ARIC Manuscript Proposal #2240

PC Reviewed: 10/8/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: CLINICAL CORRELATES OF URINARY KIM-1 IN CKD BIOMARKERS CONSORTIUM COHORTS

b. Abbreviated Title (Length 26 characters): **CORRELATES OF URINARY KIM-1**

2. Writing Group:

Writing group members: Sushrut Waikar (first), Joseph Bonventre (senior), Chi Hsu, Kathleen Liu, Harv Feldman, Joe Coresh, Venkata Sabbissetti, Dawei Xie, Robert Nelson, *OTHERS WELCOME*

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

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3. Timeline: Data analysis and drafting of manuscript to begin immediately upon receipt of KIM-1 results and clinical data from ARIC, CRIC, and Pima cohorts

4. Rationale:

KIM-1 is expressed in proximal tubules following ischemia-reperfusion injury and is thought to be a marker of tubular damage and de-differentiation. KIM-1 confers a phagocytic phenotype to

renal tubular epithelial cells and may serve to assist in clearing necrotic debris from the tubular lumen. Urinary KIM-1 has been studied mostly in the setting of acute kidney injury and nephrotoxicity. However, low levels of urinary KIM-1 are also detectable in healthy individuals. KIM-1 expression has also been demonstrated in kidney biopsies and urine samples in chronic kidney disease patients with a number of diagnoses, including diabetic nephropathy, focal segmental glomerulosclerosis, and membranous nephropathy.

The factors associated with elevated urinary KIM-1 outside of the context of acute kidney injury are not well understood. In this proposal we aim to study urinary KIM-1 concentrations in individuals participating in three prospective cohort studies: ARIC, CRIC, and Pima Indians.

5. Main Hypothesis/Study Questions:

Urinary KIM-1 concentration is increased with higher levels of albuminuria and lower levels of eGFR. In exploratory analyses we will also test whether urinary KIM-1 is elevated in those with:

- Higher hemoglobin A1C
- Family history of end stage renal disease
- African-American race
- Cystic lesions on renal ultrasound
- History of peripheral vascular disease
- History of stroke
- Older age
- Smoking history

(Note that this study is being conducted across three distinct cohort studies, and that covariate information is not uniform across the studies)

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: For analyses using ARIC data, **w**e propose a cross-sectional study from a nested case-control study of 185 incident ESRD cases and 260 frequency matched controls in which urinary KIM-1 was measured at the Bonventre lab. Results from this analysis will be pooled with and/or compared to results from CRIC and Pima.

Eligibility Criteria: Cases and controls for the original ARIC/CKD BioCon study were selected from Visit 4 (1996-98). Participants were eligible for the case-control study if:
(1) Non-missing creatinine-based eGFR (defined using the CKD-EPI equation) at Visit 4
(2) Non-missing diabetes status at Visit 4
(3) Non-missing values for UACR
(4) Free of ESRD at Visit 4 and non-missing follow-up for ESRD events from Visit 4 through December 31, 2008
(5) African Americans at centers in Minneapolis, MN and Washington County, MD and Whites in Jackson, MS were excluded from the analysis.

ESRD Case definition: Cases included incident ESRD events after Visit 4 (1996-98) identified through hospitalization surveillance through December 31, 2008. Incident ESRD cases included:
1. AKI codes (584-584.9, 586, N17.0-N17.0) as an underlying cause of death and with a prior history of CKD as indicated by creatinine rise, eGFR MDRD or surveillance ICD code; OR
2. Hospitalizations with ICD codes specified for kidney transplant, dialysis or procedural code indicating dialysis, except:
a. ICD code of traumatic anuria (958.5) with the same event date
b. ICD code of AKI (586.x and 788.9x) with same event date and without any prior CKD events as indicated by creatinine rise, eGFR MDRD, or surveillance ICD code

Control Selection: Controls were frequency matched to cases (2:1, when possible) based on the following criteria
(1) CKD-EPI estimated glomerular filtration rate (eGFR) category (<45, 45-59, 60-74, 75-89, 90-105, ≥105 mL/min/1.73 m^2)
(2) UACR category (<30, 30-299, ≥300 mg/g)
(3) Diabetes status (fasting glucose >126 mg/dL, self-reported diabetes medication use in the past two weeks, or self-reported diagnosed diabetes)
(4) Sex
(5) Race (African American, White)

Exposures: Other variables of interest were assessed at Visit 4 and include the matching factors listed above (eGFRcrea, UACR, diabetes, sex, race), urinary creatinine (used as an index for the urinary exposure of interest), and potential covariates in our multivariable adjusted models (e.g. age, systolic blood pressure, diastolic blood pressure, hypertension medication use, body mass index, smoking status). Urinary biomarker assays were for CKD Biomarkers Consortium analyses in this case-control study using pH-adjusted urine samples collected during Visit 4.

Other variables of interest:
- Higher hemoglobin A1C
- Family history of end stage renal disease
- African-American race
- History of peripheral vascular disease
- History of stroke
- Older age
- Smoking history

Outcome of interest: Urinary KIM-1 concentration at visit 4.
KIM-1 will be standardized to urinary creatinine at Visit 4 if needed. If necessary for normality, we will apply an appropriate transformation to urinary markers (e.g. log10[X], ln[X], log10[X+1])

Statistical Analyses: we will include KIM-1 results from both cases and controls in this cross-sectional study of predictors of KIM-1. We will examine whether results are comparable in cases versus controls by testing for statistical interaction (e.g., covariate * indicator variable for case/control status). Specific analyses include the following:

1) How do KIM-1 levels differ across cohorts (CRIC vs ARIC vs Pima) and by year of collection?
    a. Linear regression
        i. Dependent variable: log-transformed KIM-1
        ii. Independent variables: study (indicator variables); duration of storage (linear if appropriate)
2) How do KIM-1 levels relate to albuminuria and eGFR at the time of urine collection for KIM-1 measurement
    a. Restricted cubic splines to explore relationship
    b. Modeling dependent on (a): Spearman or Pearson correlation, linear regression
    c. NOTE: when comparing KIM-1 with albuminuria using normalized (-creatinine) values, will attribute any $R < 0.5$ to the common divisor (urinary creatinine)
3) What clinical factors are associated with higher KIM-1?
    a. Linear regression of log-transformed KIM-1
    b. Independent variables:
        i. indicator variables for demographics and available medical history variables such as race, diabetes mellitus, CHF, vascular disease, stroke, family history of ESRD
        ii. continuous (first examine using splines): age, HgbA1C, systolic BP, diastolic BP (closest to KIM-1 collection)
4) What factors are associated with extremely high levels of KIM-1?
    a. Logistic regression (top 2.5% of urinary KIM-1 levels; separate analyses for each cohort)
    b. Exploratory analyses for all variables listed above. Additional variables may be cohort specific

Anticipated methodologic limitations or challenges if present:
This is a small case-control study, so markers are only available in ~400 ARIC participants who attended Visit 4 with follow-up for ESRD. Urine samples were collected at Visit 4 (1996-98) with long-term storage prior to laboratory assays (assays performed in 2012-2013). Thus samples may have degraded with long-term storage. Another major methodologic limitation is the case:control design. We will be cautious in pooling cases and controls, as baseline levels of urinary KIM-1 are higher in cases than controls and the associations with covariates of interest may differ among the two groups. We may find disparate results in cases versus controls versus the other two cohorts, in which case interpretation will be challenging. We do believe that comparisons of KIM-1 levels across the studies will be informative.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _x___ 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 _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"?
___x_ 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)?

"Urinary biomarkers and ESRD" by Foster et al., in preparation as part of the CKD 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* _2012.13 _____)
___ 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 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.
Agreed

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.