ARIC Manuscript Proposal #3235

PC Reviewed: 9/11/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Bone Mineral Metabolism Markers and Risk for Hospitalization with Acute Kidney Injury: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
MBD and AKI

2. Writing Group:
Writing group members:
Junichi Ishigami, Morgan Grams, Erin D. Michos, Pamela L. Lutsey, Kunihiro Matsushita, others welcome

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

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3. Timeline:
Data ascertainment for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Acute kidney injury (AKI) is a major public health concern associated with excess mortality, hospital stay, and health care costs.[1-3] In the United States, the incidence of AKI has increased by >2.4 times from 2000 to 2014.[4,5] A body of evidence has revealed adverse long-term consequences of AKI including incidence of chronic kidney disease, end-stage renal disease, and mortality.[6-8] Since a number of AKI cases are considered preventable,[9,10] identification of predictors of AKI is crucial to guide early preventive interventions (e.g., consider alternatives to radiocontrast use, avoid nephrotoxic drugs)[11] in those at high risk.

Some bone mineral metabolism markers such as 25-hydroxyvitamin D and fibroblast growth factor-23 (FGF23) seem relevant in this context.[12 13,14] For example, animal models showed that vitamin D deficiency aggravated AKI through increased renal oxidative stress, inflammation, and cell injury.[15-17] FGF23 suppresses the production of vitamin D, and also induced pro-fibrotic signaling in the kidney through activation of transforming grow factor-β pathways when primed by injury.[18] Among critically ill patients, low level of vitamin D and high level of FGF23 were independently associated with increased risk of developing AKI.[19,20] However, little is known about the prospective association of bone mineral metabolism markers with risk of hospitalization with AKI in the general population, although one study explored FGF23 and AKI risk in older adults.[21]

In this proposal, we will explore whether baseline serum levels of 25-hydroxyvitamin D, FGF23, parathyroid hormone, calcium, and phosphorus are associated with incidence of hospitalization with AKI using data from the Atherosclerosis Risk in Communities Study.

5. Main Hypothesis/Study Questions:

Bone mineral metabolism markers are independently associated with risk for hospitalization with AKI. The association is particularly evident in 25-hydroxyvitamin D and FGF23.

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).

Inclusion/Exclusion criteria: We will include all ARIC study participants who attended visit 2 when all bone mineral metabolism markers of interest were measured. We will exclude individuals with history of hospitalization with AKI prior to visit 2, non-black/non-white participants, end-stage renal disease or estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2 at baseline, or informed consent restricted to cardiovascular disease research

Exposures: Exposures of interest will be serum levels of following five bone mineral metabolism markers: 25-hydroxyvitamin D (accounting for seasonality),[22] FGF23, parathyroid hormone, calcium, and phosphorus

Outcome: Primary outcome of interest will be hospitalization with AKI, which is defined as a hospitalization or death with the ICD-9-CM code 584.x regardless of diagnostic position. This ICD-9-CM has been previously reported to have high specificity (99.6%) but low sensitivity (17.4%).[23] Our primary analysis will be AKI through September 2015 using ICD-9 codes but we will also try to incorporate ICD 10 codes from October 2015 if the incidence rate of AKI is reasonable using ICD 9 and 10. Since AKI may occur merely as a result of underlying cause of hospitalization such as infectious disease and cardiovascular disease, we will restrict to AKI cases to those at primary diagnostic position for primary analysis. We will also analyze cases of hospitalization with AKI regardless of diagnostic position as secondary analysis.

Other variables of interest and covariates: Covariates will include age, sex, race, body mass index, systolic and diastolic blood pressure, smoking status (never vs. ever), alcohol consumption (never vs. ever), diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, eGFR (using creatinine and cystatin C), total cholesterol, high-density lipoprotein cholesterol, and history of cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke.

Statistical Analysis Plan: Baseline characteristics will be compared by quartiles of each bone mineral metabolism marker, as well as status of AKI (yes vs. no) using chi-square tests for categorical variables and ANOVA for continuous variables. Hazard ratios (HRs) will be estimated using multivariable Cox proportional hazards model. The model will be adjusted for covariates as described above. The level of bone mineral metabolism markers will be treated as categorical variables (e,g., quartile), but also as continuous variables modeled as restricted cubic spline. We will perform subgroup analyses in predetermined covariates of age (<60 vs. ≥60 years), sex (male vs. female), race (white vs. black), and diabetes (yes vs. no). The interaction will be statistically assessed using the log-likelihood tests.

Limitations: Outcome ascertainment of AKI relying on ICD-9 codes may be subject to misclassification. Also, an important risk factor for AKI, urinary albumin-to-creatinine ratio (ACR), was not available at visit 2. We will perform a sensitivity analysis accounting for ACR at visit 4 among those with available data.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes ____ 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? __ X __ 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)?

Based on our search, we could not identify any proposals focusing on bone mineral metabolism markers as an exposure for AKI risk. "Risk factors for acute kidney injury (MS1944)" studied several risk factors for AKI in ARIC including low kidney function, genetic determinants, and serum urate but did not list bone mineral metabolism markers as risk factors of interest. "Mineral Metabolism Biomarkers Associated with Risk of End-Stage Renal Disease in a Nested Case-Control Study: CKD Biomarkers Consortium (MS2198)" studied the association of vitamin D and FGF23 with ESRD risk, but did not list AKI as an outcome of interest. Nonetheless, key authors of MS1944 and MS2198, Drs. Grams and Matsushita, are included in the present proposal.

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* _ 2002.02, 2009.17 **__)**
__ 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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