ARIC Manuscript Proposal #2758

PC Reviewed: 5/10/2016	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Bone-Mineral Metabolism Markers and Risk for Infection-related Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
CKD-MBD and infection

2. Writing Group:
Writing group members:
Junichi Ishigami, Bernard G. Jaar, Morgan Grams, Josef Coresh, 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:

Infectious disease often requires hospitalization,[1] and results in worse outcomes including death.[2] Chronic kidney disease (CKD) is an important risk factor for infection, particularly at its advanced stage.[3] Recently, we have shown that even those at mild to moderate stages of chronic kidney disease (CKD) are at high risk for infection, raising the need of further understanding of the underlying pathophysiology in the association between CKD and infection.

In this context, abnormality in bone-mineral metabolism related to CKD has been shown as a key player behind CKD complications, such as cardiovascular disease and mortality.[4-10] Several studies suggested that bone-mineral metabolism can also contribute to CKD-infection relationship. For example, lymphocytes functions were decreased in the presence of higher phosphorus.[11] In addition, fibroblast growth factor 23 (FGF23) and vitamin D may be involved in the regulation innate immunity.[12,13] Nevertheless, the association of these bone-mineral metabolism markers with risk for infection is largely unknown except a few studies in dialysis population.[14,15]

Thus, the aim of the study will be to assess whether several bone-mineral metabolism markers, phosphorus, calcium, 25-hydroxyvitamin D, intact PTH, and FGF23, are associated with risk for incident infection-related hospitalization and subsequent risk for mortality above and beyond kidney function, in a bi-ethnic community-based cohort, the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Bone mineral metabolism markers are independently associated with risk for infection

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 criteria

- All ARIC study participants whose phosphorus, calcium, 25-hydroxyvitamin D, intact PTH, and FGF23 levels were measured at visit 2.
- White and black participants.

Exclusion criteria

- History of infection-related hospitalization prior to visit 2.
- Non-black/non-white participants
- End-stage renal disease at baseline
- Informed consent restricted to cardiovascular disease research

Exposures

- Bone-mineral metabolism markers
  - Serum phosphorus (P)
  - Serum calcium (Ca)
  - Serum FGF23
  - Serum 25-hydroxyvitamin D (accounting for seasonality)
  - Serum intact PTH

Outcome

Primary outcome

- Incidence of all-cause infection-related hospitalization, defined as ICD-9 codes indicating any pathogen-, organ- symptom-based diagnoses of infectious disease[16] (ICD codes: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383, 386.33, 386.35, 388.60, 390–393,421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0,475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494,510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3,540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3,575–575.12, 590–590.9, 595–595.4, 597–597.89, 598.0,599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4,611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9,706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8,996.60–996.69, 997.62, 998.5, and 999.3 [details in Supplemental table 1 on pages 7-8])
- A priori determined four major causes of infection
  - Pneumonia (ICD9, 480-486)
  - Kidney and urinary tract infections (590, 590.0-4, 597, 598, 599.0, 601, 604, 607, and 608)
  - Septicemia and bacteremia (038 and 790.7)
  - Cellulitis (681 and 682)

Secondary outcome

- Event rate ratio of infection-related hospitalization accounting for multiple events.
- Infection-related mortality, defined as in-hospital death or death within 30 days after discharge of infection-related hospitalization

Sensitivity analysis

- Outpatient infection events using the same ICD-9 codes from the CMS data in participants aged 65 years or older with relevant data.

Other variables of interest and covariates:

- Estimated glomerular filtration rate using serum creatinine and cystatin C
- Age
- Gender
- Race
- Body mass index (BMI)
- Sitting blood pressure (systolic and diastolic)
- Smoking status
- Alcohol consumption
- Years of education from visit 1
- Serum biomarkers
  - hs-CRP
  - Albumin
- Medication use
  - Anti-neoplastic agents
  - Steroids
- Medical history
  - Diabetes (DM)
  - Hypertension (HTN)
  - Chronic obstructive pulmonary disease (COPD)
  - Cancer

- Prior heart failure (HF)
- Prior coronary heart disease (CHD)
- Prior stroke

- Incident clinical event during follow-up
  - End-stage renal disease (ESRD) (by linkage to USRDS)

Statistical Analysis Plan:

- Baseline characteristics will be compared across quantile of mineral and bone biomarkers using chi-square tests and analysis of variance.
- Baseline levels of mineral and bone biomarkers (P, Ca, 25-hydroxyvitamin D, iPTH, and FGF23) will be continuously estimated across eGFR with the use of cubic spline models
- Baseline levels of inflammatory markers (hs-CRP) will be continuously estimated across mineral and bone biomarkers
- Kaplan-Meier estimates for cumulative incidence
- Incidence rate using Poisson regression models
- Relative risk using Cox proportional hazard models
- Models will be adjusted for potential confounders in several ways
  - Base models will be adjusted for age, sex, race, BMI, smoking status, alcohol consumption, education level, medication use of anti-neoplastic agents and steroids, and history of HTN, DM, COPD, cancer, HF, CHD, and stroke, and eGFR.
  - Alternative models may be additionally adjusted for other mineral and bone biomarkers (e.g., iPTH, P, Ca, and 25-hydroxyvitamin D for the analysis of FGF23), as well as inflammatory markers (hs-CRP)
- Sensitivity analyses
  - Subgroup analysis by age (60+ vs. <60 years), sex (men vs. women), race (white vs. black), reduced kidney function (eGFR 60+ vs. <60 ml/min/1.73m^2), DM (yes vs. no)
  - Restricting infection related hospitalization to the primary diagnosis
  - Excluding severe kidney dysfunction (eGFR <30 ml/min/1.73m^2)
  - Additional adjustment for incident ESRD as a time-varying exposure
  - Risk for non-infection related hospitalization according to bone-mineral metabolism markers (to evaluate whether their associations are unique to infection-related hospitalizations)
  - Including outpatient infection events using CMS data

Limitations

- Outcome ascertainment relying on ICD-9 codes may lead to misclassification
- Mild cases of infection not requiring hospitalization may not be captured
  - CMS data could be used to include outpatient infection events in a subset of persons aged 65+, although the number of individuals aged 65+ years at visit 2 may be limited
- Albuminuria was not measured at visit 2.
- Possibility of residual confounding may not be excluded.

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)?
To our knowledge, there is no other ARIC proposal focusing on the association between CKD-MBD and infection.

MP 2624 proposed in 2015 "Chronic Kidney Disease and Risk for Infection-Related Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study" assessed the association of CKD with risk for infection. The primary exposures of interest in the present study will be mineral and bone biomarkers though we will adjust for eGFR. Most of the authors of MP2624 including the first author are included in the current 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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Supplemental table 1: Cause of the infection and ICD-9-CM codes

ICD-9	Referred disease description
001–139	Infectious and parasitic diseases
254.1	Abscess of thymus
320–326	Diseases of the nervous system
331.81	Rye's syndrome
372–372.39	Conjunctivitis
373.0–373.2	Inflammation of eyelids (Blepharitis, Chalazion)
382–382.4	Suppurative and unspecified otitis media
383	Mastoiditis
386.33	Suppurative labyrinthitis
386.35	Viral labyrinthitis
388.6	Otorrhea
390–393	Rheumatic Fever
421–421.1	Acute and subacute endocarditis
422	Acute myocarditis
422.91–422.93	Acute myocarditis, idiopathic
460–466	Acute respiratory infections
472–474.0	Chronic pharyngitis and nasopharyingitis
475–476.1	Peritonsillar abscess
478.21–478.24	Other diseases of upper respiratory tract
478.29	Other diseases of upper respiratory tract
480–490	Pneumonia and influenza (480–488), Bronchitis, not specified as acute or chronic (490)
491.1	Mucopurulent chronic bronchitis
494	Bronchiectasis
510–511	Empyema (510) and pleurisy (511)
513	Abscess of lung and mediastinum
518.6	Allergic bronchopulmonary aspergillosis
519.01	Infection of tracheostomy stoma
522.5	Periapical abscess without sinus
522.7	Periapical abscess with sinus
527.3	Abscess of salivary gland
528.3	Cellulitis and abscess of oral soft tissues
540–542	Appendicitis
566–567.9	Abscess of anal and rectal regions
569.5	Abscess of intestine
572–572.1	Liver abscess and sequelae of chronic liver disease
573.1–573.3	Hepatitis, toxic
575–575.12	Other disorders of gallbladder

590–590.9	Infections of kidney
595–595.4	Cystitis
597–597.89	Urethritis, not sexually transmitted, and urethral syndrome
598	Stricture, urethral, unspecified infection
599	Urinary tract infection, unspecified/pyuria
601–601.9	Inflammatory diseases of prostate
604–604.9	Orchitis and epididymitis
607.1	Balanitis
607.2	Other inflammatory disorders of penis
608	Seminal vesiculitis
608.4	Other inflammatory disorders of male genital organs
611	Inflammatory disease of breast
614–616.1	Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
616.3–616.4	Abscess of Bartholin's gland, Other abscess of vulva
616.8	Other specified inflammatory diseases of cervix vagina and vulva
670	Major puerperal infection
680–686.9	Infections of skin and subcutaneous tissue
706	Acne varioliformis
711–711.9	Arthropathy associated with infections
730–730.3	Osteomyelitis, periostitis, and other infections involving bone
730.8–730.9	Osteomyelitis, periostitis, and other infections involving bone
790.7–790.8	Bacteremia (not septicemia), Viremia, unspecified
996.60–996.69	Infection and inflammatory reaction due to internal prosthetic device implant and graft
997.62	Infection of amputation stump, unspecified extremity
998.5	Postoperative infection not elsewhere classified
999.3.	Other infection due to medical care not elsewhere classified