ARIC Manuscript Proposal #2427

PC Reviewed: 9/9/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Association of 25-hydroxyvitamin D and risk of kidney disease

b. Abbreviated Title (Length 26 characters): 25(OH)D and Kidney Disease

2. Writing Group:
   Writing group members: Casey M. Rebholz, Pamela L. Lutsey, Morgan E. Grams, Lesley A. Inker, Paul L. Kimmel, Meredith Foster, Andrew S. Levey, John H. Eckfeldt, Amy Karger, Ramachandran S. Vasan, Elizabeth Selvin, Josef Coresh, others welcome

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

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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: The goal is to prepare an abstract for the American Heart Association Epidemiology and Prevention / Lifestyle and Cardiometabolic Health Scientific Sessions 2014 (abstract submission deadline: October 15th; thus ARIC abstract review deadline: October 8th). The authors anticipate having a manuscript draft ready by the time of the conference (March 3-6, 2015).
4. **Rationale:**

Abnormal serum concentrations of mineral metabolites, such as calcium, phosphate, parathyroid hormone, vitamin D, and fibroblast growth factor-23, can result from chronic kidney disease (1, 2). For vitamin D in particular, impaired kidney function decreases renal 1α-hydroxylase activity thereby reducing the conversion of 25-hydroxyvitamin D [25(OH)D] into 1,25-dihydroxyvitamin D, the active form of vitamin D. Furthermore, among individuals with chronic kidney disease, disordered mineral metabolism can lead to a higher risk of cardiovascular disease and mortality (3, 4).

While vitamin D deficiency as a consequence of kidney disease is relatively well characterized, the role of vitamin D in kidney disease progression is less established. Animal studies suggest a direct mechanism for vitamin D on kidney function via reduction in proteinuria, reduction in levels of transforming growth factor (TGF)-β, inhibition of mesangial cell proliferation, and preservation of the structure of glomerular podocytes (5-9). A prospective study of baseline levels of vitamin D and the development of kidney disease over time would demonstrate temporality and provide further support for the causality of this association. The proposed study would add to the limited and inconsistent literature on this topic (10-12).

Circulating levels of vitamin D differ by race/ethnicity, with lower levels among black relative to white individuals (12-14). In an analysis of the National Health and Nutrition Examination Survey, 25-hydroxyvitamin D explained 58% of the increased risk of end-stage renal disease among black participants relative to white participants (12). The primary explanation for why 25(OH)D levels are lower among blacks than whites is that melanin (concentrations of which are higher among those with darker skin pigmentation) reduces the conversion of 7-dehydrocholesterol to vitamin D3 by ultraviolet B radiation (15, 16). However, it is possible that blacks and whites require different levels of 25(OH)D for optimal health. Genetic variants for vitamin D binding protein, which is a carrier protein for vitamin D, differ greatly by race, with whites being predisposed to higher levels of vitamin D binding protein relative to blacks (14). Vitamin D binding protein binds tightly to vitamin D in the circulation thereby rendering vitamin D biologically unavailable and inactive (17-19). Thus, genetic variants which predispose to higher circulating levels of vitamin D binding protein could lead to lower levels of bioavailable vitamin D, resulting in adverse outcomes (14). Recent evidence suggests that levels of bioavailable vitamin D are similar in blacks and whites since, although blacks have lower levels of 25(OH)D relative to whites, they also have lower levels of vitamin D binding protein (14). Further research is warranted to better understand racial disparities in the relationship between vitamin D levels and kidney disease outcomes.

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

1) We hypothesize that vitamin D levels will be inversely associated with risk of incident kidney disease, independent of baseline estimated glomerular filtration rate, demographic characteristics, and kidney disease risk factors.
We hypothesize that the vitamin D-kidney disease association will be stronger among black than white study participants.

3) We hypothesize that the vitamin D-kidney disease association will be stronger among those with vitamin D binding protein genetic variants which predispose participants to have higher levels of vitamin D binding protein (i.e. rs7041 GG and Gc1s/Gc1s).

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: Prospective cohort study

Eligibility: Participants with missing values of 25(OH)D at baseline (ARIC study visit 2) will be excluded. Additionally, participants with prevalent kidney disease at baseline (defined according to the outcome definitions below) will be excluded from the respective analyses.

Exposure: The primary exposure variable is baseline (ARIC study visit 2) levels of 25(OH)D. 25(OH) will be adjusted for season, as previously described (20).

Outcomes: There are two main outcomes: 1) incident end-stage renal disease, and 2) incident chronic kidney disease.

1) Incident end-stage renal disease will be defined as entry into the United States Renal Data System (USRDS) registry. This definition of end-stage renal disease only encompasses those individuals that received treatment (i.e. dialysis or transplant). As a sensitivity analysis for this end-stage renal disease outcome, we will assess a composite definition that encompasses both treated and untreated kidney disease. Incident kidney failure will be defined as a hospitalization or death related to kidney failure, entry into the USRDS registry, or eGFR <15 mL/min/1.73 m^2 at a follow-up study visit.

2) Incident chronic kidney disease (stage 3+) will be defined as a hospitalization or death related to chronic kidney disease or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at a follow-up study visit and an eGFR decline of at least 25% from baseline, as previously described (21).

Statistical analysis: For descriptive purposes, we will examine the associations of 25(OH)D with other baseline (ARIC study visit 2) participant characteristics (e.g. age, sex, race). In addition, we will assess the cross-sectional relationship between baseline 25(OH)D with other mineral metabolism biomarkers (calcium, phosphate, parathyroid hormone, fibroblast growth factor-23) and measures of kidney function (eGFR based on creatinine and
cystatin C individually and together, β₂-microglobulin, β-trace protein). Means and proportions will be used to describe baseline covariates according to quintile of 25(OH)D and differences will be tested using χ² and analysis of variance tests.

Survival analysis using Cox proportional hazards regression models will be used to assess the association between baseline 25(OH)D and time until kidney disease outcome. We will consider modeling 25(OH)D by quintile, as spline terms, or according to clinical categories (≤30 and >30 ng/mL; <20, 20-30, and >30 ng/mL). The independent relationship between 25(OH)D and kidney disease outcomes will be assessed by adjusting for covariates in multivariable regression models, including age, sex, race, body mass index, high-density lipoprotein cholesterol, hypertension, diabetes, history of coronary heart disease, cigarette smoking, eGFR and other measures of kidney function (β₂-microglobulin, β-trace protein), and other measures of mineral metabolism (calcium, phosphate, parathyroid hormone, fibroblast growth factor-23).

Interaction by race and vitamin D binding protein genetic variants (rs7041, rs4588, Gc phenotype) on the association between 25(OH)D and kidney disease outcomes will be assessed in multivariable models and with stratified analyses. We will also assess the strength of the association between vitamin D binding protein genetic variants and incident kidney disease.

Methodological limitations or challenges: One limitation is the lack of measured urine albumin-to-creatinine ratio (UACR) at ARIC study visit 2, which is a strong risk factor for kidney disease progression. To address this issue, in a sensitivity analysis, we will adjust for UACR measured at the nearest time point, ARIC study visit 4 (22). Another limitation is selection bias due to loss to follow-up. Importantly, the kidney disease definitions do not rely entirely on information collected at study visits. The kidney disease definitions utilize surveillance data for deaths and hospitalization as well as linkage to the USRDS registry.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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?  ____ 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  ____ 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.csc.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)?

#2019 – 25-hydroxyvitamin D levels and incident stroke: twenty-year follow-up in a biethnic cohort – ARIC author: P. Lutsey

#2021 – Vitamin D and neurocognitive decline: the ARIC brain ancillary study – first author: E. Michos

#2064 – Vitamin D, parathyroid hormone (PTH) and fibroblast growth factor-23 in relation to colorectal cancer risk and mortality in the Atherosclerosis Risk in Communities Study – ARIC author: P. Lutsey

#2066 – Associations between vitamin D status and diabetic retinopathy in a biracial cohort – first author: A. Millen

#2143 – Association of fibroblast growth factor-23 levels with risk and progression of chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) study – first author: C. Rebholz

#2152 – Vitamin D and venous thromboembolism – first author: A. Folsom

#2198 – Mineral metabolism biomarkers associated with risk of end-stage renal disease in a nested case-control study: CKD Biomarkers Consortium – first author: C. Rebholz

#2224 - 25-hydroxyvitamin D and risk of incident heart failure: The Atherosclerosis Risk in Communities Study (ARIC) – first author: P. Lutsey

#2340 – 25-hydroxyvitamin D and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) Study – ARIC author: P. Lutsey

#2357 – Vitamin D, vitamin D binding protein genetic polymorphisms, C-3 epimer Vitamin D3 and cognitive change over 20 years: the Atherosclerosis Risk in Communities (ARIC) Study – ARIC author: E. Michos

#2360 – Change in 25-hydroxyvitamin D levels over 3-years and 10-years of follow-up: the ARIC study – ARIC author: E. Michos
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* 2009.17, PI: P. Lutsey, “Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort)  

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.
References


