ARIC Manuscript Proposal #2226

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

1.a. Full Title: Fibroblast growth factor 23, serum phosphorus, and echocardiographic measures of cardiac structure and function: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): FGF-23, P, and Echo


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

First author: Jeffrey R. Misialek, M.P.H.
Address: Division of Epidemiology and Community Health
University of Minnesota
1300 South 2nd St., Suite 300
Minneapolis, MN 55454

Phone: 612-626-7921       Fax: 612-624-0315
E-mail: misi0020@umn.edu

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).
Name: Pamela L. Lutsey
Address: Division of Epidemiology and Community Health
University of Minnesota
1300 South 2nd St., Suite 300
Minneapolis, MN 55454

Phone: 612-626-5812       Fax: 612-624-0315
E-mail: lutsey@umn.edu

3. Timeline: Data analysis will begin immediately. We anticipate completion of the manuscript within 1 year.
4. **Rationale:**

Fibroblast growth factor 23 (FGF-23), a bone-derived endocrine hormone, is an integral component of specific biological mechanisms related to phosphorus (P) homeostasis regulation, vitamin D metabolism, and bone mineralization. Physiologically, FGF-23’s primary processes include inducing urinary P excretion in response to increased serum P levels, lowering serum calcitriol [1,25(OH)2D] levels through the inhibition 1-α-hydroxylase and the expression of 24-hydroxylase, and suppressing parathyroid hormone (PTH) synthesis. Also, FGF-23 levels and renal function are inversely correlated. Individuals with chronic kidney disease (CKD) have elevated FGF-23 levels, which have been shown in previous studies to be predictive of certain outcomes such as higher mortality, higher risk of cardiovascular disease (CVD), and renal failure.

There is present uncertainty about the role of FGF-23 in the development of CVD and, if an association exists, whether it is independent of kidney function. Two hypothesized pathways through which FGF-23 may influence cardiovascular risk involve vitamin D and CKD, both of which are risk factors for CVD. The role of this growth factor in influencing vascular health, blood pressure, and thus cardiac structure remains unclear. Recently, an animal experiment showed that FGF-23 had a direct pathophysiological role in the myocardium, inducing left ventricular hypertrophy (LVH). LVH is a marker of cardiac remodeling associated with increased risk of sudden cardiac death and progression to heart failure. Aside from one study of elderly Swedes, all previous studies that have used echocardiographic parameters to examine the association between FGF-23 and LVH were conducted among individuals with CKD.

Using ARIC data we propose to explore the roughly cross-sectional association between FGF-23 and numerous echocardiographic parameters in a subset of ARIC African Americans. We will examine whether a prospective association between FGF-23 and incident LVH exists in the ARIC Visit 5 participants. We will look specifically at these associations among those with normal kidney function and African-Americans. Also, the physiologic link of FGF-23 with P and the positive association between serum P and LVH suggest that investigating serum P in this analysis of the echocardiographic parameters may yield further insight as well.

5. **Main Hypothesis/Study Questions:**

Hypothesis #1.) FGF-23 will be cross-sectionally associated with echocardiographic measures of cardiac structure and function, specifically in the left ventricular, independent of CVD risk factors and CKD.

Hypothesis #2.) Serum P will be cross-sectionally associated with echocardiographic measures of cardiac structure and function, specifically in the left ventricular, independent of CVD risk factors and CKD.
Hypothesis #3.) In the longitudinal analyses, FGF-23 and P will be positively associated with risk of incident LVH, independent of CVD risk factors and CKD.

*Biomarkers were measured at visit 2 and echo data at visit 3, an average of 3 years later. Results will be interpreted cross-sectionally, though the data collection was non-concurrent.

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 analysis of FGF-23 (measured at visit 2, 1990-1992) to risk of incident LVH defined using echo parameters at visit 5 (2011-2013).

Inclusion/Exclusion:
- Cross-sectional analysis:
  - Inclusion: African Americans in the Jackson field center examined at visit 3
  - Exclusions:
    - Missing FGF-23 or serum P at visit 2.
    - Missing echocardiographic measurements at visit 3
    - Missing covariates

- Prospective analysis:
  - Exclusions:
    - Non-whites in Minneapolis and Washington County and non-whites non-African Americans in Forsyth County
    - Missing FGF-23 or serum P at visit 2.
    - Missing LVH outcome at visit 5
    - Prevalent LVH at visit 2 (defined by Cornell voltage criteria)
    - Prevalent heart failure or myocardial infarction at visit 2
    - Missing covariates

Variables:

Primary exposure: In ARIC, FGF-23 and serum P were assessed in 2012-2013 using fasting (12 hour) blood samples from visit 2 that were frozen at -70°C until analyzed. FGF-23 was measured using a two site enzyme-linked immunosorbent assay (ELISA) (FGF-23 ELISA Kit, Kainos Laboratories, Inc., Tokyo, Japan) while serum P was measured with a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a colorimetric method.

Dependent variables:
Cross-sectional analysis: the visit 3 echocardiographic parameters that will initially be examined include the following:

**Echo parameters**
  a) Left ventricular ejection fraction (EF)
  b) Left ventricular diameter (diastole)
  c) Left ventricular mass index
  d) % fractional shortening of left ventricular diameter
  e) Left atrial diameter
  f) E/A Ratio

**ECG parameters**
  a) Increased LA size (maximum p-wave duration ≥120): yes/no
  b) ECG-LVH (Cornell voltage): yes/no

Prospective analysis:
LVH defined as recommended by the Echo working group

Other variables (from visit 2): Age, sex, race (longitudinal analysis only), center (longitudinal analysis only), education, smoking status, body mass index (BMI), diabetes (defined as a fasting glucose ≥126 mg/dL, a nonfasting glucose ≥200 mg/dL, treatment for diabetes, or a self-reported diagnosis of diabetes), systolic blood pressure (SBP), anti-hypertensive (HT) medication, lipid medication, high density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, estimated glomerular filtration rate (eGFR) calculated using both creatinine and cystatine-C, c-reactive protein (CRP), parathyroid hormone (PTH), and vitamin D

Analysis:
For the cross-sectional analysis, general linear regression will be used to examine the relationship of FGF-23 and serum P with the echocardiographic parameters. The linear model assumptions will be checked for each model. All variables will be checked for normality, and log transformations will be done if necessary. The echocardiographic parameters will be modeled as continuous variables and, when specifically looking at LVH, as a dichotomous variable. Separate analyses will be performed for each echocardiographic parameter. Using logistic regression we will also explore the cross-sectional association of FGF-23 and ECG measures of increased LA size (maximum p-wave duration ≥120) and ECG-LVH (Cornell voltage).

For the prospective analysis, logistic regression will be used to examine incident LVH at visit 5 from baseline (visit 2). FGF-23 and serum P will be modeled in separate models initially as a continuous variable and as categories.

The following models will be used to analyze the association:
- Model 1: adjustment for age and gender (race and center will be added to the analysis using Visit 5 data)
- Model 2: Model 1 + adjustment for education, smoking status, BMI.
- Model 3: Model 2 + diabetes, SBP, anti-HT medications, lipid medications, HDL, LDL
• Model 4: eGFR, CRP, PTH, vitamin D, serum P (for the FGF-23 analysis)

Effect modification by age, sex, race (prospective analysis only), and eGFR category (<60, 60-90, >90) will be evaluated by conducting stratified analysis and including multiplicative terms between the potential effect modifier and FGF-23 or serum P in the models.

Limitations:
Since echocardiographic parameters were only measured with African Americans at visit 3, we are unable to perform a racial comparison in the cross-sectional analysis. The difference in visits for the exposure and covariate measurements (visit 2) and echocardiographic measurements (visit 3) is also a limitation. The incidence of LVH between visit 2 and 3 is expected to be minimal. The difference in visits for the exposure and covariate measurements (visit 2) and echocardiographic measurements (visit 3) is also a limitation. Since there is a smaller number total for this analysis (2622 from Jackson cohort at visit 3), there is potential concern about over-adjusting in the models, and power may be limited to perform the stratified analyses by age, sex, & eGFR. Modeling the echocardiographic parameters as continuous variables may help some with the power concern. There is also the major limitation of the lack of temporality when using a cross-sectional design.

For the prospective analyses, we will follow the recommendations of the ARIC Echo Working Group and the ARIC Visit 5 Analysis Working Group. We recognize that use of the Cornell LVH criteria to exclude those with prevalent LVH at visit 2 is not ideal, and we will be certain to carefully raise this point in the manuscript discussion. Also, selection bias is of concern as people who attended the ARIC visit 5 exam may be different than those who do not attend or died and may also differ from the rest of the ARIC population in regard to their visit 2 FGF-23 levels. To help address this, inverse probability weighting will be used to model selection into the study, as recommended by the ARIC Analysis Working Group.

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 ICTDER 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.cscn.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)?


#2088: Association of fibroblast growth factor 23 (FGF-23) with incidence of atrial fibrillation: the ARIC study Alvaro Alonso, Jeffrey Misialek, John Eckfeldt, Liz Selvin, Josef Coresh, Lin Y. Chen, Elsayed Soliman, Sunil Agarwal, Pamela L. Lutsey


#2143: Association of fibroblast growth factor-23 levels with risk and progression of chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) Study Casey M. Rebholz, Morgan Grams, Josef Coresh, Elizabeth Selvin, Pamela L. Lutsey


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

     ____ A. primarily the result of an ancillary study (list number* _

     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”

- Numerous biomarkers which may be confounders and/or effect modifiers in the present analysis are being measured as part of this grant (e.g. CysC, CRP).

  ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.
References:


