

ARIC Manuscript Proposal #2249

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1.a. Full Title: Nephrolithiasis as a risk factor in the development of incident chronic kidney disease: the Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): Nephrolithiasis and CKD risk

2. Writing Group:

Writing group members: Andrew Kummer, Pamela Lutsey, Morgan Grams, Kunihiro Matsushita, Anna Kottgen, Aaron Folsom, Josef Coresh

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

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3. Timeline:

Data to be used in this proposal are already available. Analyses will begin immediately upon approval of the proposal. Manuscript preparation will then be performed over the next 3-5 months.

4. Rationale:

Physicians traditionally recognize nephrolithiasis as an acute condition resulting in flank pain and hematuria. It is also known that heavy stone burden can disrupt enough renal parenchyma to cause chronic kidney disease and even end-stage renal disease (ESRD); this form of stone disease is responsible for 3.2% of those who reach ESRD [1]. What has become more apparent, however, in population-based studies over the previous decade is that nephrolithiasis appears to be much more than a process that can cause acute, exquisite pain and/or lead to ESRD in cases of high burden, but rather a potential herald for a more systemic disorder.

Stone disease history has been associated with a greater risk of hypertension, both in cross-sectional studies [2-6] and a prospective, longitudinal study [7]. Coronary artery disease risk was also increased in a recent study, as measured by risk of myocardial infarction, angina, and need for coronary artery bypass grafting [8], as well as with coronary artery calcification [9]. In addition, diabetes and the metabolic syndrome have also been associated with nephrolithiasis [10-13]. In particular, uric acid stone formers were at a significantly greater risk of developing diabetes mellitus [11].

Recent studies have suggested that a link exists between nephrolithiasis and the development of chronic kidney disease (CKD). Case-control and cross-sectional studies have shown a link between a history of kidney stones and GFR or incidence of CKD [14,15]. Interestingly, in the NHANES cross-sectional study, this link was only found in those patients with a BMI at or greater than 27 [15].

The most definitive study done to date in the area was the 2009 cohort study released by the Mayo Clinic group led by Dr. Andrew Rule. This study demonstrated a higher likelihood of developing CKD or having an elevated serum creatinine with a history of stone disease. However, a major limitation of this study is the relative homogeneity in this cohort, as patients were mentioned to be 96% white [16]. A similar study used the Alberta Kidney Disease Network database and found similar results, and women seemed to be more affected than men in this regard [17]. However, no racial demographic information was provided other than the percent of those who were deemed aboriginal, which was very low. Since African-Americans make up 1.4% of Alberta's population [18], it is likely that this is an underrepresented group.

A previous ARIC publication reported that self-reported nephrolithiasis in Visit 3 or nephrolithiasis related hospitalization through 2005 was present in 12% of men and 5% of women. Kidney stone history was associated with several CVD risk factors, and some of these risk factors differed by race [19].

The objectives of this proposal are: (a) to examine in further depth the association between nephrolithiasis history and the later development of incident CKD in a large population-based study, (b) to determine if the combination of hyperuricemia and the history of stone disease (as a possible surrogate for uric acid stones) is a better predictor of the development of CKD, and (c) to provide the first cohort study that can best evaluate racial differences in the effects of the above two associations.

5. Main Hypothesis/Study Questions:

1. We hypothesize that incident CKD will be increased in those with a history of nephrolithiasis, compared with no such history.
2. We hypothesize that the combination of hyperuricemia and nephrolithiasis history (potential surrogate for uric acid stones) will portend a higher risk of later CKD development than nephrolithiasis without hyperuricemia.
3. Is there a difference in stone-related risk of CKD between African Americans and whites?

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).

Design: Prospective cohort study. Visit 4 serves as the baseline for this analysis, since that was when kidney stone self-reports were obtained.

Inclusions: All with info some info -on nephrolithiasis and with CKD follow-up.

Exclusions: Those with clinical CKD, ESRD, or eGFR < 60 at visit 4, or those with an incident CKD hospitalization between visits 2 and 3.

Exposure variables: Kidney stone history (self-reported at visit 3) or hospitalization with nephrolithiasis (Visit 3 to most recent follow-up), using the same general approach as Akoudad et al. Kidney stone hospitalizations will be identified from ICD codes for nephrolithiasis-related procedures and/or hospitalizations. During followup, exposure will be reclassified from no to yes when incident nephrolithiasis occurs, so long as CKD or another censoring reason has not yet occurred.

Uric acid has been previously measured in ARIC at visits 1,2,4 and 5 and recently calibrated. Hyperuricemia will be defined as similar to McAdams DeMarco in previous ARIC papers.

Outcome: CKD incidence after visit 3, based on eGFR and albuminuria data from all visits or hospitalizations for CKD and ESRD. Exposure time will end when the participant has a CKD diagnosis, loss to follow up, death, or end of follow up.

GFR will be estimated by the CKD-EPI equations using an IDMS-standardized creatinine assay using the recently completed ARIC calibration study (data distributed by the DCC; Parinello et al. manuscript in preparation). eGFR will be expressed continuously and in clinically-relevant categories (stage 5: <15, stage 4: 15-29, stage 3b: 30-44, stage 3a: 45-59, stage 2: 60-89, stage 1: ≥ 90 mL/min/1.73 m²). We will use the newly updated definitions of incident renal endpoints in the ARIC Study (Grams *et al*, manuscript in preparation). Specifically, we will evaluate incident CKD, incident kidney failure, and incident ESRD. Incident kidney events are based on measures of kidney function (such as the presence of eGFR falling below 60 mL/min/1.73 m² at a follow up visit and a >25% decline in eGFR) and/or on kidney disease-related hospitalizations, death records, and linkage to the USRDS by continuous active surveillance. Detailed descriptions of the definitions of each of these renal events and – if applicable – the underlying ICD codes are given in the ARIC documentation for the identification of incident renal disease.

Covariables (needed from all visits available): age, race, sex, center, smoking status and amount, alcohol use, coronary artery disease, congestive heart failure, cerebral infarct, peripheral vascular disease, diabetes, BMI, physical activity, TC, HDL-C, TG, CRP, SBP, antihypertensive medication use and/or hypertension status, uric acid and/or gout status.

Analysis plan:

Primary Analyses – The distribution of CKD risk factors in the study population among individuals with and without nephrolithiasis will be computed using a t-test for continuous variables or a Chi-square test for categorical variables at each visit with visit 4 considered the baseline since it has kidney measures and follows the kidney stone questionnaires (at visit 3). Cox proportional hazards models will be used to examine the multivariate association of nephrolithiasis with development of CKD. Nephrolithiasis will be modeled as present/absent at visit 4 in the primary prospective analysis and modeled as a time-dependent variable in secondary analyses. To test hypothesis one, we will evaluate two regression models: a) adjusted for age, race, and sex; and b) multivariate-adjusted for potential confounders identified in univariate analysis including baseline eGFR and (at visit 4) albuminuria. Stratified analyses and interaction evaluations will also be employed in evaluating important risk factors, particularly that of African-Americans versus Whites (hypothesis 3) as well as baseline kidney function (eGFR ≤ 60).

To test hypothesis 2, we will also test the interaction of nephrolithiasis*uric acid or stratify these populations by uric acid level.

We will check the number of participants who had multiple episodes of symptomatic kidney stones. The primary source will be hospitalization which will be highly specific but insensitive. We will also review CMS data. This will be used in a secondary analysis which attempts to examine severity of the disease.

Limitations:

- The major limitation of this study will be the lack of information regarding stone type in those with nephrolithiasis. We will use a surrogate of hyperuricemia + nephrolithiasis to represent uric acid stones, but this certainly is not a perfect replacement. Information is also limited about the severity of disease and number of symptomatic episodes.
- Being that information is gathered intermittently, creatinine/cystatin C is available less than 5 times.
- The risk factor profile between the groups with and without nephrolithiasis may have changed during follow up. A sensitivity analysis can be done using time dependent risk factors.

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>

Yes No

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