ARIC Manuscript Proposal #3549

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Changes in serum levels of mineral and bone disorder markers from mid- to late-life: their patterns, predictors, and consequences

b. Abbreviated Title (Length 26 characters): MBD in mid- to late-life population

2. Writing Group:

Writing group members: Junichi Ishigami, Manabu Hishida, Yasuyuki Honda, Amy Karger, Josef Coresh, Elizabeth Selvin, Pamela Lutsey, Kunihiro Matsushita, others welcome

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

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3. Timeline: Data for this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Mineral and bone disorders (MBD) are important complications of chronic kidney disease (CKD) particularly at its advanced stages.[1] Some MBD markers, such as fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and phosphorus are independently associated with increased risk of cardiovascular disease (CVD) and mortality in patients on dialysis[2-4] as well as those with less severe CKD.[3,5,6] However, it is uncertain whether findings for MBD biomarkers

in CKD patients are applicable to the general population.[7-11] Unique properties of MBD markers (e.g., MBD precedes decline in kidney function,[1] biological function in calcium-phosphate metabolism,[12] potentially modifiable through medication and diet[13,14]) suggest potential benefits of measuring levels of MBD markers in clinical practice or the need for clinical trials testing the efficacy of interventions to MBD markers to reduce adverse outcomes.[15,16]

Before MBD markers can be adopted in clinical practice, evidence is needed for identifying normal patterns of levels of MBD markers change over several years within individuals, risk factors for changes in levels of MBD markers, and whether changes in levels of MBD markers are associated with adverse outcomes beyond their baseline levels in the general population.

Using data from the Atherosclerosis Risk in Communities (ARIC) Study, we propose to characterize changes in MBD markers (FGF23, PTH, calcium, and phosphorus) over 3 and 20 years (from visit 2 to visit 3 and visit 5), their predictors, and their associations with clinical outcomes of mortality, CVD, and end-stage renal disease.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize patterns of changes in levels of four MBD markers (FGF23, PTH, calcium, and phosphorus) over 3 and 20 years in mid- and late-life
Aim 2: To identify key predictors of changes in levels of MBD markers over 3 and 20 years in mid- and late-life
Aim 3: To quantify the prospective associations of changes in levels of MBD markers over 3 and 20 years with outcomes of several key clinical phenotypes (i.e., mortality, CVD, end-stage renal disease) in this community-based population

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).
Study design: Observational cohort study

Inclusion/exclusion

All ARIC participants who had MBD markers measured at visit 2, 3, and 5 (for some analyses missing either of visit 3 or 5 may be acceptable).

Exposures (independent variables):

Aims 1 and 3: Exposures of interest are serum levels of MBD markers (FGF23, PTH, calcium, and phosphorus)
Aim 2: We will explore potential predictors (see Covariates below) of changes in the MBD markers

Outcomes (dependent variables):

Aim1: Describe statistics of levels of MBD markers from visit 2 (1990-1992) to visit 3 (1993-1995) and visit 5 (2011-2013)
Aim 2: Change in levels of MBD markers from visit 2 to visit 3 and visit 5
Aim 3: Mortality, CVD (heart failure, coronary heart disease, and stroke), and end-stage renal disease

Covariates:
Following covariates will be included in analysis: age, race, gender, years of education, body mass index, systolic blood pressure, diastolic blood pressure, alcohol use, diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, eGFR, total cholesterol, high density lipoprotein cholesterol, and history of cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke.

Statistical Analysis:
Baseline characteristics will be compared across levels of MBD markers using chi-square tests, and analysis of variance. Changes in levels of MBD markers will be assessed using mixed effects models (Aim 1). Subsequently, we will explore potential predictors of changes in the MBD markers listed in Covariates (Aim 2). For survival analysis (Aim 3), Cox proportional regression models will be used to quantify the prospective associations of changes in the MBD markers (e.g., visit 2 and 3, visit 3 and 5) and clinical outcomes listed above. Models will be adjusted for confounders. For sensitivity analyses, we will analyze key subgroups defined by age ($<$ vs. $\geq$ 65 years), race (black vs. white), sex (men vs. women), diabetes (yes vs. no), eGFR ($<$ vs. $\geq$ 60 ml/min/1.73m^2).

Potential limitations and proposed solutions:

- Need for calibration: We used the consistent assay for the MBD marker measurements (e.g., Kainos assay for FGF23 measurements at visit 3 and 5). We repeated measurements of ~100 visit 2 blind duplicate samples for the key analytes, and analyzed the comparability of prior (visit 2 data) and current results (visit 3 and 5 data). This data will be used to potentially recalibrate data given the large gap in time and impact of methodology changes.
- Attrition bias: Participants who were lost to follow-up earlier may be systematically different from those who stayed in the risk set particularly when examining the long-term changes in the MBD markers (e.g., change between visit 2 and 5). We will compare participant characteristics between those who did and did not attend visits, and perform sensitivity analysis using inverse probability weighting (IPW) method.[17,18]

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/mantrack/maintain/search/dtSearch.html

__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)?

For Aim 1 and 2, we will use newly collected data for analysis, and there is no related manuscript proposal. For Aim 3, we will utilize MBD markers measured at visit 2. Prior manuscript proposals related to Aim 3 include #2223 "Serum fibroblast growth factor-23, phosphorus and risk of incident stroke: The Atherosclerosis Risk in Communities Study (ARIC)" and MP#2108 "Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and total mortality: The Atherosclerosis Risk in Communities Study". All key authors of the above projects are included in our writing group.

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* _2017.20_____)

___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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