley, Richey Sharrett, Kathryn A. Carson, Wendy Post, Rebecca Gottesman, Aaron Folsom, Jim Pankow.*

1215: Association of chronic kidney disease with carotid artery plaque characteristics. *Coresh J, Astor B, Ballantyne C, Hoogeveen R, Wasserman B.*

#224: Dietary Risk factors for decreased renal function in the ARIC study. *J. Coresh, T. Shimakawa, M. Szklo, J. Nieto, P.K. Whelton, M.J. Klag.*

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

2009.17 (Lutsey PI)
- "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort"

2009.16 (Selvin PI)
- "Short-term markers of glycemia and long-term outcomes"
- This grant measured cystatin C; eGFR calculated based on cystatin C and creatinine will be used in the present analysis.

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does

not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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