ARIC Manuscript Proposal # 3151

PC Reviewed: 4/10/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of serum calcium and serum phosphorus with the measures of left ventricular structure and function: Atherosclerosis Risk in Community

b. Abbreviated Title (Length 26 characters): Ca, P, & LV structure, function

2. Writing Group:

Writing group members: Kripa Poudel, Pamela L. Lutsey, Erin D. Michos, Amil Shah, Soma Konety, Aaron R. Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KP___

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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: Spring 2018
Data analysis: 1-2 months after proposal approval
Manuscript preparation: 1-2 months

4. Rationale:

Calcium and phosphorus are the electrolytes essential for maintaining normal human physiology and biochemistry. Studies show that high serum calcium levels are associated with greater risk of cardiovascular diseases [1, 2] and cardiovascular mortality[3]. Likewise, high serum phosphorus has also been independently associated with greater risk of

cardiovascular disorders[4-7]. Additionally, among individuals with cardiovascular[8] and nephrotic disorders[9], elevated phosphorous is associated with poorer prognosis.

Different echocardiographic measures are used to evaluate the structure and function of the heart. Echocardiographic markers of left ventricular (LV) structure and function are typically used to diagnose heart failure[10], and abnormal indices have been associated with greater risk of incident AF[11], coronary artery disease[12], and stroke[13].

Previous research has examined the association of these two electrolytes with the measures of LV structure and function in patients with preexisting conditions. High phosphorus and increased calcium-phosphorus product has been associated with impaired LV function in renal patients[14, 15], and uraemic patients[16]. Likewise, acute hypercalcemia from calcium infusion was also associated with LV dysfunction in patient with renal failure and secondary hyperparathyroidism[17]. In contrast, other studies found that low calcium was associated with LV dysfunction in renal patients[18], and coronary artery disease patients[19]. However, if these results hold true in general population is not largely known. Therefore, utilizing the rich echocardiographic data of ARIC Visit 5, this study aims to further evaluate the cross-sectional association of serum calcium and serum phosphorus with the measures of LV structure and function, and to evaluate whether any observed associations are independent of traditional cardiovascular risk factors.

5. Main Hypothesis/Study Questions:

- Abnormal serum calcium will be independently associated with decreased LV systolic, decreased LV diastolic function, increased left ventricular hypertrophy and concentric hypertrophy
- High serum phosphorus will be independently associated with decreased LV systolic, decreased LV diastolic function, increased left ventricular hypertrophy and concentric hypertrophy

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 methodologic limitations or challenges if present).

The study will look into the association of serum phosphorus and serum calcium with LV systolic and diastolic function using a cross-section study design. Both the exposure data (serum Ca and serum P) and outcome data (echocardiographic measures of LV structure and function) will come from ARIC Visit 5. We'll also examine the association of the calcium and phosphorus product to the measures of LV structure and function.

Only individuals who attended ARIC Visit 5 will be included in the present analysis. We will exclude anyone with missing values for calcium and phosphorus as well as variables measuring LV structure and function. We'll also exclude individuals with race other than black and white, and blacks from the MN and MD centers. Additionally, we'll exclude those with prevalent heart failure at Visit 5 from our analysis.

Main Exposure Variables:

- Serum Calcium
- Serum Phosphorus

Main Outcome Variables:

Our outcomes variables will be similar to those used in a previous ARIC analysis.[20]

LV structure

- LV end diastolic diameter
- LV end diastolic volume index
- LV maximal wall thickness
- LV mass index
- LV hypertrophy
- LV mass to volume ratio (M:V)
- LV relative wall thickness

LV systolic function

- LV ejection fraction
- Longitudinal strain

LV diastolic function

- tissue Doppler imaging e' (TDI e')
- E/e' ratio
- Left atrial volume

Other covariates:

Age, sex, race-center, BMI, eGFR, heart rate, systolic blood pressure, physical activity, smoking and drinking status, diabetes, HDL cholesterol, LDL cholesterol, use of lipid lowering medication, use of antihypertensive medications, presence of other comorbidities like CHD

Statistical Analysis:

Logistic Regression or Linear regression, as appropriate, will be used to look at the association between serum phosphorus and calcium with the variables measuring LV structure and function. The exposure variables will be modeled as continuous or categorical (in the form of quartiles) variables as appropriate. Multivariable adjusted mean and 95% confidence intervals will be calculated for echocardiographic parameters of LV structure and function. These echocardiographic variables will be log-transformed if not linear. P-value less than 0.05 will be considered significant.

We'll use these different models to test our research question.

- Model 1: adjusted for age, sex, race-center (5-level variable)
- Model 2: adjusted for Model 1 plus BMI, EGFR, heart rate, systolic blood pressure, physical activity, smoking and drinking status, diabetes, HDL cholesterol, LDL cholesterol, use of lipid lowering medication, use of antihypertensive medications
- Model 3: adjusted for Model 2 plus the presence of other comorbidities like CHD

Any methodological limitations/challenges:

Since we are using the cross-sectional data, we cannot establish temporality and therefore causal inference is limited. Measurement error may exist, as serum electrolytes may change over time, and we'll only be considering serum values of calcium and phosphorus at Visit 5. There may be survival bias as Visit 5 individuals may represent the healthy population.

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.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)?
There are a couple of papers looking at either serum calcium/phosphorus or the echocardiographic measures but none of the existing proposals are looking at the association of serum calcium and phosphorus with the echocardiographic measures of LV structure and function.

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

11.b. If yes, is the proposal

___ 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)* _____ _____ _____)

*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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