ARIC Manuscript Proposal #4052

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: ___/___/___	**Status: _____**	**Priority: ____**

1.a. Full Title:

Plasma Biomarkers Associated with Incident Chronic Kidney Disease in Patients without Known Chronic Kidney Disease or Diabetes

b. Abbreviated Title (Length 26 characters):

Plasma Biomarkers and CKD

2. Writing Group:
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On behalf of the Chronic Kidney Disease Biomarkers Consortium

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. DL **[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:

This project will take approximately 6 months. A manuscript draft will be shared with the ARIC Publication Committee in August 2022. Journal submission is expected by September 2022.

4. Rationale:

Chronic kidney disease (CKD) affects almost 700 million adults worldwide.[1] In the United States, an estimated 37 million adults have CKD while 687,000 already have end-stage renal-disease (ESRD).[2]And despite advances in medical therapy, these estimates are expected to increase in time.[3] Therefore, initiatives regarding identification and treatment of individuals with kidney disease are of great importance.

Current identification of kidney disease revolves around measures of kidney function using serum creatinine and urinary microalbumin. These measures are insensitive and generally elevated after permanent scarring has occurred.[4] Novel kidney biomarkers may be able to change this paradigm and help identify individuals at risk of clinically significant disease before they have been traditionally been identified.

Kidney specific biomarkers include processes related to inflammation/fibrosis (TNFRI, TNFRII,[5] MCP-1, suPAR[6]), repair (YKL-40)[7], and tubular injury (KIM1). Among these, TNFRI and TNFRII have been the most consistent in association with progression and development of CKD among diabetic and non-diabetic patients. suPAR, YKL-40, and KIM1 have also been associated though less consistently across different cohorts. [8–11]

We specifically look at the association between plasma levels of TNFR1, TNFR2, suPAR, YKL40, KIM, and MCP1 and development of kidney disease in non-diabetic patients.

5. Main Hypothesis/Study Questions:

Are plasma biomarkers associated with incident kidney disease at follow-up in individuals without diabetes?

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:

This case-cohort study nested within the ARIC study has 523 cases of incident kidney disease (defined as eGFR <60 mL/min/1.73 m^2 at ARIC visit 5 or dialysis dependence identified by linkage with the US Renal Data System registry) in individuals without kidney disease (defined as GFR >60 mL/min/1.73 m^2) or diabetes at ARIC visit 4. In total there are 948 individuals included in this study.

Inclusion/Exclusion Criteria:

We included all eligible cases ascertained at ARIC visit 5 (ascertainment of the CKD outcome using eGFR occurred at visit 5) in addition to those who developed ESRD after visit 4. We excluded individuals who had missing eGFR at visit 4 or visit 5 or eGFR less than 60 mL/min/1.73 m^2 at visit 4. We also excluded individuals who had a missing value for baseline covariates. For this study, participants with diabetes at baseline (visit 4) were excluded.

Outcome: The primary outcome is incident CKD (eGFR <60 mL/min/1.73 m^2) or ESRD.

Statistical Analysis:

We will assess baseline characteristics in the overall study population and according to quartiles of each biomarker. We will assess the cross-sectional correlation between all of the plasma biomarkers, and then with uACR, eGFR-creatinine, and eGFR-cystatin.

Next, to explore the relationships of each biomarker with incident CKD, we will use multivariable logistic regression models and Cox proportional hazard regression models. We will conduct continuous analyses of the biomarkers, expressed per doubling of the biomarker level. We will also explore associations of biomarker quartiles, setting the lowest quartile as the reference category, in order to explore the functional form of the relationships.

We will conduct a sequence of models. An initial model will be unadjusted. A second model will adjust for age, gender, race, ARIC study site, body mass index, systolic blood pressure, anti-hypertensive therapy, smoking status, and history of cardiovascular disease. A third model will additionally include eGFR and urine albumin-to-creatinine ratio. We will examine the impact of adjusting for eGFR-creatinine vs. eGFR-cystatin.

We will also explore analyses that assess the association between the panel of plasma biomarkers and incident CKD. For example, we will include all the biomarkers in the same model. We will also explore the use of LASSO (least absolute shrinkage and selection operator) regression for variable selection.

Anticipated Methodologic Challenges:
The majority of cases were defined based on eGFR at visit 5. The precise time of onset of incident CKD will not be known, and there is a wide time interval between visit 4 (1996-1998) and visit 5 (2011-2013). For this reason, we supplemented the outcome ascertainment with ESRD cases identified through linkage to the US Renal Data System, which provides time of initiation of renal replacement therapy, but still not time of onset of CKD.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/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)?

#3596 – This prior manuscript proposal used the same study design, but focused on urine biomarkers in the Chronic Kidney Disease Biomarkers Consortium.

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* _2017.13_____)

___ 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 https://sites.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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